

# Prevalence of Liver Disease and Contributing Factors in Patients Receiving Home Parenteral Nutrition for Permanent Intestinal Failure

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**Background:** Liver cholestasis can be a life-threatening complication during home parenteral nutrition and may lead to combined liver–intestinal transplantation.

**Objective:** To assess the prevalence of home parenteral nutrition–related liver disease and its contributing factors in patients with permanent intestinal failure.

**Design:** Prospective cohort study.

**Setting:** Two approved home parenteral nutrition centers.

**Patients:** 90 patients with permanent intestinal failure who were receiving home parenteral nutrition were enrolled from 1985 to 1996.

**Intervention:** Clinical, biological, endoscopic, and ultrasonographic follow-up. Histologic examination of the liver was done in 57 patients (112 liver biopsies).

**Measurements:** The Kaplan–Meier method was used to determine the actuarial occurrence of chronic cholestasis and complicated home parenteral nutrition–related liver disease (bilirubin level  $\geq 60$   $\mu\text{mol/L}$  [3.5 mg/dL], factor V level  $\leq 50\%$ , portal hypertension, encephalopathy, ascites, gastrointestinal bleeding, or histologically proven extensive fibrosis or cirrhosis). Contributing factors were assessed by using univariate and multivariate (Cox model) analysis.

**Results:** 58 patients (65%) developed chronic cholestasis after a median of 6 months (range, 3 to 132 months), and 37 (41.5%) developed complicated home parenteral nutrition–related liver disease after a median of 17 months (range, 2 to 155 months). Of these patients, 17 showed extensive fibrosis after 26 months (range, 2 to 148 months) and 5 had cirrhosis after 37 months (range, 26 to 77 months). The prevalence of complicated home parenteral nutrition–related liver disease was  $26\% \pm 9\%$  at 2 years and  $50\% \pm 13\%$  at 6 years. Six patients died of liver disease (22% of all deaths). In multivariate analysis, chronic cholestasis was significantly associated with a parenteral nutrition–independent risk for liver disease, a bowel remnant shorter than 50 cm in length, and a parenteral lipid intake of 1 g/kg of body weight per day or more ( $\omega$ -6–rich long-chain triglycerides), whereas complicated home parenteral nutrition–related liver disease was significantly associated with chronic cholestasis and lipid parenteral intake of 1 g/kg per day or more.

**Conclusion:** The prevalence of complicated home parenteral nutrition–related liver disease increased with longer duration of parenteral nutrition. This condition was one of the main causes of death in patients with permanent intestinal failure. Parenteral intake of  $\omega$ -6–rich long-chain triglycerides lipid emulsion consisting of less than 1 g/kg per day is recommended in these patients.

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During use of home parenteral nutrition, chronic abnormalities on liver function tests are reported to occur in both children and adults at a rate ranging from 15% to 85% (1–6). The pathogenesis of home parenteral nutrition–related liver disease, which presents mainly as chronic intrahepatic cholestasis with or without jaundice, is multifactorial and involves patient-dependent factors, especially the short-bowel syndrome (2, 5–7), and nutrition-dependent factors, such as intravenous hyperalimentation (1, 8). Other factors involved are intestinal bacterial overgrowth and translocation (9, 10) and disruption of the enterohepatic bile acid pool with the occurrence of deconjugated toxic bile acids (1, 8). During the early months of home parenteral nutrition–related liver disease, histologic abnormalities consist of canalicular cholestasis and portal inflammation with or without fatty infiltration. Later, severe histologic changes—namely, extensive portal fibrosis or cirrhosis—have been anecdotally reported; over months and years, these conditions lead to liver failure and death (2, 5, 6, 11–13).

The natural history of home parenteral nutrition–related liver disease and its prevalence and life-threatening complications have not been described. In addition, the main postulated risk factors for home parenteral nutrition–related liver disease have not been tested by using multivariate analysis. These questions need to be answered, especially in patients receiving long-term home parenteral nutrition, in whom alternative treatments for permanent intestinal failure are intestinal or combined intestinal–liver transplantation, depending on the presence or absence of liver failure (14–16). We assessed the natural history and prevalence of home parenteral nutrition–related liver disease in 90 patients receiving long-term home parenteral nutrition and used multivariate analysis to explore contributing factors.

## Methods

### Patients

We enrolled 90 consecutive patients without AIDS or a malignant disease who received home parenteral nutrition between 1 January 1985 and 30 June 1996 in two approved home parenteral nutrition centers, Hôpital Lariboisière–St. Lazare, Paris, and Hôpital La Milétrie, Poitiers, France. Patients

were considered to have chronic, permanent intestinal failure on the basis of 1) home parenteral nutrition of long duration ( $\geq 24$  months [ $n = 78$ ]) or 2) home parenteral nutrition of short duration ( $\geq 6$  months and  $< 24$  months) but with a short-gut syndrome defined by a small-bowel remnant 60 cm or less in length and a jejunocolic anastomosis ( $n = 7$ ) or a remnant 100 cm or less in length and an end enterostomy (absent colon) ( $n = 5$ ) (17). No patients presented with liver failure, cirrhosis, or chronic cholestasis before home parenteral nutrition was started.

### Home Parenteral Nutrition Management

The conditions under which home parenteral nutrition was administered have been outlined elsewhere (16). Oral feeding was always encouraged, and none of the patients were instructed to take nothing by mouth. All patients received 20% fat emulsions; 75% of patients received Intralipid (Fresenius Kabi France, Sèvres, France) and 25% received Endolipid (B. Braun Medical S.A., Boulogne, France). Both substances were  $\omega$ -6-rich long-chain triglycerides emulsions. Before the onset of complicated home parenteral nutrition-related liver disease, patients had received neither fat emulsions containing medium-chain triglycerides nor amino acid solutions enriched with glutamine, taurine, or methyl donors.

### Criteria for Home Parenteral Nutrition-Related Liver Disease

Chronic cholestasis was defined as a value at least 1.5-fold the upper limit of normal on two of three liver function measures—levels of  $\gamma$ -glutamyltransferase, alkaline phosphatase, and serum conjugated bilirubin—that persisted for at least 6 months (18). Chronic cholestasis was attributed to home parenteral nutrition after extrahepatic causes were excluded and after therapy with potentially hepatotoxic drugs was withdrawn. No patient had received ursodeoxycholic acid before development of complicated home parenteral nutrition-related liver disease.

Complicated liver disease was considered to have occurred during home parenteral nutrition if one of the following liver complications was observed or if extensive portal fibrosis (grade 2) or cirrhosis (grade 3) was documented on liver biopsy. Liver complications were jaundice with a serum bilirubin level of 60  $\mu$ mol/L (3.5 mg/dL) or greater for at least 1 month, ascites, variceal or hypertensive gastropathy-related bleeding, portal hypertension, liver encephalopathy, and liver failure with a factor V level of 50% or less. Portal hypertension was defined as the presence of at least one of the following criteria: hepatic venous pressure gradient more than 4 mm Hg; stage 2 esophageal or gastric varices; portosys-

temic spontaneous shunts or umbilical vein recanalization documented by ultrasonography in the absence of portal-vein thrombosis; or the presence of two of the following three criteria: ascites, splenomegaly, and portal hypertensive gastropathy documented by endoscopy.

### Collection of Liver Data

Liver function tests were done at the start of home parenteral nutrition; after 3, 6, and 12 months; and yearly until the end of follow-up. They were also done if complications occurred or liver biopsies were performed. Ultrasonography was performed yearly, in case of complications, and before biopsy. Esophagogastroduodenal endoscopy was done after gastrointestinal bleeding or to assess portal hypertension. The first liver biopsy was performed if biochemical cholestasis occurred, regardless of whether it was chronic. Biopsies were repeated if abnormalities on liver function tests worsened or a liver complication occurred. Liver biopsy specimens were stained with hematoxylin-eosin, Masson, periodic acid, and Perls stains. At Hôpital Lariboisière-St. Lazare, biopsy specimens were systematically stained with Oil Red O (Sigma Chemical Co., St. Louis, Missouri) and, if the latter test was positive, with Otan-Baker stain. Fibrosis was assessed by using a semiquantitative score from 0 to 3 (0, no fibrosis; 1, fibrosis restricted to the portal area; 2, extensive fibrosis; 3, cirrhosis). Other histologic findings were assessed by using a semiquantitative score from 0 to 2 (0, absent; 1, moderate; 2, severe). Phospholipidosis was defined as infiltration of the portal tract or sinusoidal space by numerous fat-containing macrophages that stained positive with Otan-Baker stain (19). Liver biopsy specimens were examined after full agreement among pathologists on the semiquantitative grading. All biopsy specimens were re-examined by a single pathologist.

### Variables Contributing to the Development of Home Parenteral Nutrition-Related Liver Disease

The following patient variables were analyzed: age at start of home parenteral nutrition, sex, duration of home parenteral nutrition, home parenteral nutrition center, primary disease, length of small-bowel remnant and conservation of ileum after short-bowel constitution, presence of a blind-loop syndrome, persistence of primary disease activity or chronic intestinal obstruction, and presence of a home parenteral nutrition-independent risk factor for liver disease (chronic infection with hepatitis C virus or hepatitis B virus, alcohol abuse, antibodies associated with liver autoimmune disease, and portal vein thrombosis before the start of home parenteral nutrition).

The home parenteral nutrition regimen was analyzed to assess mean amounts of lipid and dextrose, expressed in g/kg of body weight per day, and the mean daily calorie input, expressed as the percentage of basal energy expenditure according to the Harris and Benedict equations (20). The latter was normalized by using a body mass index of 19 kg/m<sup>2</sup>, which corresponded to the median value in our patients receiving long-term home parenteral nutrition (21). Home parenteral nutrition regimens were analyzed until chronic cholestasis or complicated home parenteral nutrition–related liver disease occurred. If the disease did not occur, regimens were analyzed until the end of follow-up.

### Statistical Analysis

Duration of follow-up was defined as the time from the date of the start of home parenteral nutrition and the date of weaning from home parenteral nutrition, date of death, or the end of follow-up (30 June 1996, which was 6 months after enrollment of the last patient). Probability of survival, chronic cholestasis, or complicated home parenteral nutrition–related liver disease was calculated by using the Kaplan–Meier method (22). Variables were examined by using univariate and multivariate analysis. Distributions were compared by using the log-rank test according to the patient and home parenteral nutrition variables described above. A *P* value less than 0.05 was considered significant. To identify independent factors, a Cox proportional hazards model was applied to these variables with a stepwise procedure by using SPSS statistical software (version 6.1; SPSS, Inc., Chicago, Illinois), and a *P* value less than 0.1 was considered significant (23, 24). Quantitative variables were expressed as the mean ± SD in case of Gaussian distribution and as the median and range in case of non-Gaussian distribution. Probabilities and relative risks with 95% CIs are given. Chronic cholestasis and complicated home parenteral nutrition–related liver disease were studied by using univariate linear discriminant analysis to determine cutoff values of parenteral lipid, dextrose, and nonprotein energy (lipid plus dextrose) intake before performing Kaplan–Meier analysis (25).

## Results

### Patients

Ninety patients with a median age of 45 years (range, 6 to 77 years) were included in the study. Demographic characteristics, gastrointestinal characteristics, and the presence of a home parenteral nutrition–independent risk factor for liver disease are listed in **Table 1**. Of the 90 patients, 57 (63%)

**Table 1. Characteristics of 90 Patients Receiving Long-Term Home Parenteral Nutrition**

Characteristic	Patients, n (%)
Sex	
Male	50 (55)
Female	40 (45)
Home parenteral nutrition center	
Hôpital Lariboisière–St. Lazare	71 (78)
Hôpital La Milétrie	19 (22)
Primary disease	
Arterial mesenteric infarction	23 (25)
Venous mesenteric infarction	9 (10)
Radiation enteritis	24 (27)
Crohn disease	9 (10)
Small-bowel volvulus	8 (9)
Chronic intestinal pseudo-obstruction	5 (5)
Postoperative complications	7 (8)
Villous atrophy resistant to gluten-free diet	3 (4)
Miscellaneous	2 (2)
Length of small-bowel remnant	
<50 cm	45 (50)
50–100 cm	21 (23)
101–200 cm	15 (17)
No resection	9 (10)
Small-bowel status*	
Abnormal with obstruction	12 (13.5)
Abnormal without obstruction	13 (14.5)
Normal	65 (72)
Excluded bowel (rectum, colon, or small-bowel segment)	3 (4)
Known risk factor for liver disease†	15 (16.5)

\* Presence or absence of radiologic or endoscopic data defined as abnormal or normal.  
 † Five patients had hepatitis C virus infection, two had hepatitis B surface antigen, five had portal vein thrombosis before the start of home parenteral nutrition, and five had miscellaneous conditions. Two patients had associated risk factors.

underwent 112 liver biopsies percutaneously (*n* = 48), by a transjugular approach (*n* = 34), during surgical procedures (*n* = 21), or after death (*n* = 9).

Before liver complications occurred, daily lipid, dextrose, and caloric intakes were 0.64 ± 0.20 g/kg per day, 3.99 ± 1.20 g/kg per day, and 88% ± 13% of basal energy expenditure, respectively. According to univariate linear discriminant analysis, cutoff values of parenteral intake of lipid, dextrose, and nonprotein energy were similar for chronic cholestasis and complicated home parenteral nutrition–related liver disease: 1 g/kg per day for lipid intake, 4 g/kg per day for dextrose intake, and 80% of the basal energy expenditure for nonprotein energy intake.

### Survival Analysis

The median duration of home parenteral nutrition was 45 months (range, 6 to 198 months). No patient was lost to follow-up. At the end of follow-up, 53 patients (59%) were still receiving home parenteral nutrition, 10 (11%) had been weaned, and 27 (30%) had died after 53 months (range, 10 to 140 months). In 6 patients (22%), death was directly attributed to home parenteral nutrition–related liver disease. Seven patients (26%) died of sepsis (catheter-related in some cases), and in 4 patients (15%), death was related to the primary disease. Probabilities of survival were 98% (95% CI, 96% to 100%) at 2 years, 80% (CI, 71% to 89%) at 4 years, 65% (CI, 53% to 77%) at 6 years, and 56%

**Table 2. Univariate and Multivariate Analyses of Factors Contributing to Home Parenteral Nutrition–Related Liver Disease in Patients with Permanent Intestinal Failure**

Factor	Univariate Analysis		Multivariate Analysis	
	Significant Variables	P Value	Significant Variables	Relative Risk (95% CI)
Chronic cholestasis	Small-bowel length < 50 cm	0.009	Small-bowel length < 50 cm	2.1 (1.2–3.7)
	Known risk factor for liver disease*	0.008	Known risk factor for liver disease*	3.1 (1.3–4.1)
	Parenteral lipid intake ≥ 1 g/kg per day	0.004		
Clinical and biological events	Parenteral caloric intake ≥ 80% of basal energy expenditure	0.03	Parenteral lipid intake ≥ 1 g/kg per day	2.3 (1.6–5.9)
	Mesenteric infarction†	0.002		
	Chronic cholestasis	0.002	Chronic cholestasis	4.6 (1.3–13.2)
	Parenteral lipid intake ≥ 1 g/kg per day	0.007		
	Parenteral caloric intake ≥ 80% of basal energy expenditure	0.04		
Histologic events	Chronic cholestasis	0.007		
	Excluded digestive segment	0.03		
	Parenteral lipid intake ≥ 1 g/kg per day	<0.001	Parenteral lipid intake ≥ 1 g/kg per day	5.5 (2–15.7)
Histologic, clinical, and biological events	Chronic cholestasis	0.0006	Chronic cholestasis	4.8 (1.6–13.7)
	Home parenteral nutrition started before 1989	0.01		
	Parenteral lipid intake ≥ 1 g/kg per day	<0.001	Parenteral lipid intake ≥ 1 g/kg per day	3.4 (1.6–6.8)
	Parenteral dextrose intake ≥ 4 g/kg per day	0.04		
	Parenteral caloric intake ≥ 80% of basal energy expenditure	0.03		

\* Five patients had hepatitis C virus infection, two had hepatitis B surface antigen, five had portal vein thrombosis before receiving home parenteral nutrition, and five had miscellaneous conditions. Two patients had associated risk factors.

† Mesenteric infarction as a primary disease was significantly associated with a shorter small-bowel remnant ( $28 \pm 25$  cm compared with  $68 \pm 56$  cm for the other primary diseases) ( $P < 0.01$ ).

(CI, 42% to 70%) at 8 years. In univariate analysis, age younger than 41 years (the cutoff value for the youngest age tertile in our patients) and absence of disease in the bowel remnant were associated with better survival. In multivariate analysis, age 41 years or older remained the only variable significantly associated with increased risk for death ( $P < 0.001$ ) (relative risk, 4.9 [CI, 1.8 to 13.2]). In patients younger than 41 years of age ( $n = 37$ ), the probability of survival at 6 years was 84% (CI, 71% to 97%) compared with 53% (35% to 71%) for pa-

tients 41 years of age or older ( $n = 53$ ). In contrast, occurrence of home parenteral nutrition–related liver disease was not significantly associated with increased risk for death (data not shown).

### Home Parenteral Nutrition–Related Liver Disease

#### Chronic Cholestasis

Chronic cholestasis occurred in 58 patients (65%) after a median of 6 months (range, 3 to 132 months). The prevalence of chronic cholestasis was 55% (CI, 45% to 65%) at 2 years, 64% (CI, 53% to 75%) at 4 years, and 72% (CI, 60% to 84%) at 6 years. The results of univariate and multivariate analyses of factors contributing to chronic cholestasis are shown in **Table 2**.

#### Complicated Home Parenteral Nutrition–Related Liver Disease

Of the 90 patients, 37 (41.5%) developed at least one of the biological, clinical, or histologic complications listed in the Methods section (**Table 3**). The probabilities of developing a clinical or histologic liver complication were similar (**Figure 1**). The probability of developing clinical or biological complicated home parenteral nutrition–related liver disease was 26% (CI, 17% to 35%) at 2 years, 39% (CI, 28% to 50%) at 4 years, 50% (CI, 37% to 63%) at 6 years, and 53% (CI, 39% to 67%) at 8 years. The results of univariate and multivariate analyses of factors contributing to complicated home parenteral nutrition–related liver disease are shown in **Table 2** and **Figure 2**.

**Table 3. Occurrence of Complicated Home Parenteral Nutrition–Related Liver Disease in 37 of 90 Patients with Permanent Intestinal Failure**

Event*	Patients	Median Time to Occurrence (Range)
	n (%)	mo
Complicated home parenteral nutrition–related liver disease	37 (41.5)	17 (2–155)
Clinical and biological events		
Factor V level ≤ 50%	8 (9)	10 (2–117)
Bilirubin level ≥ 60 μmol/L (3.5 mg/dL)	33 (36.5)	19 (3–100)
Portal hypertension	14 (15.5)†	39 (3–155)
Ascites	7 (8)†	35 (7–95)
Digestive bleeding	2 (2)†	42 (24–65)
Encephalopathy	4 (4.5)†	104 (16–155)
Histologic events‡		
Extensive fibrosis	17 (19)	26 (2–148)
Cirrhosis	5 (5.5)	37 (26–77)

\* There were 68 clinical or biological events and 22 histologic events (2.4 per patient [range, 1 to 6 events per patient]).

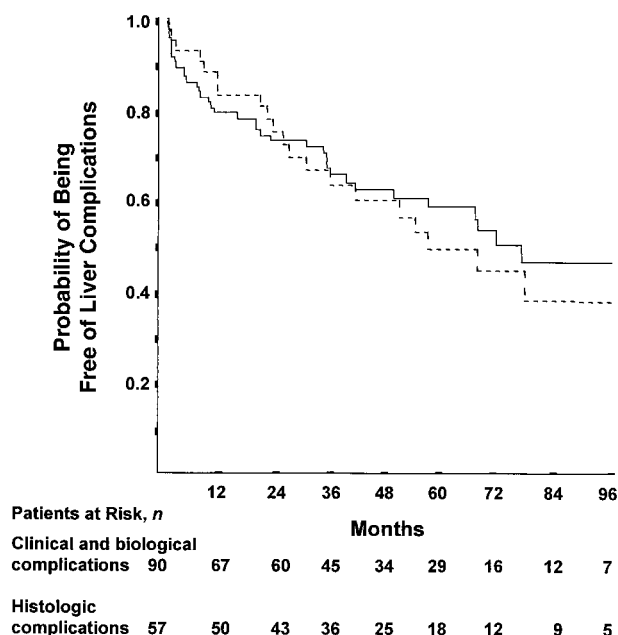
† Patients with portal hypertension before initiation of parenteral nutrition were excluded ( $n = 5$ ).

‡ Data on histologic events were collected in the subgroup of 57 patients who underwent liver biopsy.

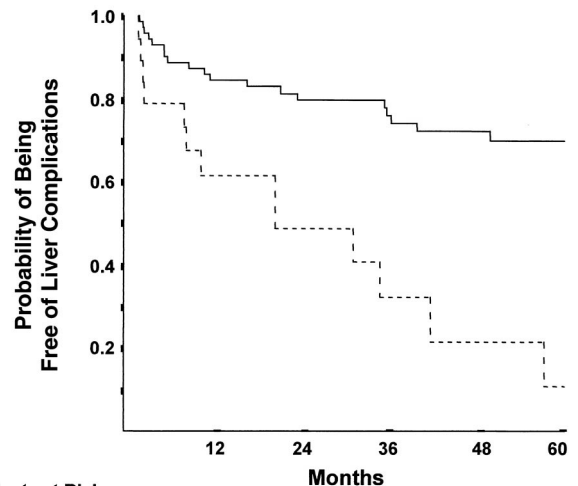
## Other Histologic Findings

Fifty-seven patients underwent a total of 112 liver biopsies. At the time of biopsy, 46 of these patients had chronic biochemical cholestasis, and 11 did not have chronic cholestasis. The median time from start of parenteral nutrition to liver biopsy was 24 months (range, 1 to 155 months) for patients with chronic cholestasis and 4 months (range, 1.2 to 87.5 months) for patients without chronic cholestasis. Histologic cholestasis was found in 35 (76%) patients with chronic cholestasis and 3 (27%) patients without chronic cholestasis. In the 20 patients without histologic chronic cholestasis (grade 0), the serum bilirubin level was  $15 \pm 27 \mu\text{mol/L}$  ( $0.88 \pm 1.6 \text{ mg/dL}$ ); this level reached  $62 \pm 70 \mu\text{mol/L}$  ( $3.6 \pm 4.0 \text{ mg/dL}$ ) in the 20 patients with grade 1 disease and  $196 \pm 123 \mu\text{mol/L}$  ( $11.5 \pm 7.2$ ) in the 18 patients with grade 2 disease. Among patients with and those without chronic cholestasis, portal inflammation was found in 40 (87%) and 10 (90%), macrosteatosis was found in 29 (63%) and 11 (100%), ductular proliferation was found in 27 (59%) and 8 (72%), and necrosis was found in 20 (43%) and 2 (18%), respectively.

Phospholipidosis or microsteatosis (or both) was found in 36 (63%) of the 57 patients who underwent biopsy. Severe phospholipidosis (grade 2) was



**Figure 1.** Probability of being free of clinical or biological complicated home parenteral nutrition-related liver disease (solid line) in 90 patients with permanent intestinal failure and probability of being free of histologic complicated home parenteral nutrition-related liver disease (dashed line) in a subgroup of 57 patients who underwent liver biopsy. The probability of developing complicated clinical or biological home parenteral nutrition-related liver disease was 26% (CI, 17% to 35%) at 2 years, 39% (CI, 28% to 50%) at 4 years, 50% (CI, 37% to 63%) at 6 years, and 53% (CI, 39% to 67%) at 8 years. The probability of developing a severe histologic lesion (extensive fibrosis or cirrhosis) was 20% (CI, 9% to 31%) at 2 years, 35% (CI, 21% to 49%) at 4 years, 45% (CI, 29% to 61%) at 6 years, and 56% (CI, 37% to 75%) at 8 years.



**Figure 2.** Probability of being free of complicated home parenteral nutrition-related liver disease in 90 patients with permanent intestinal failure, according to parenteral lipid intake. In univariate analysis, parenteral lipid intake of 1 g/kg per day or more (dashed line) significantly increased the risk for complicated home parenteral nutrition-related liver disease compared with intake of less than 1 g/kg per day (solid line) ( $P < 0.001$ ). In multivariate analysis, a parenteral lipid intake of 1 g/kg per day or more yielded a relative risk of 3.4 (CI, 1.6 to 6.8) for complicated home parenteral nutrition-related liver disease.

more often associated with extensive fibrosis or cirrhosis (62%) than was moderate or no phospholipidosis (35%); the difference was not significant ( $P = 0.17$  by Fisher test).

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## Discussion

Our study of 90 patients with permanent intestinal failure who were receiving long-term parenteral nutrition describes the natural history of home parenteral nutrition-related liver disease in adults. We included a large series of liver biopsies and used actuarial survival analysis based on a MEDLINE search using the Medical Subject Headings *parenteral nutrition*, *liver failure*, and *intrahepatic cholestasis*. Chronic cholestasis was significantly associated with the subsequent occurrence of home parenteral nutrition-related liver disease. Almost all patients who developed this disease had had abnormalities on liver function tests indicative of cholestasis, occurring after a median of 6 months after the start of parenteral nutrition. The median time to development of clinical and histologic features of severe home parenteral nutrition-related liver disease was 17 and 27 months, respectively. This study presents objective data indicating that home parenteral nutrition-related liver disease may be related to a primary intrahepatic cholestatic disorder that may evolve into extensive fibrosis or cirrhosis. Of the 11 patients who had liver biopsy and in whom liver function tests did not indicate chronic cholestasis,

only 1 (9%) presented with severe histologic lesions. In contrast, of 46 patients with liver function tests indicative of chronic cholestasis, 21 (46%) had severe histologic lesions. Moreover, the histologic features of severe home parenteral nutrition-related liver disease were similar to those described at the cirrhotic stage of other cholestatic diseases, such as primary sclerosing cholangitis and primary biliary cirrhosis. The prevalence of severe histologic lesions clearly increased during the course of home parenteral nutrition, doubling from 2 to 6 years and reaching 56% (CI, 37% to 75%) after 8 years. Early findings were canalicular cholestasis, moderate fatty infiltration, portal inflammation, and, occasionally, scattered foci of lobular hepatocyte necrosis. As described elsewhere, the most specific finding was the association among ductular proliferation, portal inflammation, and fibrosis, which may evolve into extensive (bridging) fibrosis and cirrhosis (1, 3–5, 19, 26–28). Our study also highlights the previously underestimated presence of microsteatosis and phospholipidosis in both hepatocytes and Kupffer macrophages, which require special staining for diagnosis (19).

Our results also indicate that home parenteral nutrition-related liver disease is one of the main causes of death (22%) in adults receiving home parenteral nutrition for permanent intestinal failure. Although Mughal and Irving (29) and Burnes and colleagues (30) did not report any deaths related to liver disease in 200 and 63 patients receiving home parenteral nutrition, respectively, anecdotal reports of cirrhosis during home parenteral nutrition that leads to death have been published (3, 6, 13, 31). In a series of 60 patients, Bowyer and associates (3) reported 1 case of cirrhosis leading to death and 3 cases of extensive fibrosis among 9 patients with persistent liver function abnormalities. Of note, our series of patients receiving home parenteral nutrition had a longer median follow-up time and included more patients with very short bowel (75%) than did other series; the latter condition is known to increase the rate of home parenteral nutrition-related liver disease (5–7, 32). It is likely that the frequency and the severity of home parenteral nutrition-related liver disease has been underestimated. In the International Registry of Intestinal Transplantation, 48% of the 260 reported patients underwent combined liver-intestinal transplantation for severe liver disease that occurred during home parenteral nutrition (14), suggesting that severe home parenteral nutrition-related liver disease is currently the leading indication for combined liver-intestinal transplantation (14–16). In our study, the 6-year survival rate was significantly higher for patients 15 to 40 years of age ( $84\% \pm 13\%$ ) than for patients 41 years of age or older ( $53\% \pm 20\%$ )

( $P = 0.001$ ), and the occurrence of home parenteral nutrition-related liver disease did not significantly change the likelihood of survival. Indeed, when severe home parenteral nutrition-related liver disease was diagnosed, we reduced the lipid intake in the home parenteral nutrition regimen and administered ursodeoxycholic acid or an amino-acid solution containing taurine (or both). These measures might have improved the results of jaundice and liver function tests (33–35, Cavicchi M. Personal communication) and delayed rapidly life-threatening liver failure (5, 26). However, at the end of the follow-up, outcome seemed to be poorer in patients with home parenteral nutrition-related liver disease than in patients without this disease (data not shown).

In multivariate analysis, two factors were strongly associated with the occurrence of complicated home parenteral nutrition-related liver disease: parenteral lipid input of more than 1 g/kg per day and chronic cholestasis. The latter condition was significantly related to three variables: a parenteral nutrition-independent risk factor for liver disease, a small-bowel remnant less than 50 cm in length, and parenteral lipid input higher than 1 g/kg per day. These data confirm that the short-bowel syndrome increases the risk for chronic cholestasis (5–7) through interruption of the enterohepatic circulation, resulting in abnormal bile acid metabolism (1, 4, 8, 35–37). We did not exclude patients ( $n = 15$ ) who had a risk factor for liver disease other than parenteral nutrition itself at the start of parenteral nutrition. This feature did not influence the survival rate or the risk for complicated home parenteral nutrition-related liver disease but doubled the risk for chronic cholestasis. In these patients, particular attention should be paid to the parenteral nutrition regimen from the start.

Increased risk for both chronic cholestasis and severe home parenteral nutrition-related liver disease was observed when parenteral lipid intake was more than 1 g/kg per day. In contrast, home parenteral nutrition-related liver disease was not related to parenteral intake of nonprotein energy or dextrose. We did not specifically assess total oral intake of these substances, but most of our patients developed hyperphagia (17, 38), which could obviate the need for a hypercaloric parenteral regimen. Of note, the nonprotein calorie input was only  $88\% \pm 13\%$  of the basal energy expenditure in our series. Therefore, our results, obtained using multivariate analysis, clearly indicate a deleterious role of parenteral lipids per se without additional adverse effects from excessive intake of total parenteral nutrition (4, 39). Several studies have focused on the potential role of lipids in parenteral nutrition-associated cholestasis (3, 6, 40). Anecdotal cases of jaundice have been reported after increased paren-

teral lipid intake (6, 40), especially when a dosage of 3 g/kg per day was used over 1 month (39). Clayton and colleagues (41) described severe cholestasis in five children receiving lipids in excess of 1.5 g/kg per day. In these patients, high plasma levels of phytosterolemia, a component of Intralipid, were detected (41). Microvacuolar steatosis with deposits of long-chain triglycerides and lipoprotein X (containing equimolar amounts of cholesterol and phospholipids) (42) has been reported after infusion of 20% Intralipid, which is high in  $\omega$ -6 polyunsaturated fatty acids and low in  $\omega$ -3 polyunsaturated fatty acids (19, 43, 44). Exogenous  $\omega$ -6 polyunsaturated fatty acids deposits were described in Kupffer cells and hepatocytes in two patients receiving short-term parenteral nutrition (45), and induced liver phospholipidosis was described in patients receiving long-term parenteral nutrition (19). We confirmed the high prevalence (63%) of phospholipidosis and microvacuolar steatosis during long-term parenteral nutrition with 20% fat emulsions, which contain (per g of triglycerides) half the phospholipids of the 10% fat emulsions (42). Our data suggest that induced phospholipidosis and microvacuolar steatosis in both hepatocytes and Kupffer cells play a key role in home parenteral nutrition-related liver disease pathogenesis. In *mdr-2* gene knockout mice, a model of chronic cholestasis, the animals are unable to secrete phospholipids into bile (46). Of note, these animals develop hepatic lesions similar to those described in sclerosing cholangitis, primary biliary cirrhosis, and home parenteral nutrition-related liver disease. In these mice, liver injury is characterized by a markedly increased number of the hepatocyte peroxisomes involved in fatty acids metabolism (47). In addition, it has been shown that parenteral nutrition may decrease the level of *mdr-2* RNA in mice (48) and that endotoxin challenge may decrease *mdr-2* protein expression in rats (49, 50). Moreover, therapy with ursodeoxycholic acid was effective in reducing histopathologic lesions in this model (51). We therefore hypothesize that during home parenteral nutrition, macrophage activation caused by  $\omega$ -6 polyunsaturated fatty acids overloading in conjunction with sepsis (of splanchnic or systemic origin) leads to reduced *mdr-2* gene expression. Home parenteral nutrition-related liver disease, characterized by portal inflammation, ductular lesions, and extensive fibrosis (9, 10, 52–54), may then ensue. Accumulation of fat in Kupffer cells can induce, through lysosomal or membranous abnormalities, phagocytic dysfunction; this reduced clearance of endotoxins or bacteria has been reported with lipid emulsions (55). Similarly, antibiotic treatment was reported to reduce liver function test abnormalities during short-term parenteral nutrition (56, 57). Conversely, chronic cholestasis

alone can worsen hepatic disease through intracellular accumulation of endogenous bile acids, such as cholic acid and chenodeoxycholic acid (58). Moreover, occurrence of severe liver complications, such as jaundice or portal vein hypertension, may increase the risk for translocation (9) and modify the immune system function of the liver (58, 59). One may therefore speculate that a vicious cycle is induced in home parenteral nutrition-related liver disease through  $\omega$ -6 polyunsaturated fatty acids and phospholipid accumulation in Kupffer cells causing increased susceptibility to bacteria.

In conclusion, we used actuarial survival analysis to show that the occurrence of severe cholestatic home parenteral nutrition-related liver disease increases with a longer time spent receiving home parenteral nutrition. Home parenteral nutrition-related liver disease is currently one of the main causes of death during long-term home parenteral nutrition. We show that parenteral lipid intake 1 g/kg per day or more, despite nonhypercaloric parenteral intake, is a significant contributing factor in chronic cholestasis and complicated home parenteral nutrition-related liver disease. Thus, we recommend that patients with permanent intestinal failure receive 20%  $\omega$ -6-rich fat emulsions in quantities less than 1 g/kg per day.

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