Total Parenteral Nutrition–Induced Cholestasis

Prevention and Management

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KEYWORDS

• PNALD • PNAC • IFALD • Liver disease • Intravenous nutrition • Lipids • Cytokines • Microbiota

KEY POINTS

- Intestinal failure–associated liver disease (IFALD) encompasses a wide spectrum of disease from steatosis to jaundice, although currently available biochemical monitoring tests are unreliable in detecting pathology such as inflammation and fibrosis in the hepatic parenchyma.
- Improvements in management of IFALD in the past 15 years have led to fewer patients developing end-stage liver failure.
- The management IFALD has been improved by multiprofessional working and better collaborations between expert groups, including surgeons, intestinal rehabilitation teams, and transplant centers.
- The use of line locks and additional hygiene measures for central venous catheters and amelioration in toxicity of PN solutions by addition of fish oil and reductions in omega 6 fats (linoleic acid) has been important in minimizing cholestasis.

INTRODUCTION

Terminology

Total parenteral nutrition (TPN)-induced cholestasis is a description of the onset of liver disease in the context of administration of intravenous nutrition in patients with temporary and/or permanent intestinal failure. Other terms in common usage are:

- Parenteral nutrition–associated cholestasis (PNAC)
- Intestinal failure–associated liver disease (IFALD)
- Parenteral nutrition–associated liver disease (PNALD).

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All 3 terms are often used interchangeably. IFALD is used in this article because it is a more broadly based term encompassing not only the TPN solutions, but also the patient-related factors that increase the risk of liver disease developing.

Definition

The term TPN-induced cholestasis or IFALD encompasses a wide range of disruption to liver function. It is often defined biochemically as an elevation of liver enzymes 1.5 times the upper limit of normal that persist for at least 6 months (6 weeks in children), in the absence of another cause such as viral hepatitis or drug-induced changes. Detecting TPN-induced cholestasis at this early stage of modest biochemical disturbance depends on regular monitoring, as clinical signs are usually absent. It is important to recognize these biochemical signs of liver stress, so that steps can be taken to prevent progression to more severe forms of liver disease[1] (see Management section later in this article). IFALD has been arbitrarily subdivided according to severity into 3 stages as follows (**Box 1**):

- Mild/early/type 1
- Moderate/established/type 2
- Advanced/late/type 3

Frequency and Spectrum of Disease

Most adults do not progress beyond type 1 IFALD,[2] but those who do may develop significant fibrosis as a consequence of chronic steato-hepatitis.[3] Although it is rare for adult patients to become jaundiced, up to 50% of children become overtly jaundiced (bilirubin in excess of 2 or 3 mg/L) at some point during the administration of TPN[4–6] (**Fig. 1**). Paradoxically some children with ongoing need for TPN may develop fibrosis after an episode of cholestatic jaundice has resolved.[7–9] The absence of a major disturbance to liver function tests does not mean that the hepatic acinus is free of inflammation and fibrosis; a study of the liver histology in 66 children with short bowel syndrome found that 8 had cirrhosis and in 3 of these, there was no biochemical cholestasis.[10] Because it is not always possible to obtain liver histology, other forms of screening and monitoring for liver disease are needed (see later in this article).

Box 1
Criteria for categories of intestinal failure–associated liver disease (IFALD)

Type 1 IFALD is defined as an elevation of liver enzymes alkaline phophatase and γ-glutamyl transferase 1.5 times above upper limit reference range, combined with an echogenic appearance of the liver on ultrasound; and liver histology will show steatosis (up 25% of the acinus) and some periportal fibrosis.

Type 2 IFALD is defined as alkaline phophatase and γ-glutamyl transferase 1.5 times above the normal range, bilirubin 3 to 6 g/L, abdominal ultrasound shows enlarged spleen, liver biopsy will show fatty change (more than 25% of the acinus), fibrosis affecting more than 50% of portal tracts.

Type 3 IFALD is defined when liver function tests are 3 times above normal range, platelet count less than 100×10^9, bilirubin more than 6 g/L, international normalized ratio worse than 1.5, and occurrence of spider naevi, ascites, varices, gastrointestinal bleeding from erosions or varices.

Adapted from Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation 2008;85:1379; with permission.