

## Hepatotoxicity Associated with Parenteral Nutrition

### Description/Etiology

Parenteral nutrition (PN), the intravenous administration of complete and balanced nutrition, is used to deliver nutrients to patients with compromised or nonexistent bowel function. Many patients have no current alternative to long-term or even lifelong PN. Although it offers life-saving nutritional support to patients, there is a risk of hepatotoxicity and fatal hepatobiliary effects associated with PN. Hepatobiliary abnormalities that commonly develop include cholestasis (i.e., cessation of bile flow), steatosis (i.e., degeneration, infiltration, and abnormal accumulation of fat in the liver), cirrhosis (i.e., end-stage liver disease characterized by diffuse parenchymal cell damage, failure of hepatic cell function, and compromise of hepatic blood flow), and biliary sludge (i.e., bile mixed with cholesterol crystals and calcium salts).

Although it is not understood why hepatobiliary complications frequently develop following use of PN, several etiologic factors have been proposed; these include prolonged hyperinsulinemia resulting from constantly elevated blood glucose levels, the underlying disease state for which PN is prescribed, the presence of sepsis, lack of enteral intake, nutrient deficiencies, and toxic levels of nutrients. Liver enzyme and serum bilirubin levels may indicate a liver abnormality; however, they have limited use as a specific marker for PN-associated hepatotoxicity as the enzyme levels do not remain constant and will fluctuate over time. Abdominal ultrasound, CT scan, MRI, and endoscopic retrograde cholangiopancreatography (ERCP) are helpful in determining the presence of complications. Liver biopsy remains the gold standard for determining the presence of fatty liver, inflammation, cholestasis, or other complications such as fibrosis or cirrhosis. Optimal prevention and treatment guidelines for hepatotoxicity associated with PN have not been developed; current recommendations focus on stimulating biliary flow and avoiding gallbladder stasis and include

- › cyclic infusion of PN instead of continuous (e.g., cycling regimens usually range from 10 to 16 hours with glucose-free breaks), especially when PN is expected to be prolonged
  - A definitive regimen recommendation is currently unavailable because of continued research on the risks associated with excessive per-hour infusions of dextrose and lipids that can occur with the shorter infusion times characteristic of cyclic treatment
- › introduction of enteral nutrition (EN; i.e., intestinal feeding) or oral feeding between cyclic PN, if possible
  - EN or oral feeding usually prevents gastrointestinal (GI) tract atrophy, loss of mucosal immunity, and bacteria abnormalities; EN may prevent PN-associated liver dysfunction
- › treatment of small bowel bacterial overgrowth/translocation with daily antibiotics (e.g., metroNIDAZOLE)
- › prevention of excessive caloric intake (e.g., limiting glucose infusion rates to  $\leq 4$  mg/kg/min and PN formulation calories from dextrose to  $\leq 65\%$ )
- › limiting lipid intake to 1 g/kg/day and 30% of daily calories
- › amino acid intake of 0.8–1.5 g/kg/day to avoid deficiencies or excess
- › prevention of deficiencies in choline, taurine, and carnitine (i.e., normal endogenous substances essential to hepatobiliary metabolic processes) with their supplementation in PN solutions

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- › pharmacotherapy, including ursodeoxycholic acid (UDCA) to stimulate bile production and promote gallstone dissolution and cholecystokinin-octapeptide (CCK-OP) to reduce gallbladder and biliary sludge formation
- › surgery (e.g., prophylactic cholecystectomy, isolated small intestinal transplantation, or combined intestinal and liver transplantation) if appropriate for patients with intestinal failure who are dependent on PN

## Facts and Figures

Liver dysfunction associated with PN is reported more frequently in neonates and infants than in adults. The reported incidence of PN-associated hepatotoxicity varies greatly from study to study, likely due to variability in patient populations and PN regimens. In adult patients receiving PN, the reported incidence of elevated liver enzymes is 25%–100%. In children, the reported incidence of PN-associated hepatic complications is 25%–60%. Biliary sludge develops in 6% of adult patients at 3 weeks after initiation of PN, in 50% of adult patients during weeks 4–6 after initiation of PN, and in all adult patients after week 6 of receiving PN. The prevalence of PN-associated cholestasis in infants is reported to be 30%–70%. In neonates with PN-associated liver disease who cannot be weaned off PN or fail to receive a liver/small intestine transplant, the mortality rate approaches 100%.

## Risk Factors

A combination of factors increases risk of developing PN-associated hepatotoxicity, including

- › patient-dependent factors and preexisting disease states (e.g., low birth weight, low gestational age, primary disorder of the GI tract [e.g., inflammatory bowel disease, short bowel syndrome < 50 cm], gastroschisis [i.e., a congenital defect in which an opening forms in the abdominal wall and organs push outside of the body], omphalocele [i.e., a rare congenital defect of the abdominal wall in which the liver, intestines, and other organs remain outside of the body], jejunal atresia [i.e., malformation of the jejunum], malnutrition, liver disease, immature biliary secretory system, the presence of tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], chemotherapy toxicity from treatment for hematologic malignancies, and sepsis)
- › PN-specific factors (e.g., longer-term PN administration [e.g., > several weeks], PN administered continuously instead of in cycles or interrupted by EN, excessive caloric load in formula, and unbalanced formula levels of carbohydrates, amino acids, or lipids)

## Signs and Symptoms/Clinical Presentation

Although both children and adults develop biliary sludge and cholelithiasis, the clinical presentation of liver dysfunction in infants and children more commonly includes cholestasis; steatosis and steatosis-related hepatitis are more common in adults. Steatosis is characterized by hepatomegaly.

## Nutritional Assessment

### › Patient Medical History

- Obtain a history of previous use of EN or PN, duration, and any associated complications
- Get a detailed history on the condition that precipitated the need for PN
- Ask the patient about pertinent family medical history including diabetes; cardiovascular disease; and liver, gallbladder, or pancreatic disease

### › Patient Dietary History and Assessment

- Ask the patient about usual oral dietary intake
- Determine if the patient has any allergies or intolerances to foods or food additives
- Calculate estimated energy and fluid needs based on current weight, health status, and results of current biochemical laboratory tests

### › Anthropometric Data

- Review height and weight in the patient's chart
- Ask the patient about usual body weight and any recent changes in body weight
- Ask the patient about any recent issues with edema

### › Laboratory Tests and Diagnostic Tests of Particular Interest to the Nutritionist

- Liver enzyme elevations commonly peak within 4 weeks of PN initiation, although levels fluctuate and not all patients have consistent increases; liver dysfunction is usually shown by abnormal levels/elevations of gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase; increased bilirubin levels occur less frequently

- Histologic examination of biopsied liver tissue can show abnormalities that suggest hepatotoxicity; steatosis is the most common early histologic finding
- › **Other Diagnostic Tests/Studies**
  - Ultrasound of the gallbladder and liver can show gallstones and liver irregularity or enlargement
  - CT scan and MRI in addition to an ultrasound can confirm the presence of steatosis

## Treatment Goals

- › **Promote Optimum Physiologic Status and Reduce Risk of Complications**
  - Monitor vital signs and all physiologic systems, and frequently review laboratory reports, especially for liver function abnormalities and potential deficiencies of choline, taurine, and carnitine; report abnormalities and treat, as ordered
  - Monitor nutritional intake; provide alternate EN feeding or oral feeding as soon as possible per treating clinician order
  - Follow facility pre- and postsurgical protocols if patient becomes a surgical candidate (e.g., for liver transplantation); reinforce pre- and postsurgical education, and ensure completion of facility informed consent documents
- › **Support Emotional Well-Being and Educate**
  - Assess patient and family coping ability and for knowledge deficits regarding hepatotoxicity associated with PN; provide emotional support; educate and encourage discussion about feeding options, potential PN-related complications, treatment risks and benefits, living with a chronic condition, and individualized prognosis
  - Encourage support group attendance and seeking information to increase current knowledge of recent treatment developments
  - Request referral to a social worker or case manager, if appropriate, for identification of resources for in-home services, support groups, caregiver respite, hospice, and sources of education

## Food for Thought

- › Researchers performing a systematic review of literature before March 2015 identified 23 randomized controlled trials (RCTs) regarding risk of hepatotoxicity in infants and children related to intravenous lipid emulsions. The investigators concluded that data from existing RCTs suggests that lipid emulsions containing fish oil have significantly fewer hepatotoxic effects than lipid emulsions containing soybean oil. They also found that that data from existing RCTs were not adequate to determine effects of prolonged PN on infants and children and that no meta-analysis of data could be performed due to heterogeneity of study designs (Hojsak et al., 2016)
  - Research comparing nutrition and inflammation status advantages of olive or soybean oil-based intravenous lipid emulsion concluded the olive oil-based lipid emulsion was not inferior to the soybean oil-based emulsion (Salazar et al., 2021)
  - Research comparing liver tissue of patients with/without parenteral nutrition-associated liver disease identified impairment with mitochondrial energy metabolism, hepatic glycolipid metabolism disorder, and oxidative stress injury as likely associative factors (Maitiabola et al., (2020)

## Red Flags

- › Elevated conjugated bilirubin and GGT are considered the most sensitive indicators of cholestasis
  - Serum amyloid A levels on days 7 and 14 of parenteral nutrition in premature infants may show a significant correlation with conjugated bilirubin levels, with day 7 levels most sensitive in prediction parenteral nutrition-associate cholestasis
- › Cholestasis in neonates can rapidly progress to liver failure

## What Do I Need to Tell the Patient/Patient's Family?

- › Identify and address patient's and family members' learning needs regarding hepatotoxicity associated with PN. Emphasize the importance of long-term medical surveillance and seeking immediate medical attention if new or worsening signs and symptoms develop
- › Educate to contact the Oley Foundation for Home Parenteral and Enteral Nutrition at <http://oley.org/> for information on support groups and suggestions for improved quality of life

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