Nutritional Support outside the Hospital: Home Parenteral Nutrition (HPN) in Adult Patients

Module 19.4
Metabolic Complications of Home Parenteral Nutrition and Indications for Intestinal Transplantation in Chronic Intestinal Failure

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Learning Objectives
- Identifying the main metabolic complications of home parenteral nutrition (HPN) in adult patients;
- Preventing and treating these complications;
- Identifying patients candidates for intestinal transplantation.

Content
1. Introduction
2. Fluid, electrolyte and acid base balance abnormalities
3. Hyper and hypo-glycemia
4. Essential fatty acids deficiency (EFAD)
5. Vitamin and trace element deficiency or excess
6. Intestinal failure associated liver disease (IFALD)
7. Gallbladder sludge and stones
8. Renal function impairment and stones
9. Metabolic bone disease
10. Indications for intestinal transplantation (ITx)
11. Summary

Key Messages
- Patients on HPN may develop several metabolic complications that can be prevented and treated through appropriate monitoring and management by an expert multidisciplinary team;
- HPN metabolic complications are multifactorial conditions; pathogenetic factors can be categorized as “intestinal failure-related” and “parenteral nutrition-related”;
- Further understanding is still needed, especially in renal, bone and liver HPN associated complications to improve preventive and curative measurements;
- Impending or overt liver failure (due to IFALD) and invasive intra-abdominal desmoids are clear indications for a life-saving intestinal transplantation; in all the other conditions, the indication for intestinal transplantation need a case-by-case evaluation;
- Early referral to expert intestinal rehabilitative-centers is recommended for patients with chronic intestinal failure if PN requirements anticipated to be more than 50% at 3 months from initiating therapy, in order to devise the most appropriate treatment strategy.
1. Introduction

Metabolic complications of HPN will be identified in order to assure prevention and curative measurements: fluid, electrolytes and acid-base disturbances, alterations in glycemic control, essential fatty acid deficiency (EFAD), vitamin and trace metal deficiencies or toxicity, liver abnormalities, gallbladder sludge and stones, renal function impairment and stones and bone disease.

Metabolic complications of HPN are multifactorial conditions. Pathogenic factors can be categorized as “intestinal failure-related” and PN-related.

Appropriate monitoring is the cornerstone for the prevention and early identification of metabolic complications. According to the ESPEN guidelines in adult patients (1, 2):

- Monitoring should usually take place at the supervising hospital by the nutrition support team.
- Monitoring can also be carried out by a home care agency with experience in HPN and may involve both the hospital and the general practitioner.
- Intervals between monitoring visits vary, but will typically be 3-4 months in clinically stable patients. The clinically unstable patient will need more attention.
- Biochemistry (serum and urinary electrolytes, serum bicarbonate, kidney function, liver function, glucose, haemoglobin, iron, total protein and albumin and C-reactive protein), and anthropometry should be measured at all visits.
- Measurement of trace elements and vitamins are recommended at intervals of 6-12 months.
- Bone mineral density assessment by DEXA scanning is recommended at yearly intervals.
- Patients and caregivers have to be trained to perform regular monitoring of signs and symptoms of dehydration, fluid balance, and 24-h urine output at home.

Interested readers can refer to the ESPEN guidelines for Chronic Intestinal Failure (CIF) (1) and for HPN (2) in adults and to other reviews, for a comprehensive understanding of this topic (3-5).

2. Fluid, Electrolyte and Acid-Base-Balance Abnormalities

Alterations in fluid, electrolyte and acid-base balance may frequently occur in patients with high gastrointestinal losses. Tight monitoring is required, especially in the early period of HPN, in order to prevent these complications.

Frequent episodes of acute dehydration or persistent dehydration with volume depletion can lead to chronic renal failure. Chronic dehydration, sodium depletion, hypokalemia and hypomagnesemia are the main causes of chronic fatigue occurring in patients on long term HPN (1).

The daily parenteral water requirement varies from 25 to 35 mL/kg for the normal hydrated individual. Digestive balances of water/Na, especially for short bowel patients (SBS) type I, with a high output stoma, are required to evaluate needs (1, 5). Input, output records should be look at by patients during establishment initial balance and during attempt of weaning off HPN (3). For patients on HPN who have normal renal function the urine output should be at least 0.8-1 L per day.

Hypernatremia and hyponatremia are more commonly related to a deficiency or an excess of hydration, respectively, rather than to the amount of sodium in the PN formula. However, in patients with an high output stoma, increased intestinal losses of sodium can result in hyponatremia due to sodium depletion. Sodium deficiency is better detected by measuring urinary sodium concentration that decreases before the appearance of hyponatraemia. A urinary sodium concentration below 10 mmol/L is a diagnostic criteria for sodium depletion. Treatment should aim to a urinary sodium concentration greater than 20-30 mmol/L (1).
Magnesium depletion is also a frequent finding in patients with a SBS, due to magnesium malabsorption. Magnesium deficiency is also better detected by urinary magnesium that decreases before serum concentrations (1).

Potassium deficiency is less common, usually due to malabsorption in patients with extreme SBS. A refractory hypokalaemia can be due to a magnesium depletion which impairs many of the potassium transport systems and increases renal potassium excretion; this hypokalaemia is resistant to potassium treatment but responds to magnesium replacement (1).

Hypophosphatemia may occur in severely malnourished and/or acutely ill patients who are at risk of refeeding syndrome at the time on starting PN in hospital, but is a rare finding in HPN patients who are usually in stable metabolic and clinical condition (6, 7).

Calcium balance will be discussed in the section on metabolic bone disease.

Serum concentrations of chloride and bicarbonate should be routinely measured in patients on long-term HPN for CIF to monitor acid-base balance. Both metabolic alkalosis may develop primarily due to protracted losses of gastric secretion losses with decompressive gastrostomy or chronic vomiting in patients with intestinal pseudo-obstruction. A metabolic acidosis may occur due to D-lactic acidosis (with increased anion gap) in patients with SBS with a colon in continuity. An excess of chloride in the PN admixture may also be the cause of a hyperchloremic metabolic acidosis with a normal anion gap (1).

3. Hyper and Hypo-Glycaemia

ESPN guidelines recommend that HPN patients have optimal blood glucose control, based on blood glucose below 180 mg/dl (10.0 mmol/L) during HPN infusion and normal HbA1c levels (if diabetic), through regular monitoring (1). Management of hyperglycaemia range from decreasing the glucose load in the PN admixture, prescribing oral hypoglycaemic medication, giving a daily dose of injectable insulin, or adding insulin to the HPN admixture. However, no recommendation is given on addition of insulin to HPN admixtures due to lack of evidence-based data regarding insulin prescription for HPN patients who have hyperglycaemia. A common practice is to add short-acting insulin in the PN admixture, even though availability of insulin within the admixture may be variable depending on adsorption on to the plastic in the bag and/or tubing and giving set thereby limiting availability to the patient. The potential advantages of this practice include consolidating insulin dosage into the PN formula and minimizing the risk of hypoglycaemia if the dose is correct; if the PN is not administered neither is the insulin. In HPN patients with diabetes, glycemic control is easily achieved with fast-acting insulin added into the nutritive mixture (1-2 U/10 g of dextrose) (1).

The use of a programmable pumps for appropriately reduced rates at the end of the cyclic nocturnal PN infusion is mandatory to avoid rebound hypoglycaemia in some patients (8). The latter complication can be observed, even with reduced rates of infusions, when cyclic PN follows several weeks of continuous PN infusions. To avoid this problem, transition between the continuous and cyclic approach should be made over a week; e.g. minus 2 h infusion per day from 24 h to 10 h of PN infusion.

4. Essential Fatty Acids Deficiency

The essential fatty acids (EFA) (linoleic acid and α-linolenic acid) cannot be synthesized by humans and external supplementation is necessary. Patients on HPN are at high risk of development of EFA deficiency (EFAD) if they are receiving a lipid free PN admixture and no oral or enteral fat. In this condition, the clinical signs of EFAD may develop within 2-6 months of fat-free PN, represented by dermatitis, alopecia, neurological and haematological effects. If patients take some oral/enteral fat, EFAD is rarely a problem (1, 9, 10).

Laboratory examination of EFA supplementation relies on the assessment of the triene (n-9 eicosatrienoic acid):tetraene (n-6 arachidonic acid) ratio (T:T ratio, the Holman index). A T:T value > 0.2 indicates EFA deficiency, even without appearance of clinical
5. Vitamin and Trace Element Deficiency or Excess

Micronutrient deficiencies were recognised in the early years of long term HPN. ESPEN guidelines (1, 2) suggest for both vitamins and trace elements: a) to evaluate regularly the clinical signs and symptoms as well as biochemical indexes of deficiency or toxicity; b) to measure serum concentration at the onset of HPN and the at least once a year; c) to adjust doses in HPN as needed; c) to select the route of supplementation according to the characteristics of the individual patient.

The first commercial parenteral vitamin and trace element formulations for HPN were defined by FDA in 1979 (11). In 2009, a research expert panel challenged the appropriateness of these formulation and agreed on the need for several changes (12), including reduction of copper, manganese and chromium, and increases in the content of iodine and iron. Furthermore it was indicated that the addition of 150 μg of vitamin K to the adult formula would meet the requirement for ɣ-carboxylation status of noncoagulation Gla proteins. It was pointed out, however, that lipid emulsions already contain variable amounts of vitamin K (soybean oil, 150–300 μg /100 g; safflower oil, 6–12 μg /100 g).

There are no studies that addresses the time and dosing of intravenous supplementation in adults on HPN. In those patients who need HPN containing macronutrients, 7 days per week, daily administration of both vitamin and trace elements intravenously is a common practice. Less frequent provision may be sufficient to maintain normal nutritional status, depending on the degree of oral/enteral feeding and intestinal absorption. The last may also be the case in patients receiving HPN less than 7 days per week. When patients are to be weaned from HPN, appropriate oral and/or intra-muscular supplementation must be provided. Patients with malabsorption and/or high intestinal losses are at particular risk of zinc and fat soluble vitamin (ADE) deficiencies (4, 7, 13). Fe deficiency may occur because of occult faecal blood loss (14). Vitamins C, PP, B and other may not be optimal with current allowances if HPN dependence is at its highest level, i.e., during periods of exclusive HPN. Care should be taken not to provide excess in patients with cholestasis or renal failure.

Adequate amount of micronutrients with antioxidant properties are required (15), but greater than needed micronutrients have a harmful effect, yeald an apparently paradoxical propensity to increased peroxydation (16, 17). Thus, large doses of micronutrients should not been used routinely. Zn and Fe have been demonstrated to increase the acute phase reaction response and should not be given during periods of sepsis or inflammation, having the capability to aggravate both (17, 18). In chronic cholestasis, trace metals (especially Cu and Mn) may accumulate in the liver due to decreased cholerresis: then decreasing or stopping that input is recommended (4). Furthermore, excess Mn accumulates in the basal ganglia and can be responsible for Parkinsonian-like symptoms in HPN patients (4, 19, 20). Reduction of the Mn supply is eventually followed by disappearance of abnormal (hyperdense signal in T1 weighted) magnetic resonance brain imaging (4). Aluminium IV load was, in the past, higher than the IV inpu considered safe (21): the quality of glasses and the interaction between glasses and trace elements, phosphorus and/or amino acids solutions to store IV nutrients have all been implicated in ist excessive delivery. Aluminium toxicity is rarely seen at present times but patients with renal insufficiency are at risk. It accumulates in brain, bone and liver where harmful effects have been demonstrated especially in children in which impairment of cognitive function has been reported (21).

The following rule should be kept in mind: a deficit in micronutrient is rarely single and excess(s) can be present with deficiencies masking the effects.

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Table 1
Clinical features of micronutrient deficiencies (D) or toxicities (T) during HPN

<table>
<thead>
<tr>
<th>Nutrient (D, T)</th>
<th>Presentation</th>
</tr>
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<tbody>
<tr>
<td>Al (T)</td>
<td>Porotic ± painful osteopathy</td>
</tr>
<tr>
<td>Cr (D)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Cu (D)</td>
<td>Aplastic anemia ± mild leucopenia</td>
</tr>
<tr>
<td>Fe (D)</td>
<td>Liver thesaurismosis, perls</td>
</tr>
<tr>
<td>I (D)</td>
<td>Goitre (nil po)</td>
</tr>
<tr>
<td>Mo (D)</td>
<td>Coma, ? Metabolism Uric acid; Neuromyelopathy</td>
</tr>
<tr>
<td>Mn (T)</td>
<td>Extrapyramidal syndrome</td>
</tr>
<tr>
<td>Se (D)</td>
<td>Cardiomyopathy / Heart Failure</td>
</tr>
<tr>
<td>Zn (D)</td>
<td>Acrodermatitis, diarrhea, hair loss</td>
</tr>
<tr>
<td>Vit A (D)</td>
<td>Night blindness, xerophammia, dark field adaptation, defective bone mineralization</td>
</tr>
<tr>
<td>Vit D (D)</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>Vit E (D)</td>
<td>In vitro plateled hyper-aggregation and H202 -induced RBC hemolysis. Signs and symptoms suggestive of subacute combined degeneration (postero-lateral columns) in the presence of normal B12, ophthalmoplegia</td>
</tr>
<tr>
<td>Vit K (D)</td>
<td>Bleeding tendencies,defective II, VII, IX, XII; Bone mineralization defect (Gla proteins)</td>
</tr>
<tr>
<td>B1, Thiamine (D)</td>
<td>Wermicke's encephalopathy; Cardiomyopathy; Refractory lactic acidosis</td>
</tr>
<tr>
<td>B2, Riboflavin (D)</td>
<td>Cheilosis, red swollen tongue, folliculitis</td>
</tr>
<tr>
<td>B6, Pyridoxine (D)</td>
<td>Sideroblastic anemia, Convulsions</td>
</tr>
<tr>
<td>Folic acid (D)</td>
<td>Megaloblastic anemia ± cytopenia</td>
</tr>
<tr>
<td>Vit B12 (D)</td>
<td>Irritability, megaloblastic anemia, Cordonal posterior syndrome</td>
</tr>
<tr>
<td>Biotine (D)</td>
<td>Dermatitis, alopecia, hypotonia in 1 child</td>
</tr>
<tr>
<td>C, ascorbic ac. (D)</td>
<td>Scurvy, bleeding sore gums, peri joint and bone hemorrhages</td>
</tr>
</tbody>
</table>

6. Intestinal Failure-Associated Liver Disease (IFALD)

There is no standardised definition of IFALD. In the ESPEN guidelines for CIF, the term IFALD refers to liver injury as a result of several factors related to CIF, including, but not limited to PN, and no other evident causes (eg. viral, autmmune, toxic) (1).

The diagnosis of IFALD is based on clinical, biochemical, radiological and, when required, histological information. Increased liver enzymes 1.5 upper normal limit >6 months in adults (>6 weeks in children) has been frequently used in clinical studies (22, 23, 24).

The lack of a standardized definition makes it difficult to have accurate data on incidence and prevalence of IFALD. Cross sectional studies have reported a prevalence of alterations of the liver function tests in 5-85% of patients on HPN (children > adults) (1, 2, 25, 26). Similarly, the incidence of clinically advanced liver disease varies in published studies from 0% to 50% (1).

Cavicchi et al investigated the natural clinical and histological evolution of IFALD in 90 long-term HPN adult patients followed up with a median duration of 5 years (24). After 2 years of HPN, glucose based-HPN was associated with macrovacuolar steato-hepatitis and severe liver disease in fewer than 25%of patients (27) whereas lipid based-HPN, i.e., ternary mixtures including standard soybean-based lipid emulsions of more than 1 g/Kg/d, was associated with portal inflammation, ductular abnormalities, microvacuolar steatosis and severe cholestatic liver disease in 50%of patients (26). In a more recent study, Luman...
et al. (28) evaluated 107 patients receiving HPN for a median of 40 (range 4-252) months, but reported that no patients suffered from a conjugated bilirubin greater than 60 µmol/L (3.5 mg/dL) and/or decompensated liver disease.

A retrospective study investigated the histological abnormalities associated with IFALD in 89 patients who underwent biopsy or liver transplantation while on TPN (29). Cholestasis and steatosis were observed in 81% and 39% of cases respectively. Cholestasis was more common in infants (< 6 months) and steatosis in older children and adults. About one half of patients showed ductopenia, a previously unreported finding in PN patients. A feature of perivenular fibrosis was observed more frequently in patients with high-stage portal fibrosis and the finding of a combination of portal and perivenular fibrosis was considered a characteristic of PN injury. Infants are more susceptible to PN-related hepatocellular injury and develop fibrosis, as well as progression to high-stage fibrosis more rapidly than older children and adult. Progression of IFALD can ultimately end in liver failure, a mandatory indication for consideration for life-saving combined liver and small bowel transplantation (ITx), the patient otherwise being destined to die. In published series, the IFALD-related deaths accounted for 4-5% and 14-60% of total death on HPN in adults and children, respectively (30, 31, 32).

Monitoring the evolution of IFALD is therefore mandatory to judge the timing of patient referral for ITx. Unfortunately, no association was found between the biochemical markers of liver injury and the histological degree or the rate of progression of hepatocellular injury or fibrosis. A recent study in adults on HPN which aimed to validate transient elastography (Fibroscan®) demonstrated correlation with cholestasis rather than hepatic fibrosis or cirrhosis (33). Therefore serial liver biopsies may be required, even thought this also may be misleading owing to patchy hepatic injury.

There is no formally agreed categorisation of the severity of adult IFALD. In 2007, an international panel of experts, on the basis of the serum levels of the biochemical markers of cholestasis, of the abdominal ultrasound and liver histology features as well as of clinical feature, categorized IFALD into early/mild, established/moderate, and late/severe (34).

**Table 2**

**Proposed classification of IFALD degree**

<table>
<thead>
<tr>
<th></th>
<th>Type 1-early</th>
<th>Type 2-established</th>
<th>Type 3-late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes (ALP, γGT)</td>
<td>&gt;1.5 x normal for &gt; 6 weeks</td>
<td>&gt;1.5 x normal for &gt; 6 weeks</td>
<td>&gt;1.5 x normal for &gt; 6 weeks</td>
</tr>
<tr>
<td>Total bilirubin (with increased direct fraction)</td>
<td>&lt; 50 µmol (3 mg/dl)</td>
<td>50-100 µmol/L (3-6 mg/dl)</td>
<td>&gt;100 µmol/L (6 mg/dl)</td>
</tr>
<tr>
<td>Hepatic ultrasound</td>
<td>Some echogenicity</td>
<td>Enlarged spleen, biliary sludge, marked echogenicity</td>
<td>Enlarged spleen, irregular liver, ascites, varices</td>
</tr>
<tr>
<td>Histology</td>
<td>Fibrosis in up to 50% portal tracts, steatosis in adults</td>
<td>Extensive fibrosis (&gt;50% portal tracts). Obvious steatosis</td>
<td>Coagulopathy and thrombocytopenia C/I for biopsy</td>
</tr>
</tbody>
</table>

IFALD is a multifactorial condition. Pathogenetic factors can be categorized as "host/IF-related" and "PN-related". The host/IF factors are represented by sepsis, intestinal anatomy and oral/enteral nutrition. The PN-mechanisms consist in the infusion modality and in nutrient deficiency or excess (23, 25, 26).

Most of the data about the pathogenesis and treatment of IFALD derive from animal studies or from clinical research in infants and children. Few data have been provided by studies in adults. Recurrent catheter-related blood stream infection (CRBSI) is an established factor contributing to the development of IFALD, especially cholestasis, in both children and adults. Small intestine bacterial overgrowth (SIBO) occurring in dysmotile and/or dilated bowel loops may be associated with loss of intestinal barrier function, increased intestinal permeability and bacteremia or absorption of bacterial cell wall...
products capable of activating the innate immune system. Activated Kupfer cells within the liver, stimulates the release of proinflammatory cytokines and generates the inflammatory cascade (23, 25, 26).

Cavicchi et al. (24) and Luman et al. (28) demonstrated that a small bowel remnant of ≤50 cm or ≤100 cm, respectively, was independently associated with chronic cholestasis in adults receiving long-term HPN. The more reliable mechanism is the alteration in enterohepatic bile salt circulation following bile salt malabsorption.

The presence of food in the gut drives post-resection intestinal adaptation and is a major stimulus for secretion of gut hormones, resulting in improvement of intestinal motility and decreasing the stasis known to be implicated in the pathogenesis of IFALD. Data demonstrating the benefit of oral/enteral nutrition are limited to studies in infants and neonates (26), but it is likely the lack of oral feeding plays a role in the development of IFALD in adults too.

In comparison with 24-hour continuous infusion, cyclic infusion has been shown to reduce the risk of liver complications as well as to reduce serum liver enzymes and PN conjugated bilirubin in patients on long-term HPN. Metabolic studies demonstrated that cyclic (usually 10-14 hours) is associated with a reduction in hyperinsulinaemia, lower dextrose use, increased lipid oxidation and lower fat deposition in the liver (26, 35, 36).

Excess of energy, delivered as either glucose or fat, promotes hepatic steatosis. Glucose overfeeding can result in greater plasma insulin concentration, hepatic lipogenesis, and the build-up of triglycerides within hepatocytes. Fat supplied intravenously is carried by liposomes, rather than chylomicrons, which results in steatosis, characterized by fat deposition in Kupffer cells and hepatic lysosomes (23, 25, 26).

Soybean based lipid emulsions (SO-LEs) in excess of 1 g/kg/day have been shown to cause liver damage, especially cholestasis, with associated morbidity and mortality (26, 37). Implicated mechanisms would be the high content of proinflammatory ω-6 polyunsaturated fatty acid (PUFA), linoleic acid, the peroxidation of PUFA, the low content of α-tocopherol, the high content of plant sterols and the activation of the liver reticuloendothelial system (23, 25, 26). Linoleic acid is the precursor of arachidonic acid, a precursor of proinflammatory eicosanoids. Furthermore, SO-LEs have a high content of long-chain PUFAs that are prone to oxidation and a relatively low concentration of α-tocopherol, a major lipophilic anti-oxidant. In animal studies, phytosterols, plant-based naturally occurring sterols, have been shown to interrupt hepatocyte farnesoid X receptor signaling and the expression of downstream bile acid transporters, thus decreasing bile flow (25, 26). The non-oxidised fraction of LEs is taken up by the liver (Kupffer cells and hepatocytes), and spleen (reticuloendothelial cells), bone marrow, and lungs. Fat overloaded reticuloendothelial cells undergo acute or chronic activation, leading to haematological disorders, liver dysfunction, and cholestasis (23, 25, 26).

Excess amino acids may be associated with development of IFALD in children, and deficiency of taurine and cysteine, may play a role, in premature infants, but not in adults. Hepatic steatosis may be induced by protein and/or EFA deficiency as well as deficiencies in choline and carnitine (1, 23, 25, 26).

Prevention and treatment of IFALD rely on avoiding and promptly treating any infective/inflammatory foci (particularly CRBSI and SIBO) maintaining some oral/enteral feeding, cycling PN infusion, and avoiding glucose and LEs overfeeding. Surgical strategies to optimize intestinal anatomy and function have also to be considered. Available data in adults do not support PN supplementation with taurine and carnitine, whereas choline replacement have been reported to improve liver transaminases, but sufficient quantities are unstable in PN solutions. A few studies would support the efficacy of oral ursodeoxycholic acid, which displaces hepatotoxic bile salts and protects against hepatocellular injury (1, 23, 25, 26).

The most debated strategy concern the type and the amount of LE (1, 23, 25, 26, 38, 39). For IFALD prevention it is recommended that the SO-LEs dose is limited to less than 1 g/kg/day. A few studies have been carried out on the efficacy of LEs with a lower content of ω-6 PUFA (MCT/soy or olive/soy oil based LEs), generally enriched with fish oil (soybean/MCT/olive/fish or soybean/MCT/fish, but also pure fish oil based LEs). Further to the lower content of the pro-inflammatory ω-6 PUFA, the potential advantages of fish oil

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containing LEs are due to the content of the anti-inflammatory ω-3 PUFAs, docosahexaenoic and eicosapentaenoic acid, to the higher content of the anti-oxidant α-tocopherol and the lower of absent content of phytosterols. Animal studies have shown that intravenous fish oil improves biliary flow and decreases cholestasis, reduces de novo lipogenesis, stimulates β-oxidation, and decreases hepatic steatosis.

In the presence of IFALD, especially cholestasis, reducing or temporally discontinuing LEs should be considered and balanced against the risks of giving insufficient energy or increased amount of glucose. Some case reports (40, 41), case series (42, 43), and reviews (44, 45), to support the role of pure fish oil LE or newer combination LEs in improving liver function in children and adults with IFALD. However, in most of the studies, a high dose of SO-LEs was replaced by 1 g/kg of fish oil, so it cannot be excluded that reversal of cholestasis was due to the withdrawal of SO-LE. Furthermore, some animal and human studies, suggest that liver fibrosis persists, or even progresses, despite normalization of cholestasis markers, after giving fish oil (42, 46, 47). Therefore, more data are required before their routine use can be recommended to treat IFALD.

A schematic view of physiopathology and the associate preventive and curative treatments of IFALD are summarised on Table 3.

Table 3
Proposed physiopathology and the associated preventive and curative measures for IFALD

<table>
<thead>
<tr>
<th>Pathogenic factor</th>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td>Lack of oral feeding</td>
<td>Minimal oral/enteral feeding</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>Non-transplant surgery: restore intestinal continuity, intestinal lengthening, STEP, ... Ursodeoxycholic Acid 20-30 mg/kg/d</td>
</tr>
<tr>
<td>Small intestine bacterial overgrowth</td>
<td>Oral metronidazole, other antibiotics Prophylactic prokinetic drugs in dysmotility (ev erythrocine)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Treat rapidly and optimize CVC management</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>α-tocopherol (and other antioxidant ?) supplementation</td>
</tr>
<tr>
<td>Excess PN Energy</td>
<td>Avoiding overfeeding Maintenance low–mid range BMI</td>
</tr>
<tr>
<td>Excess PN Amino acids</td>
<td>Avoiding amount exceeding needs</td>
</tr>
<tr>
<td>Excess PN Glucose</td>
<td>&lt; 7 mg/kg/min Cyclic PN (stop for 8 hr)</td>
</tr>
<tr>
<td>Excess PN Lipids</td>
<td>Soybean-based LEs ≤ 1 g/kg/day ↓ ω-6 PUFA: LCT-MCT, Olive Oil, Fish Oil ↓ Phytosterols: FO, LCT-MCT, OO ↓ Phospholipids: LE concentration 30% &lt; 20% &lt; 10%</td>
</tr>
<tr>
<td>PN amino acid deficiency</td>
<td>Taurine enriched AA solution (children)</td>
</tr>
<tr>
<td>Other PN deficiencies</td>
<td>IV choline, 2 g/d Oral Lecithin, 20 g x 2/d</td>
</tr>
<tr>
<td>PN Toxicities</td>
<td>Balanced LE to avoid EFA</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Avoid Aluminium contamination</td>
<td>Mn and Cu removal in case of cholestasis</td>
</tr>
</tbody>
</table>

### 7. Gallbladder Sludge and Stones

The prevalence of gallstones in patients on HPN is significantly increased (1, 2). They occur in 45% of those with a short bowel (with and without a colon), and are more common in men than in women (48). In large series, biliary lithiasis and/or sludge was observed during HPN in one third of patients (49, 50). Probabilities of developing gall stones were 6.2, 21.2 and 38.7% at 6, 12, and 24 months, respectively (50). Biliary complication rate (acute cholecystitis, cholangitis, acute pancreatitis) occurred in 12% to 50% of positive patients (49, 50). Because of high rate of morbidity/mortality associated with biliary complications, prophylactic cholecystectomy has been proposed at the time of the last resection in patients with a short bowel, but no consensus exists about this strategy (1, 51).

The main pathogenetic factors are reduced gallbladder contractility and disruption of the enterohepatic circulation of bile salts (4, 51, 52). Lack of enteral intake during exclusive HPN induces gallbladder stasis which is the main factor causing gallbladder sludge (calcium bilirubinate and cholesterol crystals). The latter can disappear upon enteral CCK stimulation, or - if the causative factor persists - evolve to lithiasis in weeks to months. Too long bowel rest with surgery is similarly a sludge provocation factor. Drugs to decrease intestinal losses, like octreotide, opiates and anti-cholinergic drugs, reduces post-prandial gallbladder contractility. Extensive ileal resection/disease may cause disruption of the enterohepatic circulation and consequent loss of bile salts should lead to an increase in cholesterol saturation. Finally, when SIBO develops, secondary (more lithogenic) bile acids (lithocolic acid) are formed by intestinal bacteria.

The main recommendation (1) for preventing biliary sludge or stone formation is to encourage oral and/or enteral feeding as soon as possible after a period of oral fasting. Messing et al. showed that biliary sludge is reversible in the majority of the patients within 4 weeks after resuming oral feeding (52). The use of narcotics or anticholinergics should be limited as much as possible. Besides the effect of resuming oral feeding on biliary sludge, treatment of biliary stones is similar to that in the general population.

### 8. Renal Function Impairment and Stones

Serious progressive renal impairment may occur over years in HPN patients (1, 3). An early retrospective study showed that the decline in the creatinine clearance was greater than that one seen in controls (53). Nephrotoxic drugs, bacteraemia / fungemia, high load of amino acid solution explained 50% of the 3.5% annual decline in creatinine clearance seen in 33 adult patients followed up for a median of 8 years. Abnormal tubular function was observed in 58% of patients (53).

Mineral water imbalances, chronic dehydration (diuresis should be more than 0.8-1 L/d), trace metal depots, hyperoxaluria and or nephrolithisis (up to 25% in type II and III SBS patients; i.e., those with large steatorrhea and presence of all or part of the colon incontinuity) may contribute to the problem (4, 48).

In a prospective study, a decrease (-38±15%) in glomerular filtration rate was observed in 21 of 40 (52.5%) long term HPN patients, with age taken into consideration (54). Urologic or nephrologic diseases were more frequent in these 21 patients. Moreover, a urinary sodium/potassium excretion ratio < 1 in 8/21 patients and mean plasma renin and aldosterone were significantly higher in these patients than in the 19 who had normal glomerular filtration rate, thus indicating that dehydration was involved in the decrease in renal function.
Renal function was examined in another study by more parameters in 16 patients with SBS, of which 50% showed a reduced kidney function. Also, this study addressed how electrolyte excretion is influenced by infusion therapy, but the study did not report on the mechanisms of renal impairment (55). The only recent study of renal function and CIF is retrospective and also includes patients who underwent ITx. The annual decline in renal function was of 2.8% in HPN patients and 14.5% in transplant recipients (56).

The major risk factor for renal function in HPN for CIF are frequent episodes of acute dehydration, chronic dehydration, frequent episodes of CRBSI, the use of nephrotoxic medications, presence of pre-existing renal disease, renal stones (urinary infections and obstructive uropathy) and nephrocalcinosis from calcium oxalate in the renal parenchyma (1, 57, 58).

Renal stones and nephrocalcinosis are primarily linked to increased absorption of oxalate, hypovolemia and dehydration and they are favored by magnesium deficiency and metabolic acidosis with urinary citrate deficiency (1, 57, 58). Oxalate normally binds to calcium in the gut lumen and thus only a small fraction of ingested oxalate is available for absorption in the colon; however in patients with SBS with a colon in continuity, more oxalate may be absorbed since fatty acids sequester calcium and inhibit the complexing of oxalate. Absorbed oxalate may precipitate in the renal tubules inducing tubular damage and necrosis and atrophy. Calcium oxalate renal stones have been shown to occur in about 25% of SBS patients with a retained colon at a median time of 30 months after the surgery. Preventive measures with reduced intake of oxalate and the use of cholestyramine have been reported, but are not always successful. A low fat diet or replacing LCT with MCT and oral calcium supplementation at meal time have also to be considered (1, 57, 58).

For the prevention of renal failure and stones, the ESPEN guidelines on CIF (1) in patients with SBS with a colon in continuity recommend regular monitoring of renal function and fluid balance, to avoid episodes of dehydration, to avoid metabolic acidosis, to prevent and promptly acute and chronic infections, and to advise a low oxalate and low fat diet, in addition to an increase of oral calcium, and to give citrate supplementation.

### 9. Metabolic Bone Disease

Metabolic bone disease (MBD) is the most frequent metabolic complication associated with HPN. A multicentre cross-sectional study from the ESPEN HAN & CIF special interest group evaluated, the prevalence of MBD in 165 patients on long term HPN. A reduced T-score bone mineral density (< -1 SD of sex paired peak bone Ca) was observed in 84% of patients, bone pain in 35% and spontaneous bone fractures in 10% (59). Osteoporosis (T-score < -2.5 SD of sex paired peak bone Ca) was present in 41%. A single center survey reported osteoporosis in 67% and fractures in 10% (60). The incidence of MBD in the HPN population remains unknown, but follow-up studies on relatively large patient groups (61-63) indicate that long-term HPN is not invariably associated with a decrease of BMD, and in some cases bone density does in fact increase during treatment with HPN.

Histomorphometric studies showed the presence of either osteomalacia or osteoporosis (64). It must be considered that osteomalacia, a frequent fate in chronic malabsorptive diseases, is a cofounder of the mere presence of osteoporosis because its low rate of Ca deposition in the increased osteoid. Thus, establishing a normal vitamin D status is therefore of primary importance and a prerequisite before discussing specific treatment for osteoporosis (62, 64). Analysis of the dynamic histomorphometric indices shows a low bone formation rate in most patients, which seems characteristic of HPN-associated MBD (64, 65). The results of a study on markers of bone turnover also demonstrated a low rate of bone formation (66).

The pathogenesis is multifactorial, being due to general and life-style elements, underlying disease and PN-related factors (62, 64). Age, menopause, reduced physical activity, lower sunlight exposure alcohol and tobacco abuse, may all be involved. Intestinal malabsorption of calcium and vitamin D, metabolic acidosis due to intestinal losses of bicarbonate as well as to d-lactic acidosis, chronic inflammation, malnutrition and drugs, such as chronic corticosteroids administration, are factors due to the underlying disease.
Aluminium toxicity due to the highly contaminated amino acid solutions derived from casitone hydrolysis was the first reported PN-related pathogenic factor. This is no more the case with the modern crystalline amino acid solutions. PN-induced hypercalciuria has been reported by cross-sectional studies which show a positive correlation with the amount of infused amino acids, glucose, sodium and calcium with the PN solution. On the contrary, urinary calcium is negatively correlated with intravenous phosphate load. Calcuria is greater with cyclic infusion than with continuous infusion. Furthermore, metabolic acidosis, due to titratable acids produced mainly by the metabolism of neutral and sulphur-containing amino acids, can induce bone calcium reabsorption. A few studies suggest an impairment of PTH secretion due to iv 25-vitamin D infusions or an altered response to PTH due to iv Ca infusion, thus decreasing the physiological activity of PTH on bone remodelling. Deficiency or toxicity of micronutrients may also interfere with bone metabolism; vitamin K, vitamin C, copper, floride, boron and silicon deficiency and vitamin A, cadmium, strontium and vanadium toxicity are all directly implicated. A direct role of PN in inducing the release and/or regulation of the activity of cytokines known to impair bone metabolism has also been suggested. Vitamin D insufficiency or deficiency (serum concentration of 25-hydroxivitamin D < 30 or < 20 ng/mL, respectively) has been reported in most (77-100%) of adult patients on HPN, who were receiving IV multivitamin supplementation which included for each infusion day the recommended amount of 200 IU vitamin D3 (cholecalciferol) (67-69). Those patients who did not receive HPN daily were at higher risk of deficiency and an increased risk during transition from HPN to enteral nutrition has been observed.

Optimisation of the parenteral solution for the prevention of metabolic bone disease requires control of the nutrient infusion (1, 62, 64). The calcium, magnesium, and phosphate content of the PN must be adjusted to maintain serum concentrations and 24-h urinary excretions within the normal range. In children, an optimal phosphate:calcium molar ratio required for bone mineralization is approximately 1:1. In adults, it is suggested that calcium and phosphate are given starting from a ratio of 1:2 and adjusting it as needed (e.g. 15 mEq (7.5 mmol) of calcium and 30 mmol of phosphorus to the PN solution each day) (62). Amino acids and sodium should not be added in amounts greater than losses because of the risk of sodium induced hypercalciuria. Acetate are useful to avoid acidosis and to maintain serum bicarbonate in the normal range. Aluminium contamination of the PN admixture should be less than 25 µg/L. Vitamin D nutritional status should be corrected and normal status maintained to avoid osteomalacia. Treatment of MBD with iv biphosphonates (clodronate, pamidronate or zolidronic acid) has been described (70, 71). Only anecdotal reports have been provided on recombinant PTH (teriparide) or the human IgG2 monoclonal Ab that competes with RANKL for RANK binding sites and prevents osteoclast-mediated bone resorption (denusumab). A few reports suggest that intestinotrophic hormones, like growth hormone and glucagon-like peptide-2 may also improve bone mineral density (64).

10. Indications for Intestinal Transplantation

Treatment options for irreversible chronic intestinal failure are lifelong HPN or intestinal transplantation (ITx). The defining component of any ITx is the small intestine (jejunoleum), without or with colon. On the basis of the transplanted organs, four types of transplant are described: a) isolated small bowel transplant, including jejunum and ileum; b) combined liver-intestine transplant, including liver with jejunum and ileum; c) modified multivisceral transplant, including stomach, jejunum and ileum with or without liver; d) multivisceral transplant, including stomach, pancreas, duodenum, jejunum and ileum with or without liver. A portion of a colon can also be transplanted (72).

The data on safety and efficacy indicate HPN as the primary treatment for CIF and ITx as the treatment for patients with a high risk of mortality on HPN (32, 73). The expected 5-year survival rate on HPN is around 70% in adults and 90% in children (32). The International ITx Registry shows an actuarial 5-year patient and graft survival of 58% and 50%, respectively, for patients transplanted since 2000 (72).
The indications for ITx were initially developed by expert consensus in 2001 and were categorized as HPN failure, high risk of death due to the underlying disease, or CIF with high morbidity or low acceptance of HPN (31, 74):

- **HPN-failure**
  - Impending (total bilirubin above 3-6mg/dL/54-108 μmol/L, progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis) due to IFALD
  - CVC-related thrombosis of ≥ 2 central veins
  - Frequent and severe CVC-related sepsis: 2 or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungaemia; septic shock and/or acute respiratory distress syndrome
  - Frequent episodes of severe dehydration despite intravenous fluids in addition to HPN

- **High risk of death attributable to the underlying disease**
  - Invasive intra-abdominal desmoid tumours
  - Congenital mucosal disorders
  - Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel < 10 cm in infants and < 20 cm in adults)

- **IF with high morbidity or low acceptance of HPN**
  - Need for frequent hospitalization, narcotic dependency or inability to function
  - Patient’s unwillingness to accept long-term HPN

Those indications were based on retrospective analyses of national and international registries and individual center cohorts of patients. In 2004, the Home Artificial Nutrition and Chronic Intestinal Failure working group (HAN&CIF group) of ESPEN carried out a prospective comparative study to evaluate the appropriateness of the 2001 indications for ITx (75-77). The results showed that only IFALD-related liver failure and intra-abdominal invasive desmoids were indications for life-saving ITx, the other conditions to be considered indications for a potential rehabilitative ITx in case-by-case carefully selected and accurately informed patients. A subsequent retrospective study carried out on children by a Canadian intestinal rehabilitation center confirmed the results observed by the ESPEN HAN&CIF group (78).

In the last decade, there have been many advances in the pre-transplant management of CIF resulting in much better patient outcomes, mainly due to the improvement in prevention and treatment of IFALD and in the medical and non-transplant surgery options aimed at intestinal rehabilitation (72, 79, 80). This improvement has modified the strategy of treatment of CIF, moving from a straight referral for ITx of any patients with a potential risk of death on HPN to the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, in order to maximize the opportunity for weaning from HPN, to prevent HPN-failure, and to ensure timely ITx when this is needed (1, 32, 34, 72, 79, 80).

For this purpose, a special working group at the Xth International Small Bowel Transplantation Symposium held in 2007 devised the following recommendations (34): a) collaboration between care givers and intestinal rehabilitation centres should be initiated if PN requirements are anticipated to be more than 50% at 3 months from initiating therapy; b) IF programme needs to include intestinal rehabilitation and ITx or have active collaborative relationship with centres that perform ITx; c) national registers for IF patients should be established and participation by all prescribers of HPN should be expected.

### 11. Summary

- The pathogenesis of HPN metabolic complications is multifactorial; HPN-related and IF-related factors are involved; monitoring and management by an expert multidisciplinary team is the cornerstone for their prevention and their appropriate treatment;
- Fluid, electrolytes and acid-base balance alterations may frequently occur in patients with high gastrointestinal losses. Tight monitoring is required, especially in the early...
period of HPN, in order to prevent these complications through a tailored PN prescription;
- Hyper-glycemia can occur during PN infusion and hypo-glycaemia at PN stopping;
- Essential fatty acid deficiency is rare, but it may be expected in patients totally dependent on parenteral nutrition if no intravenous lipid emulsion is supplied for a period of months;
- Micronutrient deficiencies/toxicities are underestimated, because overt clinical features are rare; a deficit is rarely single and can be masked by an excess;
- Intestinal failure associated liver failure is less severe in adults (steatosis and steatohepatitis) than in children (chronic cholestasis, inflammation and fibrosis), but it remains the most life-threatening complication;
- Gallbladder stone and sludge are frequent; pathogenesis is mainly related to intestinal failure-associated factors;
- A decrease of renal function has been reported in about 50% of patients; chronic dehydration, nephrotoxic drugs, bacteriemia/fungemia, high load of amino acid solution have a pathogenic role;
- Renal stones, most frequently calcium-oxalate stones, occur in about 25% of patients with a short bowel syndrome with a retained colon;
- Metabolic bone disease is the most frequent complication associated with HPN; it is often present before starting the treatment, due to underlying disease factors;
- Impending or overt IFALD-associated liver failure and invasive intra-abdominal desmoids are indications for life-saving intestinal transplantation; in the other conditions, a case-by-case evaluation is required;
- Early referral to expert intestinal rehabilitative-centers is recommended for patients whose PN requirements are anticipated to be more than 50% at 3 months from initiating therapy, in order to devise the most appropriate treatment strategy.

12. References


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