Parenteral Nutrition-Associated Liver Disease in Pediatric Patients: Strategies for Treatment and Prevention

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Introduction

Parenteral nutrition (PN) has revolutionized the nutritional care of patients who cannot fully use the gastrointestinal tract [1]. Today more than 30,000 patients, young and old, depend on long-term PN for survival, and more than 350,000 patients in the USA receive PN on a yearly basis [2]. Despite its common usage, PN is associated with a number of significant morbidities. Parenteral nutrition-associated liver disease (PNALD) has become one of the most challenging complications associated with prolonged administration of PN. As PNALD progresses to a more permanent injury to the liver, patients are at high risk of additional morbidity and even mortality [3, 4]. A number of recognized risk factors have been attributed to PNALD, but it appears that no single factor is fully responsible as a causative agent or factor. Thus, the multifactorial nature of PNALD has been an incredible challenge to both clinicians and researchers, and the process unfortunately remains incompletely understood. This chapter discusses the current knowledge of PNALD, the potential causative factors, as well as treatment and preventive strategies.

Background

Parenteral nutrition (PN) describes the intravenous administration of complete and balanced nutrition in order to support anabolism and maintain or promote weight gain whenever the gastrointestinal tract cannot and should not be used for adequate nutrition in patients with or at risk for malnutrition. PN is composed of the energy-yielding macronutrients [amino acids, dextrose, intravenous fat emulsions (IVFEs)], micronutrients (vitamins and trace elements), electrolytes, and fluids. PN components are tailored to individual patient needs based on nutritional status and nutritional requirements, underlying clinical conditions, concomitant medication therapy, and laboratory and diagnostic parameters [5]. Although PN is a life-saving therapy in patients with intestinal failure, it can be associated with infectious and metabolic complications. PNALD is one of the most

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challenging and morbid complications associated with PN. PNALD is typically associated with long-term PN use and includes cholestasis, steatosis, and cholelithiasis. This chapter reviews the epidemiology, risk factors, and etiologies of PNALD and discusses the different approaches to its prevention and treatment.

Epidemiology

The reported overall frequency of PNALD in clinical studies varies from 7.4 to 84 %. This wide variation is due to the heterogeneity of study subjects, differences in the definition of PNALD, and the variation in the composition and duration of PN therapy. For instance, overall liver complications were reported in 40–60 % of home-dependent PN children [6], whereas 33 % of premature infants who received PN for more than 7 days reportedly developed PNALD [7]. In another study of premature neonates (median gestational age of 26 weeks), the frequency of PNALD was considerably higher and ranged from 56 to 85 % [8]. In a retrospective review of 176 premature infants who received PN, cholestasis occurred in 24 % of infants especially in those with lower gestational age (34 vs. 36 weeks; $p < 0.01$) and those who received longer duration of PN (76 vs. 21 days; $p < 0.001$) [9].

Clinical Features

A transient elevation of liver transaminases and alkaline phosphatase may occur within 1–2 weeks of PN initiation, but levels return to normal upon termination of PN without necessarily denoting permanent liver damage. However, prolonged PN use increases the risk for severe liver disease that may progress to liver failure if not appropriately addressed [10, 11].

Histopathology

The liver histologic changes related to PN vary in relation to the extent and type of PNALD. Pathologic features may include portal inflammation, canalicular and intralobular cholestasis, periportal inflammation, pseudoacinar formation, portal-portal bridging, steatosis, portal and pericellular fibrosis, and cirrhosis [12, 13]. Some of the earlier processes of PNALD are discussed below.

Steatosis

Hepatic steatosis, or fat accumulation in the hepatocytes, is mostly the result of excessive carbohydrate administration. Excess dextrose increases insulin levels, and when the amount of carbohydrates exceeds the metabolic rate of the substrate, this results in carbohydrate conversion to fat (lipogenesis) in the hepatocytes. Overfeeding from intravenous fat emulsion may also cause hepatic steatosis by causing excessive fat accumulation in the liver, but is a far less common process. Other possible causes may include choline and carnitine deficiencies. Hepatic steatosis is mostly asymptomatic and liver transaminases are poor clinical markers of the degree of fatty infiltration [14]. Therefore, the diagnosis of hepatic steatosis is mostly incidental but should be ruled out in PN-dependent patients who present with malaise, abdominal pain, and hepatomegaly. Hepatic steatosis can be reversed with rebalancing carbohydrate and IVFE intake and through avoidance of overfeeding before advanced liver disease occurs. A balanced PN typically provides 50–60 % of total daily calories from dextrose; 20–30 % of calories from IVFEs, with the lipid dose not exceeding 3 g/kg/day in infants and 2 g/kg/day in other children; and the remaining 10–20 % of calories from amino acids [15].

Cholelithiasis

Cholelithiasis or gallstone formation in PN-dependent patients is the result of bile accumulation secondary to decreased gallbladder contractility when fasting. The lack of oral or enteral feeding results in decreased secretion of cholecystokinin (CCK), a peptide hormone that is secreted in the duodenum in response to food

and stimulates gallbladder emptying. In the absence of gallbladder contractility during fasting, bile accumulates in the gallbladder, which facilitates the formation of calcium bilirubinate sludge and cholesterol gallstones [16, 17]. Approximately 10 % of infants receiving chronic PN develop gallstone disease [18]. While the etiology of cholelithiasis in PN patients was initially presumed to be due to the lack of CCK secretion, a prospective randomized controlled trial showed that treatment with cholecystokinin-octapeptide (CCK-OP), a synthetic peptide derivative of CCK, failed to reduce the incidence of gallstone formation [19]. This suggests that the etiology of these stones may actually be due to an abnormality of bile production itself. Patients with short bowel syndrome (SBS) are at increased risk for cholelithiasis due to impaired enterohepatic cycling with ileal resection, decreased bile flow during fasting, and the canalicular accumulation of toxic bile acids [20, 21]. Cholelithiasis may be prevented or delayed by early initiation of oral or enteral feeding. Cholecystectomy may be considered in symptomatic cases.

Cholestasis

PN-associated cholestasis (PNAC) is the most clinically challenging form of PNALD. Its time to onset is difficult to accurately predict due to its association with different risk factors. In a retrospective study of premature infants who received PN, the median time to development of cholestasis was 23 days, with 77 % of infants developing cholestasis within 5 weeks of PN initiation [9]. Biochemical markers of PNAC typically include elevations of serum bilirubin and γ-glutamyl transpeptidase (GGT) concentrations. More specifically, serum conjugated bilirubin concentrations of 2 mg/dL or higher are commonly used in clinical practice as a biochemical marker of cholestasis [22, 23]. Patients with progressive liver disease develop jaundice, hepatosplenomegaly, and ascites. The presence of jaundice along with steady elevation of serum bilirubin concentrations is a predictor of higher mortality risk [4].

Outcomes

While most patients with PNALD undergo resolution of the condition once off PN, the disorder is associated with a significant morbidity and mortality rate in those who remain on PN. Despite biochemical resolution of PNALD signs in most patients, normalized biochemical markers of PNALD are not always indicative of a normalization of liver histology. Liver fibrosis may continue to be apparent despite normal biomarkers [24]. For those infants who have progressive PNALD, the disease will eventually result in overt liver failure and death. In a study of surgical neonates, almost one-third of patients died with long-standing PNALD [25]. In a more recent study of children with SBS, PNALD was the greatest risk factor for patient mortality [26]. Patients with PNALD should be treated aggressively with a multimodal approach in an attempt to ameliorate the progression of the disease and to avoid invasive surgical procedures, intestinal transplantation, and death. For children with intestinal failure, a multidisciplinary approach to care has been associated with better outcomes.

Risk Factors

Risk factors associated with PNALD are predominately related to the underlying clinical condition(s), but PN components (e.g., soybean-based intravenous fat emulsions) may also contribute. Several risk factors have been identified that contribute to PNALD including prematurity and low birth weight, prolonged PN duration, sepsis, SBS, bacterial overgrowth and translocation, bowel rest, and lack of enteral feeding [23]. Necrotizing enterocolitis (NEC) is a significant risk factor for PNALD [27]. In neonates with NEC who underwent surgical treatment, independent risk factors for PNALD [defined as serum direct bilirubin concentration of 2 mg/dL or higher, or serum *alanine aminotransferase* (*ALT*) of at least twice the upper limit of normal] also included small bowel resection or presence of a proximal jejunostomy, PN duration, and preoperative exposure to PN especially for 4 weeks or longer [8]. Gestational age and cholestasis in

neonates receiving PN are also independent risk factors to poor postnatal growth [28]. A systematic review of the risk factors associated with PNALD that was conducted by the American Pediatric Surgical Association Outcomes and Clinical Trials Committee provides a critical appraisal of the evidence relating the nutrient and non-nutrient risk factors and liver disease [27].

Prematurity and low birth weight are risk factors for PNALD considering the physiologic immaturity of the liver excretory systems. PNALD was reported in 50 % of premature infants with a birth weight below 2,000 g [29]. The frequency of PNALD gradually increased from 1.4 to 13.7 % in infants with increasing prematurity from over 36 weeks' to before 32 weeks' gestation, respectively [30]. In a study of 24 premature infants (mean gestational age of 32.5 weeks and birth weight of 1,840 g), PN duration, fasting, gastrointestinal surgery, and maximum caloric and carbohydrate intake in PN were significant risks of PNALD [7]. Considering the available data, it remains debatable whether prematurity alone is an independent risk factor for PNALD considering the presence of confounding variables in premature infants that may also influence the development of PNALD and the lower quality of available studies [27].

The duration of PN administration is a strong predictor of developing PNALD [27]. In a study of surgical neonates, the frequency of PNALD was 35 % in those who received PN for at least 2 weeks, but increased to 58 and 75 % with PN administration for at least 30 and 90 days, respectively. All neonates developed PNALD whenever PN was given for more than 180 days [25].

The number of septic episodes in PN patients also increases the risk of cholestasis [27]. In one study, surgical neonates had a 30 % increase in plasma bilirubin concentrations during recurrent episodes of sepsis [31]. Sepsis may induce cholestasis possibly via the toxic effects of endotoxins or lipopolysaccharides on the hepatobiliary system. Endotoxin may cause direct hepatocellular injury or possibly mediate the formation of cytotoxic bile acids and stimulate the release of hepatotoxic inflammatory mediators such as tumor necrosis factor (TNF) and interleukins 1 and 6

[23]. Endotoxins also downregulate critical canalicular transporter proteins, including bile salt export protein, which may change the composition of bile or result in the accumulation of potentially cytotoxic substances within the liver [32–34].

SBS [35] resulting from extensive resection of the small intestine is associated with malabsorption and metabolic abnormalities that require long duration of PN. PNALD including cholestasis, hepatic fibrosis, and liver failure are the leading causes of death in patients with SBS [36]. Predisposing factors to PNALD in SBS patients include prolonged duration of PN, reduced intestinal length and loss of epithelial barrier integrity, intestinal bacterial overgrowth, and abnormal bile acid excretion in patients with ileal resection [23]. The shorter the remaining small bowel length, the higher is the risk for developing PNALD [4]. Conversely, for any length of small bowel, the presence of cholestasis in a child with SBS markedly increases the risk of death attributable to PNALD [26].

Bacterial translocation from the intestinal tract especially gram-negative bacteria producing endotoxins has been also postulated to be a risk factor for PNALD. Animal studies have shown that the lack of enteral feeding during PN infusion along with intestinal dysmotility leads to bacterial overgrowth that causes intestinal inflammation and disruption of the gut barrier. It has been hypothesized that intestinal-derived lipopolysaccharide (LPS) permeates through this disrupted gut barrier, enters the portal circulation, and binds to Toll-like receptor 4 (TLR4). This leads to Kupffer activation, resulting in the release of a cascade of proinflammatory cytokine signaling in early stages of PNALD. Figure 17.1 shows a schematic concept of this theoretical mechanism driving the development of PNALD. Potentially, the use of broad-spectrum antibiotics to suppress the intestinal microflora or the ablation of TLR4 signaling may attenuate this liver injury [37]. Combined small bowel atrophy, decreased intestinal immunoglobulin A (IgA) levels, production of hepatotoxic cytokines, and disruption of the intestinal microflora and bacterial overgrowth all may occur as a result of bowel rest. Therefore, bacterial overgrowth combined with intestinal permeability could result in bacterial translocation
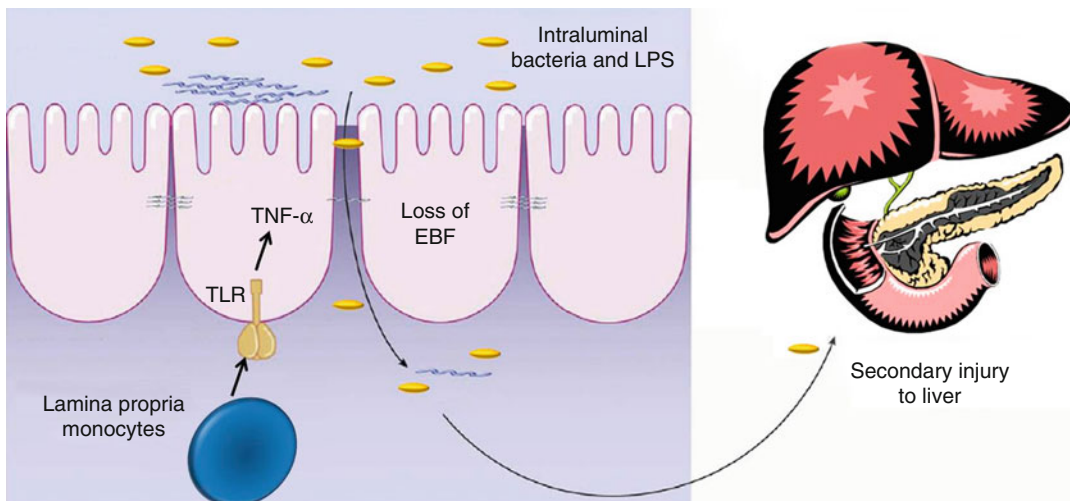
Fig. 17.1 Schematic of the potential mechanism which may drive the development of PNALD. Loss of epithelial barrier function (*EBF*) occurs from a loss of enteral feeding or injury to the bowel from inflammatory processes leading to an upregulation of tumor necrosis factor-alpha (*TNF-α*) from lamina propria monocytes. This results in translocation of bacterial and lipopolysaccharide (*LPS*) which pass into the portal venous system and secondarily incurs injury to the liver

(passage of intestinal microflora from the intestines into the mesenteric lymph nodes, blood, or organs) leading to direct toxic effects of bacteria on the liver or cytokines causing hepatocyte injury. Significant correlation has been reported between bacterial overgrowth and cholestasis and PN dependence [38, 39]. In 1985, Freund and colleagues examined the effect of oral metronidazole on hepatic dysfunction during PN administration in rats [40]. The administration of metronidazole at a dose of 15 mg/kg/day significantly decreased the hepatic lipid content, suggesting the possible involvement of anaerobic bacteria as part of the multifactorial pathogenesis of PNALD. Although the toxic effects of bacterial infections on the liver are established, the evidence remains lacking for the routine use of oral antibiotic therapy to prevent bacterial translocation and decrease hepatocyte damage in PN patients [27].

Trace Elements and PNALD

Manganese, Copper, and Aluminum

Manganese and copper are trace minerals that are routinely supplemented in PN. They are mainly eliminated via the bile and therefore may accumulate during cholestasis. Manganese accumulation especially in patients with hyperbilirubinemia may have direct toxicity on the canalicular membrane [41]. In a group of 57 children who received PN for more than 14 days, there was a significant correlation between blood manganese and plasma bilirubin and AST concentrations [42]. Although an association has been reported between elevated blood manganese and increased plasma GGT and alkaline phosphatase concentrations [43, 44], no firm conclusion could be drawn that high manganese levels cause cholestasis in PN patients. In clinical practice, manganese should be monitored on a monthly basis in patients receiving long-term PN and restricted if levels are elevated.

Although liver toxicity is a feature of copper accumulation, copper toxicity has not been reported in PN patients. However, copper accumulation may still occur. Autopsies from patients with SBS who received copper supplementation in their home PN revealed copper accumulation in the liver and kidneys, especially in those who died of liver failure [45]. Potentially subclinical copper accumulation may occur in home PN patients with cholestasis especially when higher copper doses are given [46]. However, copper deficiencies may

occur and have been reported in PN-dependent patients when copper intake is restricted, some of which can be lethal [47]. Copper levels, along with clinical markers of copper deficiency and/or overload, should be monitored every 1–3 months for patients on long-term PN therapy with the provided dose adjusted accordingly. While historical recommendations indicate empiric reduction in manganese and copper provision in PN in the setting of PNALD, current evidence does not support this practice. Rather, individualized dosing of manganese and copper should be guided by clinical status and measured serum concentrations in order to detect any accumulation and prevent any toxicity or deficiency [27].

Aluminum is a known contaminant of PN solutions [48]. Aluminum accumulation may cause bone, liver, blood, and central nervous system toxixicities. Although aluminum-induced liver toxicixity has been not reported in PN patients, animal studies have reported that aluminum in PN may induce portal inflammation and liver injury by possibly blunting the bile canaliculi microvilli in a way similar to findings in PNALD patients [49, 50]. Although the Food and Drug Administration has mandated PN component product labeling for aluminum and recommended maximum daily exposure limits [48], aluminum contamination in PN remains problematic [51]. Therefore, periodic monitoring of serum aluminum is recommended especially in patients at risk for aluminum accumulation such as premature infants, PN-dependent patients, and those with decreased renal function.

Non-pharmacologic Management Strategies

Early Initiation of Enteral Feeding

The most effective therapy for PNALD is achievement of enteral nutrition either orally or via a feeding tube [52]. Cholestasis develops more commonly in pediatric patients who are unable to tolerate any enteral feeding [27]. Enteral feeding exposes the intestinal tract to nutrients causing the release of endogenous hormones that promote intestinal epithelial cell growth, intestinal adaptation, and reversal of mucosal hypoplasia induced by starvation [23, 53]. Even small, trophic volumes of feedings via continuous administration or small bolus amounts have shown clinical benefit by reducing intestinal stasis and translocation of bacteria, improving bile flow, and avoiding oral aversion [23]. Trophic feeding exposes the intestinal tract to nutrient and hormonal stimulation which results in intestinal epithelial cell growth, enzyme activity, and motility [53]. Once tolerance to trophic feedings is established, advancing slowly toward caloric goal over a period of weeks to months may be achieved with a proportional decrease in PN administration, as clinically tolerated. When intolerances (e.g., abdominal distension or high stool output of 30–40 mL/kg/day) to enteral feedings occur, the rate of enteral feeding may be decreased, the enteral formula may be changed when indicated, and pharmacologic management of diarrhea may be initiated [54]. If dependence on PN is a result of intestinal resection or SBS, specialized enteral formulas may be chosen to optimize nutrient absorption depending on the length and segment of the remaining bowel.

Cycled Parenteral Nutrition

A proposed method for reducing PNALD is to "cycle" daily PN infusion, that is, to have a PN-free period during the day. Cycling PN promotes the cyclic release of gastrointestinal hormones and better approximates feeding rhythms or normal eating patterns that avoids the continuous compulsive effects of nutrients on the liver [5, 52]. Although originally cyclic PN was used in adults to free patients from the infusion apparatus especially those on long-term PN, a clinical benefit of this practice has been also demonstrated in its effects on improving serum bilirubin levels in PN-dependent patients [55]. However, maintaining euglycemia during PN-free periods is a concern in young children, especially in neonates and infants due to the immaturity of their protective metabolic functions such as decreased gluconeogenesis, glycogenolysis, and ketogenesis

and limited glycogen stores. Nevertheless, it remains an approach for stable older infants, children, and adolescents for the management of PNALD. Cycled PN is achieved by ramping up and ramping down the infusion over 1–2 h, with the remainder of the volume infused at a continuous rate over the remaining time of the cycle [5]. For patients who cannot tolerate PN cycling, slow advancement of PN cycle (e.g., starting with 22-h infusion and then advancing the cycle slowly by 2 h every few days) with close monitoring is recommended. If cyclic PN is employed, it is important to monitor blood glucose control throughout the cycle, often by capillary blood glucose measurements. One approach is to monitor blood glucose levels three times daily while on cycled PN: immediately before the start of PN (lowest value), 4 h into the cycle (highest value), and 30 min post-PN infusion in order to check hypoglycemia at the end of the cycle. Closer monitoring of fluid and electrolyte balance is also indicated as the PN cycle is advanced. In general, one should avoid cycling PN until at least 25 % of nutrients are concomitantly given via the enteral route in order to avoid hypoglycemia during PN off times.

The benefit of cyclic PN in preventing PNALD in young infants receiving PN has not been consistently demonstrated. In a study that evaluated the effects of cyclic PN on infants with gastroschisis, 107 patients were analyzed, 36 of which received a cyclic PN and 71 of which did not [56]. The duration of the PN cycle was initially 20 h with a dextrose-containing solution infused during the off period to avoid hypoglycemia. The cycle was extended up to 6–12-h off of PN daily as patients grew and became older; however, a standard cycle for all included patients was not defined. The time to onset to hyperbilirubinemia was found to be significantly longer in those patients receiving cyclic PN as compared to those on continuous PN: cycled 5.7 % (95 % CI 0–13.1 %) versus continuous 22.3 % (95 % CI 9.9–33 %), $p = 0.005$ at 25 days of therapy. At any time during the course of PN, after adjusting for other confounding factors, patients who received continuous PN were 2.86 times more likely to develop hyperbilirubinemia

as compared to those patients on cycled PN; however, this result was not statistically significant. Conversely, in another study of cyclic PN in very-low-birth-weight infants (weight ≤1,250 g), early cycling of PN did not significantly reduce the development of cholestasis [57]. Rather, other factors such as duration of PN as well as the time to full enteral feedings were identified as independent risk factors for the development of PNALD. For very young patients, if cycling is considered, it cannot be implemented unless the patient is already tolerating some amount of enteral feedings or a dextrose-containing solution is infused during off PN times so as to avoid hypoglycemia [27].

Further, the risks involved with cycling PN in critically ill patients including metabolic abnormalities such as electrolyte, acid–base, and fluid balance abnormalities make continuous infusion preferred in this group of patients [58]. For older, clinically stable patients, or those tolerating concomitant enteral administration of nutrients, cyclic PN may be a consideration as a preventative strategy for PNALD and as an improvement in quality of life for long-term PN patients.

Alternative Lipid Strategies

IVFEs are a source of calories and essential fatty acids (linoleic and alpha-linolenic acid). Currently, the available IVFE products in the USA are derived from soybean oil. These formulations have been considered as an independent risk factor in the development of PNALD [59]. Interest in intravenous fat emulsion and its association with PNALD has mounted within the last decade, and much work has recently been done investigating novel approaches to lipid therapy. Although the exact mechanism whereby IVFEs cause PNALD is not yet fully elucidated, several mechanisms have been proposed including the effects of proinflammatory omega-6 fatty acids possibly causing hepatocyte damage or apoptosis or the cell membrane peroxidation induced by long-chain polyunsaturated fatty acids [60, 61]. Soybean-based fat emulsions contain high levels of phytosterols, which have been shown to impair

bile drainage and contribute to hepatobiliary dysfunction [27]. Phytosterols are contaminants of IVFEs and are inefficiently metabolized by the liver. The accumulation of one plant phytosterol, in particular stigmasterol, may be a major contributor to the development of liver toxicity and PNALD by binding to membrane proteins and reducing bile synthesis and flow [62]. While liver enzyme levels may remain close to normal, liver biopsies of patients with high serum plant sterol levels have shown liver fibrosis indicating that elevated serum plant sterol levels may mirror the formation of liver fibrosis, although a definite cause-effect relationship between phytosterols and PNALD has not been proven [24]. An additional mechanism by which IVFE may contribute to PNALD is that soybean-based fat emulsions are rich in omega-6 fatty acids, which may cause hepatocyte damage or apoptosis due to a proinflammatory mechanism [27]. Due to these factors and the available data, several strategies can be undertaken to minimize the effects of IVFEs on the liver and include (1) soybean-based FE minimization or (2) the use of alternatives IVFE such as fish oil-based emulsions and combination fat emulsions. However, data supporting either approach are mostly reliant upon retrospective or uncontrolled studies, therefore limiting the strength of supporting evidence. Results of studies for each approach are promising, but long-term outcomes and safety data are needed from well-designed trials.

IVFE Minimization

The definition of IVFE minimization has not been consistently described; however, typically it is defined as receipt of less than 1 g/kg/day of IVFE [63]. The benefit of IVFE minimization was first described in the adult literature in 1982, by Allardyce [64]. For pediatric patients, this technique was first described by Colomb et al., in a group of ten infants with severe cholestasis [65]. The authors acutely terminated IVFE administration and noted the marked decline in bilirubin levels in these patients. A follow-up, prospective study by Cober and Teitelbaum supported this IVFE minimization strategy for the prevention of PNALD [66, 67]. In this single-center prospective

study, patients who developed PNALD (direct bilirubin >2.5 mg/dL) on standard soybean-based IVFE at a dose of 3 g/kg/day received an IVFE regimen of 1 g/kg/day twice weekly. These patients were compared to a well-matched historical control group that received standard IVFE dosing. Thirty-one patients were evaluated, and in the serum direct bilirubin levels in those treated with IVFE minimization were found to significantly decline over time compared to the control group. Specifically, the group receiving IVFE minimization was found to have a downward trend in bilirubin (estimated slope −0.73 mg/dL/week) as compared to the standard cohort, which showed a rise in bilirubin levels across study weeks (estimated slope 0.29 mg/dL/week). A significant difference in the slopes was identified between the groups, $p = 0.0017$. Additionally, the number of patients achieving resolution of PNALD was significantly greater in the IVFE minimization group ($n = 13$) as compared to the control group ($n = 3$), $p = 0.013$. It is important to note that in this study, eight patients developed reversible, mild essential fatty acid deficiency (EFAD) while receiving twice weekly IVFE. There were no physical manifestations of EFAD observed other than biochemical markers (triene-to-tetraene ratio ≥ 0.05). For those patients who developed EFAD, however, the lipid regimen was altered to 1 g/kg/day three days per week and then again to 2 g/kg/day three days per week, if needed. These changes resulted in resolution of EFAD in all patients. Finally, there were no significant differences in overall growth between the two groups.

Conflicting results were demonstrated in a retrospective study conducted by Nehra and colleagues [61]. Neonates requiring long-term parenteral nutrition support, defined as ≥ 21 days of therapy, were divided into two groups: (1) [$n = 29$] those receiving IVFE at a dose of 1 g/kg/day and (2) [$n = 32$] those receiving IVFE at a dose between 2 and 3 g/kg/day and who were evaluated for the primary outcome of development of cholestasis, defined as direct bilirubin of >2 mg/dL for ≥ 2 consecutive weeks. The incidence of cholestasis was not statistically significant between the two groups, with 15/29 patients

in the group receiving 1 g/kg/day and 14/32 patients in the group receiving 2–3 g/kg/day developing cholestasis, $p = 0.61$. Likewise, the time to develop cholestasis was found to be similar between both groups. In this study, once cholestasis developed, patients were expeditiously attempted to transition to full enteral feeds or transitioned to a fish oil-based fat emulsion. A limitation to this study is its retrospective nature as well as slight differences in study populations between the two groups.

These two studies regarding IVFE minimization reveal important, but conflicting, findings relevant to reduced doses of fat emulsion and the effect on prevention of PNALD. Each study has its own limitations, and several questions still remain regarding this approach to treatment such as optimal dose of IVFE, timing of initiation of IVFE minimization, as well as short- and long-term outcomes as well as the safety associated with this treatment approach. These questions may be answered in a well-designed prospective study that randomizes patients in a matched fashion to IVFE minimization and standard therapies in order to evaluate effectiveness of this strategy in reducing the development of PNALD. These studies must also be designed to evaluate important findings such as EFAD, growth restriction, and both short- and long-term neurodevelopmental effects.

Use of Fish Oil-Based IVFE

In contrast to soybean-based fat emulsions which contain omega-6 fatty acids, fish oil-based emulsions are almost completely omega-3 fatty acids, which are believed to have several beneficial effects and to play a role in the resolution of PNALD [63]. The benefits of fish oil-based emulsions in preventing PNALD as compared to soybean-based IVFEs may be due to several factors which include a reduction in detrimental phytosterols and proinflammatory mediators. Fish oil FE may have an additive benefit of being a substrate for the formation of a favorable prostaglandin composition and also contain an antioxidant alpha-tocopherol, which has immunomodulatory effects. The only available fat emulsion composed of fish oil is Omegaven®

(Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). A recent study that compared Omegaven to four other fat emulsions in a murine model demonstrated that inclusion of fish oil had positive effects on hepatic outcomes [68]. The first clinical report of fish oil-based emulsion, published in 2006, demonstrated complete reversal of PNALD in two infants with intestinal failure-associated liver disease [69]. The clinical utility has subsequently been demonstrated in several case reports [70–76]. Further, the use of fish oil-based emulsion was studied in 42 infants who developed PNALD while receiving soybean-based FE who were predicted to require PN for a minimum of 30 days [77]. These infants were compared to a cohort of 59 infants that received standard soybean-based fat emulsion. Infants who received fish oil-based fat emulsion received it at a dose of 1 g/kg/day, whereas the historical cohort received soybean-based fat emulsion at a dose ranging from 1 to 4 g/kg/day. Direct bilirubin levels decreased over time in the fish oil cohort as compared to an increase in levels seen in the standard soybean cohort ($p < 0.0001$). Forty-five percent ($n = 19$) of the patients in the fish oil group versus 4.1 % ($n = 2$) in the soybean oil group demonstrated reversal of cholestasis during the study period. Further, the risk of death or the need for transplantation was lower in the group receiving fish oil-based fat emulsion. From a safety standpoint, fish oil-based emulsion was, overall, well tolerated with fewer patients developing hypertriglyceridemia; however, two patients did develop EFAD in the fish oil group. Continued safety has been substantiated with continued use under a compassionate-use open study [78]. This study is limited by its short follow-up period as well as the fact that a quarter of the patients received PN for less than 3 weeks [77]. Additionally, it is not known whether the beneficial effects were due to the fish oil emulsion itself or due to the reduced dose (1 g/kg/day) of fat emulsion. However, a prospective randomized trial is underway that will examine conventional soybean oil-based fat emulsion versus fish oil-based fat emulsion at a goal dose of 1 g/kg/day, which may help to answer this question.

Another study evaluated the effects of fish oil IVFE on 12 children with SBS and severe PNALD (direct bilirubin >2.9 mg/dL) [79]. Study results showed that nine patients had complete resolution of hyperbilirubinemia within 24 weeks of treatment. Four of these patients were receiving a combination of fish oil and soybean oil, whereas five patients were receiving fish oil alone. Despite the small sample size, results indicate a possible clinical use of combined fish- and soybean-based IVFE to prevent PNALD while preserving adequate caloric and fatty acid intake. Combination fat emulsion may more closely approximate the optimal fatty acid intake and may lead to more physiologic outcomes as well as benefits in growth and development [63].

While not intravenous, the use of enteral fish oil has also recently been examined and deserves a brief mention [80, 81]. While benefits were seen in a small subset of patients, the use of enteral fish oil relies on at least a partially functional intestine. Therefore, the beneficial effects may be confounded by the fact that a functional intestine may also tolerate enteral feeds and demonstrate intestinal adaptation [63]. Therefore, resolution of PNALD may be due to improved intestinal adaptation and tolerance of enteral feeds rather than the presence of enteral fish oil.

Composite Intravenous Fat Emulsion Formulation

In addition to single-component fat emulsions, a few novel fat emulsions have been developed. SMOFlipid (Fresenius Kabi) is a combination fat emulsion that contains soybean oil, medium-chain triglycerides, olive oil, as well as fish oil resulting in an omega-6 to omega-3 fatty acid ratio of 2.5:1 [63]. While SMOFlipid is not currently available in the USA, several studies have shown safety and efficacy of this emulsion [82–85]. A study of 28 children between the ages of 5 months and 11 years requiring long-term home PN compared the liver effects of SMOFlipid and standard soybean-based fat emulsion at a target dose of 2 g/kg/day [82]. At 4 weeks, patients who received SMOFlipid had lower mean serum concentrations of ALT, AST, and GGT as compared

with the soybean-based IVFE group. Further, the mean change in serum total bilirubin was significantly greater in the SMOFlipid group ($p < 0.01$) with a decrease seen in the SMOFlipid group as compared with an increase in the standard fat emulsion group. In addition to these benefits, several case series have been published that demonstrate a reversal of elevated direct bilirubin with the use of SMOFlipids [86–88].

IVFEs available outside of theUSA, such as Lipofundin MCT (B. Braun), which is a combination of soy and coconut oil, and Clinoleic (Baxter), which is a combination of olive and soy oils, may also play a role in the management of PNALD [63]. There have been a few clinical studies evaluating the efficacy of these agents; however, more data is warranted before use of these agents can be universally recommended. The American Society of Parenteral and Enteral Nutrition recently published a position paper on alternative fat emulsions, which calls for expanded availability of and further research on the alternative fat emulsions so that the ideal formula may be identified for special patient populations [89].

Pharmacologic Management

Phenobarbital

Phenobarbital is a barbiturate, a sedative hypnotic, and an anticonvulsant medication that has been used to stimulate choleresis in patients with various forms of cholestatic liver disease [90]. For the treatment of PNALD, several theoretical mechanisms exist. Its effect is thought to be associated with the activation of enzymes, which stimulate the flow of bile [91, 92]. Additionally, phenobarbital may increase bile salt production, decrease serum bile acids and bilirubin, increase the conjugation of bilirubin and accelerate hepatic clearance of bile acids, and possibly affect the hepatic activity of the Na, K-ATPase pump [92, 93]. In an early case report, phenobarbital efficacy was demonstrated 36 h after phenobarbital initiation at a dose of 5 mg/kg/day in a patient with progressive liver disease and

cirrhosis secondary to PNALD [93]. However, despite its theoretical benefit and effectiveness seen in individual cases, other case reports have not shown similar benefit. A retrospective study performed in 1986 evaluated the effects of phenobarbital in PN-dependent neonates weighing less than 1,500 g [92]. Two groups of patients were evaluated: (1) those who received parenteral nutrition ($n = 21$) and (2) those who received parenteral nutrition plus phenobarbital at an initial intravenous dose of 5 mg/kg/day with therapeutic drug monitoring to maintain serum phenobarbital concentrations between 15 and 25 mcg/dL ($n = 10$). For infants who received phenobarbital therapy, indications included seizure treatment or prophylaxis. Interestingly, more patients in the phenobarbital group developed PNALD as compared to those who did not receive phenobarbital (60 % vs. 33 %). Thus, phenobarbital did not offer protection against the development of PNALD and, in fact, may have contributed to its development [91, 92].

The use of phenobarbital for the treatment of PNALD has fallen out of favor due to conflicting and minimal evidence supporting its use, in addition to advancements made in other more efficacious therapies. However, in severe cases, phenobarbital may be considered on an individual basis when other alternatives are not possible or have been exhausted. Patients should be monitored for possible phenobarbital-associated adverse effects such as hypotension, bradycardia, respiratory depression, sedation, and thrombophlebitis with intravenous use and vitamin D deficiency especially with extended use, to name a few [90].

Ursodiol

Ursodiol, or ursodeoxycholic acid, is a hydrophilic dihydroxylated bile acid, which typically comprises a small fraction (1–3 %) of the secondary bile acid pool in humans, is released by the gallbladder, and is then solubilized and absorbed in the jejunum and terminal ileum, respectively [94, 95]. After oral administration of exogenous ursodiol, passive absorption in the small and large intestines (30–60 %) and the colon (20 %) results, followed by conjugation in the liver, secretion into the biliary tree and the intestines, and then extensive enterohepatic recirculation and reabsorption in the terminal ileum [94–96]. While the exact mechanism of action of ursodiol in the treatment of PNALD is unknown, proposed mechanisms include correction of bile acid deficiency, improvement in and stimulation of bile flow, and displacement of toxic hydrophobic bile acids such as chenodeoxycholic acid, in addition to the provision of immunomodulatory and cytoprotective effects [94, 95, 97–99]. During chronic administration, ursodiol becomes the primary biliary and plasma bile acid, ultimately displacing cytotoxic bile acids and increasing bile secretion and flow [95, 96, 100].

After administration of ursodiol (10–30 mg/kg/day in 2–3 divided doses) to pediatric patients with PNALD, a marked and sustained improvement in liver biochemistry levels has been demonstrated, including direct bilirubin, serum ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT), with the earliest improvements seen in direct bilirubin and GGT [100–102]. Ursodeoxycholic acid has shown to decrease the extent and duration of PNALD in both medical and surgical populations and in very-low-birth-weight infants, neonates, infants, and older children and in those children with short bowel syndrome (SBS). By and large the results have been positive, with results showing a decreased extent and the duration of PNALD [101–105]. Early response may be seen within the first 2 weeks of therapy; however, complete resolution may take up to 4 months [102]. Interestingly, in a recent prospective study, those children with SBS had an earlier and more pronounced response to ursodiol as compared to those children without SBS, indicating that even those children with significant intestinal loss respond well to treatment with ursodiol at a higher dose of 30 mg/kg/day in divided doses [105].

Tauroursodeoxycholic acid (TUDCA), an agent similar to ursodeoxycholic acid, was evaluated by Heubi et al. in a prospective, randomized clinical trial designed to evaluate TUDCA's

prophylactic effects on lowering peak conjugated bilirubin levels in infants on long-term PN [106]. The dose evaluated was 30 mg/kg/day in two divided doses. Study results showed that TUDCA was ineffective in preventing or reducing the severity of PNALD in neonates. Further studies may be needed to further delineate the role of TUDCA in the treatment and prevention of PNALD.

The timing of initiation of ursodiol therapy has yet to be fully defined, and a major limitation is that the drug must be given enterally. While some centers may initiate at the earliest signs of cholestasis, others wait until full enteral feeding has been achieved. However, evidence suggests benefit with initiation at the earliest onset of PNALD, if enteral tolerance is possible [104, 105]. While there is no consensus on the minimal amount of enteral feeds required prior to initiating oral ursodiol, it may be recommended to achieve tolerance of at least 5 mL/h prior to initiating oral medications. Likewise, the optimal duration of therapy is still unknown. A rebound rise in markers of cholestasis may be seen after discontinuation of ursodiol; however, normalization occurs after re-initiation of therapy [105]. In general, ursodiol is very well tolerated; however, mild diarrhea has been described in some cases. The long-term effect of ursodiol on progression and prognosis on PNALD is unknown. Further, it is uncertain how the well-controlled study on TUDCA failed to show efficacy, where the less controlled studies were beneficial. Thus, evidence from large, prospective, randomized, and placebo-controlled studies is still needed.

Other Therapies

Cholecystokinin-octapeptide (CCK-OP) is the active portion of cholecystokinin gastrointestinal peptide that can improve intrahepatic bile flow [107]. Although early investigations showed promise for the role of CCK-OP in the management of PNALD [107–109], later larger well-designed studies showed no clinical role of CCK-OP in the prevention or treatment of PNALD. In a double-blind, multicenter, randomized control trial conducted at eight centers, CCK was studied in a total of 243 infants at a dose of 0.04 mcg/kg intravenously twice daily and failed to show a significant effect in conjugated bilirubin levels, incidence of sepsis, time to enteral feedings, length of intensive care unit stay, or hospital length of stay [110]. Since that time, no additional trials have been published with alternative dosing strategies or differing results [27]. Thus, routine use of CCK is not recommended for treatment of PNALD in pediatric patients.

Glutamine, one of the most abundant amino acids in the plasma and human milk, has been suggested as an exogenous supplement to reduce sepsis, enhance gastrointestinal integrity, and improve immune function [111]. Glutamine supplementation may also have protective effects on the liver, especially in those patients receiving long-term PN through the increase of glutathione stores in the liver. In 2010, the effects of intravenous glutamine supplementation on hepatic function and mortality and the time to full enteral nutrition were evaluated in 28 neonates. Significant decreases in total bilirubin and AST concentrations were observed in patients supplemented with glutamine, although no other study endpoints were found to be significant. The effects of enteral glutamine are currently being investigated. At this time, however, the routine use of parenteral or enteral glutamine, for the prevention or treatment of PNALD, is not recommended until substantive data are available.

Amino acids such as cysteine and taurine have been presumed to be nonessential in older children and adults; however, they are conditionally essential in neonates and infants [112]. However, taurine deficiencies have been noted in individuals with short bowel syndrome receiving long-term PN, and taurine is needed for the successful conjugation of bilirubin to bilirubin diglucuronide. Thus, efforts to increase plasma taurine levels have been investigated. One investigation by Helms et al. revealed that plasma taurine concentrations may be selectively increased with the addition of cysteine (40 mg/g of amino acids) to infant parenteral nutrition [112]. Supplemental taurine has also been investigated in the setting of PNALD [113]. In a multicenter, prospective

study conducted between 1996 and 2001, the effect of supplemental taurine on the development of PNALD was evaluated. When evaluated overall, taurine did not demonstrate benefit; however, when stratified by gestational age and indication, taurine showed benefit in those patients who were premature and those with a history of necrotizing enterocolitis (NEC). Specifically, the conjugated bilirubin was reduced in premature infants receiving taurine 0.5 mg/dL [0.17–1.18] versus 3.45 mg/dL [1.79–5.11] in those not receiving taurine, $p = 0.07$. For those patients with NEC, conjugated bilirubin was 4.04 mg/dL [2.85–5.23] in those receiving taurine versus 8.29 mg/dL [5.61–10.96] in those who did not receive taurine, $p = <0.01$. Therefore, the investigators concluded that taurine supplementation may be beneficial in a subset of higher risk patients but may also be considered as a standard in all neonatal amino acid solutions.

Prevention and Treatment of Sepsis

Recurrent sepsis has been closely associated with the development or worsening of PNALD [31]. Recurrent sepsis was associated with a 30 % increase in bilirubin levels. Thus, several strategies can be undertaken to decrease the risk or frequency of sepsis in patients on long-term PN. The prevention of sepsis should be a priority in the treatment of patients dependent on long-term PN.

Enteral Antibiotics

For patients on long-term PN, translocation of bacteria from a disused intestine increases the risk of systemic and catheter-related bloodstream infections (CRBSIs) due to decreased gut barrier integrity [114, 115]. The theory that lack of intestinal stimulation during periods of prolonged fasting and PN administration may lead to a change in the gut microbiology (i.e., microbiota) and increased risk of bacterial translocation possibly leading to sepsis has led to the use of enteral antibiotics to treat intestinal microbial overgrowth and ultimately prevent bacterial translocation. However, this practice is not universally accepted due to a relative lack of evidence-based data. While intravenous medications such as metronidazole have not been shown to be effective [116], cycled enteral antibiotics (CEA) as a preventative strategy have demonstrated efficacy. Eradication of abnormal flora, selective decontamination via CEA, may be considered in high risk patients, such as patients with missing ileocecal valve and those with frequent episodes of bacteremia or CRBSIs [115, 117]. While it is recognized that total eradication of intestinal bacteria is not possible, therapy should be aimed at reducing symptoms as well as decreasing abnormal flora as well as decreasing the number of potential pathogens. There are several approaches to CEA. Typically CEA is a combination or successive administration of enteral antibiotics, followed by an antibiotic-free period, which allows the microbiota of the gut to recover [115]. In a recent study by Dobson and colleagues, the use of enteral metronidazole 7.5 mg/kg three times daily for 2 weeks, followed by a combination of enteral colistin 25 mg four times daily with enteral tobramycin 20 mg four times daily for 2 weeks, followed by a 2-week antibiotic-free period before restarting the cycle, was retrospectively evaluated in pediatric patients receiving PN for at least 28 days [115]. A significant reduction in sepsis rates for those patients treated with CEA was observed.

The ideal choice of enteral antibiotics has not yet been fully elucidated; however, the combination should target organisms typically found in the gut, such as anaerobes (i.e., metronidazole, amoxicillin-clavulanate) and gram-negative organisms (i.e., aminoglycosides, ciprofloxacin, or colistin). In some cases, antifungal coverage (i.e., fluconazole, nystatin) may be considered. Preferably, the combination of antibiotics should be nonabsorbable from the gut so as to limit systemic exposure and minimize adverse effects. One approach may be to continuously administer a combination of antibiotics, while a second approach consists of sequential, cyclic administration of antibiotics with an antibiotic-free period in between cycles.

Antibiotic-Lock Therapy

Catheter-related bloodstream infections (CRBSIs) account for a major source of morbidity and mortality among patients receiving long-term parenteral nutrition. Indeed, the National Nosocomial Infections Surveillance System notes that CRBSIs occur 2.7–9.1 per 1,000 catheter days, on average [118]. Systemic treatment with antibiotics may last from 7 to 21 days, depending on the type of infection, and treatment success rates are less than 100 %, due to difficulty in eradication of organisms from biofilms that form in the catheter lumen [119]. The biofilm is a protein-fibrin matrix that, in essence, traps bacteria and then allows for bacterial duplication and continued shedding into the bloodstream [120]. One technique that may be employed to prevent difficult infections is antibiotic-lock technique, a technique that involves filling the central venous access device with a specific antibiotic solution. The antibiotic is in direct contact with the catheter lumen and thus the biofilm, allowing for greater eradication of infectious pathogens, typically in a shorter amount of time (i.e., 1–2 weeks) [121]. The Infectious Diseases Society of America recognizes this technique as an approach to treating and salvaging central venous access devices [122]. Implementation of this technique requires knowledge of the infectious organism for treatment, and for prophylaxis, the decision to use a specific antibiotic based on previous infection history dictates the antibiotic of choice. There are many types of antibiotic-lock therapy, typically consisting of vancomycin, gentamicin or tobramycin, or fluconazole, to name a few. Solutions usually contain an anticoagulant such as heparin, as well, in order to maintain catheter patency as well as aid in degradation of the fibrin sheath in the biofilm layer [121]. Antibiotic-lock therapies have been studied in several patient populations with long-term indwelling central venous access devices with overall favorable results.

Ethanol-Lock Therapy

In addition to targeted antibiotic-lock therapy, the use of ethanol-lock therapy has been shown to be an effective therapy to prevent infections [114]. Ethanol-lock therapy was first introduced in 2003 for use in oncology patients; however, use has expanded to include several other patient populations, including those patients with intestinal failure-associated liver disease (IFALD) on long-term PN [123, 124]. Ethanol is antimicrobial and fungicidal (protein denaturation) as well as fibrinolytic (prevention of fibrin sheath formation) at concentrations ranging from 40 to 100 %, and it offers the advantage of covering multiple organisms rather than targeting specific organisms with specific antibiotic-lock therapy [125, 126]. The risk of development of antimicrobial resistance is also limited with the use of ethanol-lock rather than antibiotic-lock therapy. A meta-analysis published in 2012 evaluated the use of ethanol-lock therapy as compared to heparin-lock therapy in a total of 53 patients from four observational studies [114]. Overall, while some variability exists in study methods, a 70 % ethanol solution dwelled in the catheter for at least 2 h ranging from daily to 3 days per week at a volume of 0.2–3 mL is reported. The results of the meta-analysis revealed a mean rate difference of CRBSIs of 7.67 (95 % CI 5.87, 9.47; $p<0.0001$) and a reduction in risk of CRBSIs by 81 % (RR 0.19, 95 % CI 0.12, 0.32; $p<0.0001$). Despite these more robust findings, the combined results revealed only weak evidence that ethanol-lock therapy decreases the need for catheter replacement. The number needed to treat (NNT) in included studies in the meta-analysis ranged from 108 to 150 ethanol-lock days to prevent one CRBSI, a clinically relevant effect. Interestingly, the microbiological cause of infection, when infections do occur while receiving ethanol-lock therapy, may be altered, as demonstrated by Cober et al. [127]. Specifically, infections were caused by *Staphylococcus aureus* and *S. epidermidis* only, rather than by some of the more common pathogens such as *Enterococcus* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Candida* spp.

Safety concerns with ethanol-lock therapy include the loss of catheter integrity as well as systemic exposure to ethanol. Ethanol's effect on both polyurethane and silicone catheters has been reported in the literature; reports of a lower

breakage force as well as decreased elasticity have been reported [114]. The clinical significance of these observations is not yet known; however, the greater observed effects on polyurethane have led to avoidance of concomitant use with polyurethane catheters and to limit use of ethanol-lock therapy to silicone-based catheters only [125–128]. Additionally, ethanol-lock therapy has not been well studied in peripherally inserted central venous catheters or implantable ports [126]. It is of the utmost importance to determine the type of catheter a patient has prior to initiating ethanol-lock therapy. Similarly, the clinical significance of systemic exposure to small volumes of ethanol is unknown. One study allowed systemic flushing of ethanol without reported adverse effects [126]; however, it is recommended to withdraw the ethanol solution whenever able [125]. Of note, upon administration of the first dose of ethanol-lock therapy, the solution must be withdrawn to prevent introduction of bacteria into the patient after initial disruption of the biofilm layer [127]. Furthermore, Cober et al. provide estimated blood ethanol levels if the entire ethanol lock is infused into patients, which allows for a targeted safety margin where the ethanol-lock volume will not exceed half of the anticipated intoxication blood level [127]. Finally, by limiting use to patients who weigh at least 5 kg, systemic effects of ethanol, should exposure occur, will be limited [125, 127, 128]. Additionally, studies have not reported any observable signs or symptoms of intoxication [126, 127]. Other adverse effects of ethanol-lock therapy are rare and may include thrombotic events [114, 126–129].

Ethanol-lock therapy is typically compounded using a 98 % dehydrated ethanol, USP, and sterile water for injection to make a final concentration of 70 % ethanol [125, 127]. This solution has been found to be stable at room temperature for up to 14 days [130]. It is incompatible with citrate and heparin, so catheters must be flushed with normal saline before and after administration in order to prevent incompatibilities [130]. The volume of the ethanol lock should be individualized based on the volume of the patient's central venous access device. This may be done by aspirating from the catheter until blood return is noted and then using this volume plus 0.1–0.2 mL as the ethanol-lock volume [125, 127].

Supportive data for ethanol-lock therapy comes mainly from retrospective studies as well as case reports and case series. More robust data from randomized, controlled trials is warranted. It has been suggested that these studies should focus on the lowest effective concentration of ethanol, optimal dwell time, optimal administration regimen (i.e., daily vs. 3 days/week), as well as clinically relevant side effects [129]. At this time, ethanol-lock therapy is not endorsed by the Infectious Diseases Society of America, despite published convincing data; however, it is noted that supporting evidence is growing and the role in prevention in CRBSI is becoming clearer [122]. Interestingly, in a recent investigation that evaluated the effects of a national shortage of the ethanol product used to compound medicinal ethanol-lock therapy (98 % dehydrated ethanol), failure of CRBSI prophylaxis was demonstrated when use was rationed, further supporting the use of this therapeutic modality [131].

Surgical Options

Surgical therapy in intestinal failure consists of maintaining bowel length at initial presentation and subsequent autologous intestinal reconstructive surgery. In those patients in whom bowel adaptation does not occur and whose liver disease progresses while on parenteral nutrition, small bowel or multivisceral transplantation remains the therapeutic option.

Bowel Conservation

Patient outcomes in intestinal failure (IF) patients are dependent on the remaining length of the small bowel [26, 132]. But the combination of PNALD and loss of small bowel represents an additive risk factor for mortality in infants with SBS (Fig. 17.2) [26]. It is, therefore, crucial at initial operation that every effort be made to maintain as much bowel length as possible. This often requires multiple explorations with the resection of only frankly necrotic bowel at each procedure.
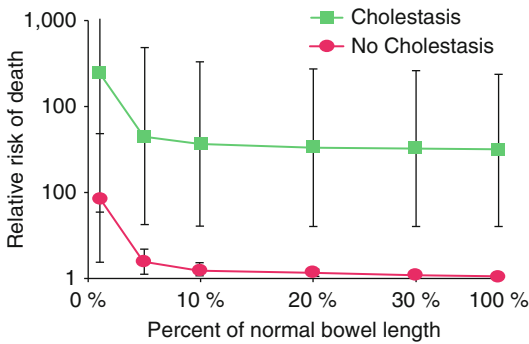
Fig. 17.2 Relative risk of death in a cohort of 102 infants and children with SBS stratified by their percent of normal small bowel length. Note an almost 100-fold great risk of death for any length of small bowel in infants with associated PN-associated cholestasis (Modified from previously reported data [27])

Enteral feeds allow intestinal adaptation and bowel growth that can allow for expedited weaning from PN. The process of adaptation, however, often results in significant small bowel dilation with those segments characterized by poor transit and significant stasis [133]. While ostomies are often crucial in the management of neonates and children with SBS, early ostomy closure can improve electrolyte and fluid balance and has been shown to be associated with a faster wean from PN [134–136]. Other derangements that occur in IF include decreased intestinal transit time that can lead to stasis, bacterial overgrowth, and malabsorption as well as diarrhea and electrolyte derangements. These problems cannot always be treated adequately with supplementation or changes in enteral formulas. Surgical interventions in IF are aimed at eliminating or minimizing these complications with an ultimate goal of restoring enteral autonomy [133].

Autologous Intestinal Reconstruction Surgery

While the goals of early surgical and continued medical management in IF involve maintaining bowel length, initiating early enteral feeds, and avoiding the potentially fatal complications of long-term PN, a significant number of children will progress to surgical therapy in an attempt to increase their bowel length [137]. Surgical bowel lengthening is primarily indicated when children have reached a plateau in the ability to advance enteral feeding and a continued dependence on PN [136].

Over the years numerous surgical procedures have been used to increase bowel length and/or slow intestinal transit time. Earliest among these procedures were reversed intestinal segments, recirculating bowel loops, colonic interposition, as well as tapering or plicating dilated bowel segments [138–141]. Intestinal tapering as a primary surgical modality in pediatric IF is often not an option given the significant number of patients with limited short bowel length. Most of the promising data regarding reversed intestinal segments was obtained in dogs, and although some successful data exist for adults, these results were not replicated in children perhaps because the preferred length of bowel to be used was variable across procedures [142, 143]. Recirculating bowel loops involved creation of a circular loop of bowel to effectively increase mucosal surface area and allow for increased nutrient absorption. These procedures, however, were often complicated by obstruction, volvulus, and stasis that limited their widespread use [139, 144]. Colonic interposition procedures – which involved inserting an isoperistaltic segment of colon along the small bowel length – were first described in dogs before being applied to children [140, 145]. Success in these first case series to be reported were mixed and related to the remnant small bowel length as well as the length of colon which was interposed [146, 147]. Long-term success in the pediatric population using this procedure has not been defined although some isolated case reports exist that show that, at least in isolated instances, success is possible [148, 149]. Due to the complex nature of some of these procedures as well as only modest clinical success, these have essentially been replaced by a variety of autologous intestinal reconstruction procedures with small bowel transplantation remaining a viable option in children with progressive liver disease and PN dependence [150, 151].

Autologous intestinal reconstruction surgery (AIRS) consists of a number of different surgical

procedures, all of which use the patient's own bowel to improve length and absorptive capacity. The three main AIRS procedures in use today include the Bianchi procedure and its modifications, the Iowa procedure, and the serial transverse enteroplasty (STEP).

The longitudinal intestinal lengthening and tailoring operation (LILT) was first described by Bianchi in 1980 [152]. This procedure takes advantage of the fact that the small bowel is supplied by a mesentery which can be divided in half without compromising intestinal blood supply. In order to perform a Bianchi procedure, the mesentery is carefully divided into its two halves along the length of dilated small bowel. The bowel is then stapled to create two new lumens along the mesenteric sheets. The bowel is then anastomosed in an isoperistaltic manner. The result is a doubled length of bowel of half its original diameter. The obvious benefits of this procedure include its ability to easily double the length of small bowel and to halve its diameter – in this manner dramatically increasing the mucosal absorptive surface available to nutrients and decreasing the stasis and potential bacterial overgrowth of intestinal contents. The biggest drawback to this procedure is the technical skill required and the increased morbidity inherent in the number of bowel anastomoses required as well as the suture or staple line along the small bowel [153]. In addition, the Bianchi procedure can only be performed once on a given segment of bowel given its reliance on longitudinal division of the mesentery [154]. Numerous authors have reported long-term success using this procedure although complications consisting of adhesive bowel obstruction, anastomotic strictures, and redilation of the involved bowel are not uncommon [133, 155–157]. A modification of the original Bianchi procedure has been reported which decreases the number of anastomoses required, but details of the long-term success of this procedure have not yet been reported in the literature [153].

The most recently developed and widely used intestinal lengthening procedure is the serial transverse enteroplasty (STEP) [158]. In this technique a stapling device is used to create alter-
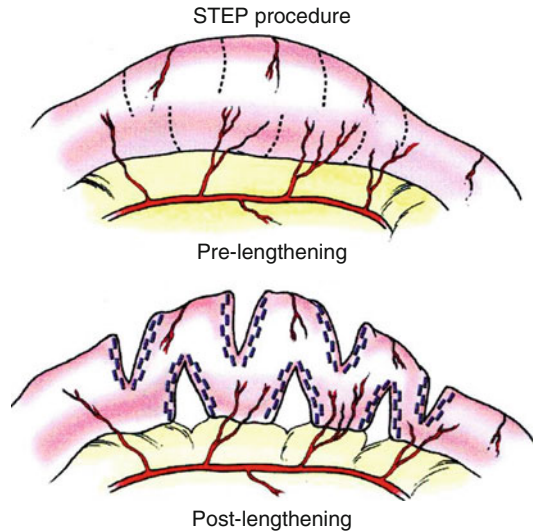
Fig. 17.3 Diagram showing the pre- and postoperative appearance of small bowel before and after serial transverse enteroplasty (STEP) procedure (Reproduced with permission from Keith Georgeson)

nating mesenteric and antimesenteric divisions in a length of dilated small bowel (Fig. 17.3). The advantages of this procedure are that it both lengthens and tapers dilated small bowel, it is relatively easy to perform, and it can be used in a bowel that does not exhibit uniform dilation [159, 160]. Other advantages include the ability to repeat the procedure when the small bowel, invariably, dilates again [154, 161, 162]. Using a registry of STEP procedures performed worldwide, long-term results were published in 2007. In this cohort of 38 patients from 19 centers, small bowel length was increased from 68 ± 44 cm pre-STEP to 115 ± 87 cm post-STEP, a relative increase of 67 %. All but three patients had improved enteral nutrition tolerance following the procedure. Operative complications were considered relatively minor and consisted of leakage from a staple line in two patients and two bowel obstructions that were managed conservatively. Five patients developed progressive liver dysfunction and were referred for transplantation. Three patients died of progressive liver failure and/or sepsis [160]. A second report on the long-term outcomes of the STEP procedure demonstrated that these children exhibit improved

growth parameters including increased weight-for-age, height-for-age, and weight-for-height Z scores [159, 163]. Two reports have been published that describe the ability to repeat the STEP procedure following a previous lengthening procedure [154, 162].

Conclusion/Summary

In summary, PNALD remains a serious and potentially life-threatening disease process. While it appears that the mechanisms of action may be multifactorial, many approaches can impact the severity of this disease. Concerted efforts to modify intravenous fat emulsion administration, reduce the incidence of bacterial translocation, and prevent the occurrence of sepsis, use of bile acid therapies and conserve intestinal length all can effectively reduce or even prevent the development of this very difficult hepatic process.

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