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 HPN in adult patients;
- Preventing and treating these complications;
- Identifying patients who are candidates for intestinal transplantation;

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Key Messages

- Metabolic complications of HPN are still frequent but they can be significantly decreased through present knowledge, expertise and continued attention;
- Most metabolic complications are multifactorial and interrelated;
- A nutrition support team, education, and complete, but non-exclusive, HPN adapted to the type of chronic intestinal failure (CIF), are able to lower the rate of metabolic complications;
- Further understanding is needed, especially in renal, bone and liver associated complications to prevent, ameliorate, and devise curative treatments;
- Impending or overt parenteral nutrition/intestinal failure-associated liver failure and invasive intra-abdominal desmoids are clear indications for life-saving intestinal transplantation, whereas major central venous catheter complications and ultra-short bowel syndrome may be indications for pre-emptive/rehabilitative intestinal transplantation in selected patients;
- Early referral to expert intestinal rehabilitative centres is recommended for patients with CIF if PN requirements are anticipated to be more than 50% at 3 months from initiating therapy.
1. Introduction

The following long-term HPN metabolic complications will be identified in order to assure prevention and curative treatments: liver abnormalities, gallbladder sludge and stones, bone disease, renal function impairment, as well as vitamin deficiency and trace metal deficiency or toxicity. Hyperglycaemia, fluid and electrolyte disturbances and gastrointestinal effects of HPN will be briefly considered: readers are also referred to recent reviews (1 - 7).

Appropriate monitoring is the cornerstone for the prevention and early identification of metabolic complications. According to ESPEN guidelines in adult patients on HPN (7):
* 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 months. The clinically unstable patient will need more attention.
* Biochemistry (electrolytes, kidney function, liver function, glucose, haemoglobin, iron, 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 months.
* Bone mineral density assessment by DEXA scanning is recommended at yearly intervals.

2. Fluid and electrolytes

Digestive balances of water and sodium, especially in Type I short bowel patients (SBS) with a high output stoma, must be carried out to evaluate needs (6). Hydration should be enough to produce a urine output of more than 1 L/d. Input/output records should be looked at carefully during the initial establishment of balance and during attempts at weaning from HPN (3).

Chronic fatigue can be caused by chronic dehydration, hypokalaemia, and/or hypomagnesaemia, the latter inducing refractory hypocalcaemia. Hypernatraemia can be caused by poor control of oral fluid intake with dehydration, excess loss of hyposmotic water especially if there is a post-duodenal intestinal remnant shorter than 1 m (6).

It is also important to measure enterostomy - or high output fistulae – output to know if there is a discrepancy between expected output and observed output, because such a gap should prompt a search for causes of excessive enteric losses, as well described in a recent review (3).

Refeeding syndrome (including pseudo-hyperthyroidism with hypophosphataemia and cardiopulmonary insufficiency) is beyond the scope of this review (1, 8, 9) mainly because HPN is usually conducted in "stable" patients after adjustment of PN requirements and when cyclic PN is feasible. Indeed cyclic PN (10) is contraindicated in severely malnourished patients as well as in uncontrolled cardiac patients.

3. Overall complications of hyperglycaemia

On meta-analysis, it has been shown that in clinical practice, infectious complications, are more frequent during PN than during enteral tube feeding (EN) (relative risk for EN: 0.66; 95% confidence interval (CI) = 0.56-0.79) independently of whether catheter sepsis was included in the analysis (11). Interestingly, the non-infectious complications were higher in EN (RR = 1.36; 95%CI: 0.96-1.83) than in PN. The higher risk of infection (catheter and non-catheter related) during PN may be partially explained by a higher incidence of hyperglycaemia (4). Thus, tight glucose control (12) might be a goal in respect of decreasing overall infectious complications during HPN, if one extrapolates from the ICU setting (13).
In HPN patients with diabetes, glycaemic control is usually easily achieved by the addition of short-acting insulin into the nutritive mixture (1-2 U/10 g of dextrose). The use of programmable pumps for appropriate reduced rates at the end of the cyclic nocturnal PN infusion is then important to avoid rebound hypoglycaemia (10). The latter complication can be observed, even with reduced final rates of infusion, when cyclic follows several weeks of continuous PN infusion. To avoid this problem, transition between continuous and cyclic administration should be made over a week or so; eg, a reduction of 2 hours infusion time per day from 24 h to 10 h of PN infusion. It is noted also that some centres prefer to avoid the addition of insulin to HPN regimens, instead using a sequence of subcutaneous injections timed to coincide with maximal HPN glucose delivery.

4. Intestinal consequences of HPN

They are more related to the causes of CIF than to HPN per se. Post-resection intestinal adaptation occurs in SBS (6). Bacterial translocation has not proved to be associated with bowel rest alone in man, but occurs with gut occlusion or pseudo obstruction (4, 14). These patients benefit from sequential antibiotic treatment to decrease intestinal bacterial overgrowth (6). Contrary to most animal models, exclusive TPN, i.e., bowel rest, is associated neither with mucosal atrophy nor with intestinal immune dysfunction assessed through the intestinal immunoglobulin profile (4).

5. Micronutrient deficiencies and excess

Micronutrient deficiencies were recognised in the early years of long term HPN. Regular provision through commercial parenteral vitamin and trace metal preparations avoida them, since these preparations provide 1.5- to 2-fold basal requirements, as they are intended also for patients who are either nutritionally depleted or who have increased losses (3,7).

The current commercial parenteral vitamin and trace metal formulations for HPN reflect definitions set by the American FDA in 1979 (15). A recent and extensive expert review challenged the appropriateness of these formulations and agreed on the need to make several changes (16), including the reduction of copper, manganese and chromium, and an increase in the content of iodine and iron. Although it was indicated that the addition of 150 μg of vitamin K to the adult formula would meet the requirement for γ-carboxylation status of noncoagulation Gla proteins, it was recognized that lipid emulsions contain variable amounts of vitamin K (soybean oil, 150–300 μg /100 g; safflower oil, 6–12 μg /100 g).

Care should be taken both to provide adequate micronutrient intakes in patients fed intravenously for less than 7 days per week or with abnormal losses, and not to provide excess in patients with cholestasis or renal failure. When less than 5 cycles per week are used it is advisable to double the vitamin provision in each cycle. When patients are 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 (3, 17, 18). Iron deficiency may occur because of occult faecal blood loss (19). Vitamins C, and many of the B vitamins may not be optimally maintained with current allowances if HPN dependence is at its highest levels, as in periods of exclusive HPN. Essential fatty acid deficiency (of the n-6 series is frequently seen even with apparently sufficient intake of usual fat emulsions (18,20,21) implying perhaps a more generous use of fat emulsions enriched in the n-6 series at least in diseases having a propensity to inflammation. This will of course be balanced against the potential for liver damage with long-term excess provision of soya-derived lipid (see section 6 below).

Adequate amounts of micronutrients with antioxidant properties are required (22), but greater than needed quantities may have harmful effects, meaning an apparent paradoxical propensity to increased peroxidation (23, 24).
Thus, large doses of micronutrients should not be used routinely. Zinc and iron have been demonstrated to increase acute phase reaction response and should not normally be given during periods of sepsis or inflammation, having the capability to aggravate both (24, 25). In chronic cholestasis, trace metals (Cu and Mn) may accumulate in the liver due to decreased choleresis: decreasing or stopping that input is recommended (3). Furthermore, excess manganese accumulates in the basal ganglia and can be responsible for Parkinsonian-like symptoms in HPN patients (3, 26, 27). Reduction of the manganese supply is followed by a very gradual disappearance of the abnormal (increased signal in weighted T1) magnetic resonance brain imaging (3). The intravenous aluminium load was, in the past, higher than is safe for IV input (28), but the quality of glasses and the interaction between glasses and trace metals, phosphorus or amino acids solutions in storage of IV nutrients have been improved. Together with the substantial move towards storage of nutrients in plastic containers, aluminium toxicity is now rarely seen, but patients with renal insufficiency remain at risk. Aluminium accumulates in brain, bone and liver where harmful effects had been demonstrated, especially in children in whom important impairment of cognitive function has been reported (29).

Monitoring micronutrients is performed by blood testing, which should be limited to no more than 2 to 3 times/year in stable long term patients (3, 7). The following rule should be kept in mind: a deficit in micronutrients is rarely single, and excess(es) can be present with deficiencies masking them.

Table 1 Clinical features of micronutrient deficiencies and excesses during HPN

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al **</td>
<td>Porotic ± painful osteopathy– this is from EXCESS</td>
</tr>
<tr>
<td>Cr</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Cu</td>
<td>Aplastic anaemia ± mild leucopenia</td>
</tr>
<tr>
<td>Fe</td>
<td>Liver thesaurismosis, PERLS</td>
</tr>
<tr>
<td>I</td>
<td>Goitre (nil po)</td>
</tr>
<tr>
<td>Mo</td>
<td>Coma, abnormal metabolism of uric acid; Neuromyelopathy</td>
</tr>
<tr>
<td>Mn **</td>
<td>Extrapyramidal syndrome – this is from EXCESS</td>
</tr>
<tr>
<td>Se</td>
<td>Cardiomyopathy / Heart Failure</td>
</tr>
<tr>
<td>Zn</td>
<td>Acrodermatitis, diarrhoea, hair loss</td>
</tr>
<tr>
<td>Vit A</td>
<td>Night blindness, xerophthalmia, dark field adaptation, defective bone mineralization</td>
</tr>
<tr>
<td>Vit D</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>Vit E</td>
<td>In vitro platelet hyper-aggregation and H202-induced RBC haemolysis. Signs and symptoms suggestive of subacute combined degeneration (postero-lateral columns) in the presence of normal B12, ophthalmoplegia</td>
</tr>
<tr>
<td>Vit K</td>
<td>Bleeding tendencies, defective factors II, VII, IX, XII; abnormal bone mineralization (Gla proteins)</td>
</tr>
<tr>
<td>B1,Thiamine</td>
<td>Wernicke's encephalopathy; Cardiomyopathy; Refractory lactic acidosis</td>
</tr>
<tr>
<td>B2,Riboflavin</td>
<td>Cheilosis, red swollen tongue, folliculitis</td>
</tr>
<tr>
<td>B6,Pyridoxine</td>
<td>Sideroblastic anaemia, Convulsions</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Megaloblastic anaemia ± cytopenia</td>
</tr>
<tr>
<td>Vit B12</td>
<td>Irritability, megaloblastic anaemia, Cordonal posterior syndrome</td>
</tr>
<tr>
<td>Biotin</td>
<td>Dermatitis, alopecia, hypotonia in children</td>
</tr>
<tr>
<td>C, ascorbic ac.</td>
<td>Scurvy, bleeding sore gums, peri-joint and bone haemorrhages</td>
</tr>
</tbody>
</table>

6. IF/PN associated liver disease (IF/PNALD)

Comprehensive reviews have been published (2, 30, 31). Abnormalities of liver function tests occur in both children and adults on HPN, at a frequency of between 15 and 85% (7). The presentation of IFALD differs in the preterm neonate from that of term infants,
older children, and adults. Chronic cholestasis with associated inflammation and more rapid progression to fibrosis, portal hypertension and end-stage liver disease is the predominant feature in neonates and children, whereas steatosis and steatohepatitis with a slower evolution are the principal lesions in adults (30). IF/PNALD led in the past two decades to liver failure in one every 5 adult patients on long-term HPN (32) being then responsible for either death or being put on a waiting list for combined liver-intestine transplantation (33). Prevention of IF/PNALD is therefore of crucial importance from the first days of PN, and the first months of an HPN regimen must be managed carefully in order to avoid chronic cholestasis (≥ 6-month duration). These facts plead for the management of these patients in centres expert in the whole spectrum of intestinal failure therapy (33).

Chronic cholestasis, if not reversed, can lead to IF/PNALD and then to severe liver disease. Liver abnormalities in HPN patients may progress to severe histological changes with portal fibrosis and/or cirrhosis, which may, in the longer-term (months to years) result in liver failure and death (7). Its natural clinical and histological evolution was investigated in 90 long-term adult HPN patients followed up with a median duration of 5 years (34). After 2 years of HPN, glucose based-HPN was associated with macrovacuolar steato-hepatitis and severe liver disease in less than 25% of patients (35) 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 (34).

When liver function tests becomes abnormal, the occurrence of extensive fibrosis and liver failure can be accelerated within several months if a high degree of PN dependence is maintained, (i.e. poor oral intake and ongoing IV hyperalimentation) (36, 37). In HPN patients, jaundice with increased conjugated and unconjugated bilirubin, splenomegaly and thrombocytopenia, can be significantly associated with noticeable sea-blue histiocyte (activated macrophages CD 68+) infiltration of the bone marrow without haemophagocytosis (38). This reflects accumulation of polyunsaturated fats (PUFA), coming from excess long term standard lipid delivery through ternary mixtures, within the reticuloendothelial cells (36, 38).

Microvacuolar steatosis, phospholipidosis (39), accumulation of phospholipids, polyunsaturated triacyl glycerol within hepatocytes and hyperplasia of macrophages, (i.e. Kupffer cells in and around sinusoids or in or around portal areas) (39, 40) are especially seen when ternary nutritive mixtures are used. This explains why microsteatosis was not described with the use of IV fat infusions whereas hepatocyte macrosteatosis was easily demonstrated, for example, with high concentration glucose infusions.

Recently, a classification of IF/PNALD into early/mild, established/moderate, and late/severe degree has been proposed (41) (table 2).

<table>
<thead>
<tr>
<th>Enzymes (ALP, γGT)</th>
<th>Billirubin</th>
<th>Ultrasound scanning</th>
<th>Hepatic histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1-early</td>
<td>&gt;1.5 x normal</td>
<td>&lt; 50 µmol/l</td>
<td>Some increased hepatic echogenicity</td>
</tr>
<tr>
<td>for &gt; 6 weeks</td>
<td>(3 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2-established</td>
<td>&gt;1.5 x normal</td>
<td>50-100 µmol/l</td>
<td>Enlarged spleen, biliary sludge, marked hepatic echogenicity</td>
</tr>
<tr>
<td>for &gt; 6 weeks</td>
<td>(3-6 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3-late</td>
<td>&gt;1.5 x normal</td>
<td>&gt;100 µmol/l</td>
<td>Enlarged spleen, irregular liver, ascites, varices</td>
</tr>
<tr>
<td>for &gt; 6 weeks</td>
<td>(6 mg/dl)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Proposed classification of IF/PNALD degree

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The pathogenesis of IF/PNALD, yet not fully understood, is intricate and multifactorial (30,31). It involves: (a) patient-dependent factors, especially very short-bowel syndrome and an excluded colon; and (b) nutritional factors, especially "intravenous hyperalimentation" or high soya rich PUFA triglyceride emulsion (more than 1 g/Kg/d) even without hyperalimentation (35). Deficiency states (e.g. Se, Vitamins E & C, choline, taurine) and/or excesses of nutrients (e.g. certain amino acids, Fe, Mn, Al, Vitamin A, phytosterols) may also contribute to liver disease during HPN.

It is clear from clinical observation that more than one factor is, most of the time, needed to provoke this complication, suggesting a second hit physiopathology notably through sepsis – of whatever origin - or intestinal bacterial translocation. A schematic view of physiopathology and the associate preventive and curative strategies are summarised in **Table 3** (30,31).

**Table 3. Proposed pathophysiology and associated preventative and curative strategies for IF/PNALD**

<table>
<thead>
<tr>
<th>Pathogenetic factor</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of oral feeding</td>
<td>Minimal enteral feeding</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>Non-transplant surgery: restore intestinal continuity, intestinal lengthening, eg STEP, Ursodeoxycholic acid 20-30 mg/kg/d Intestinal transplantation to protect the liver</td>
</tr>
<tr>
<td>Intestinal bacterial overgrowth</td>
<td>Oral metronidazole, other antibiotics Prophylactic erythromycin (↑ gastric motility)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Treat rapidly and optimize CVC management</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Vit E and other antioxidant supplementation ?</td>
</tr>
<tr>
<td>Excess PN Energy</td>
<td>Avoiding overfeeding Maintenance of low–mid range BMI</td>
</tr>
<tr>
<td>Excess PN Amino acids</td>
<td>Avoiding amounts exceeding needs</td>
</tr>
<tr>
<td>Excess PN Glucose</td>
<td>&lt; 7 mg/kg/min Cyclic PN (stop for &gt;8 hr)</td>
</tr>
</tbody>
</table>
| Excess PN Lipids Soybean LE (n-6 PUFA) | Limit soybean ≤ 1 g/kg/day  
↓ n-6 PUFA: LCT-MCT, olive oil, fish oil  
↓ Phospholipids: LE concentration 30% < 20% < 10%  
↓ Phytosterols: FO, LCT-MCT, OO |
| Phospholipids                        |                                                                            |
| Phytosterols                         |                                                                            |
| PN amino acid deficiency             | Taurine enriched AA solution (children) Oral or IV glutamine (?)            |
| Other PN deficiencies                | Iv choline, 2 g/day Oral lecithin, 20 g x 2/day Iv carnitine, 1 g/day Balanced LE to avoid EFA |
| PN toxicities                         | Avoid aluminium contamination Restriction of Mn and Cu in cholestasis       |
7. Gallbladder sludge and lithiasis

The prevalence of gallstones in patients with HPN is significantly increased (7). They occur in up to 45% of patients with a short bowel (with and without a colon), and are more common in men than in women (42).

In large series of long-term HPN patients, biliary lithiasis and/or sludge is observed during HPN in about one third of patients (43, 44). The probabilities of developing gallstones were 6.2, 21.2 and 38.7% at 6, 12, and 24 months, respectively (44). Biliary complications (acute cholecystitis, cholangitis, acute pancreatitis) occurred in 12% to 50% of positive patients (43, 44). Because of the high rate of morbidity/mortality associated with biliary complications, prophylactic cholecystectomy has been proposed at the time of the last/defining resection in patients expected to have a short bowel (45).

The main pathogenetic factors are reduced gallbladder contractility and the disruption of the enterohepatic circulation of bile salts (3, 46, 47). Lack of enteral intake during exclusive HPN induces gallbladder stasis, which is the main factor inducing 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. Over-long bowel rest after surgery is a parallel provoking factor for sludge. Similarly, drugs to decrease intestinal losses, like octreotide, opiates and anti-cholinergic drugs, reduce post-prandial gallbladder contractility and increase the risk of stone formation. Extensive ileal resection/disease causes disruption of the enterohepatic circulation, and the consequent loss of bile salts leads to an increase in cholesterol saturation. Finally, when small bowel bacterial overgrowth develops, secondary (more lithogenic) bile acids (such as lithocolic acid) are formed by intestinal bacteria.

8. Renal function impairment

Serious progressive renal impairment may occur after many years in HPN patients (2). A largely unexplained decline in the creatinine clearance is greater than that seen in controls (48). Nephrotoxic drugs, bacteraemia / fungaemia, and high amino acid load were thought to explain 50% of the 3.5% yearly 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 (48).

Mineral and water imbalances, chronic dehydration (diuresis should be more than 1 L per day), trace metal depots, hyperoxaluria and/or nephrolithiasis (up to 25% in type II and III SBS patients; i.e., those with steatorrhea and the presence of at least part of the colon in continuity) may contribute to the problem (3, 42).

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 (49). Urological or nephrological diseases were more frequent in these patients. Moreover, the urinary sodium/potassium excretion ratio was < 1 in 8/21 patients, and the mean plasma renin and aldosterone concentrations were significantly higher in these patients than in the 19 who had normal glomerular filtration rate, thus indicating that a dehydration status was involved in the deterioration in renal function.

9. Metabolic bone disease

A multicentre cross-sectional study from the ESPEN HAN & CIF special interest group evaluated the prevalence of metabolic bone disease (MBD) in 165 patients on long-term HPN. A T-score bone mineral density (< 2.5 DS of sex paired peak bone Ca) was observed in 84% of patients, bone pain in 35% and spontaneous bone fractures in 10% (50). A single centre survey reported osteoporosis in 67% and fractures in 10% (51).

The same authors looked at the evolution of bone mineral density with DEXA after HPN of 1.5 and 5.5 years duration respectively, in more than 50 patients each, showing, with no specific treatment, a modest but significant increase in lumbar spine (trabecular bone) and no significant change in the femoral neck (cortical bone of lower rate of remodelling than trabecular bone) (50, 51).
Younger age of chronic intestinal failure occurrence, before acquisition of the bone peak, brings a higher risk for osteoporosis during HPN (51). Thus, it can be suggested that HPN, in expert centres is not a causative factor for osteoporosis, but that low bone mineral density may either predate HPN in chronic intestinal diseases or be aggravated during the stormy period of acute intestinal failure with associated sepsis, inflammation and immobilisation (5, 51, 52).

Histomorphometric studies show the presence of either osteomalacia or osteoporosis (53). It must be considered that osteomalacia, a frequent fate in chronic malabsorptive diseases, is a confounder of the mere presence of osteoporosis, because of the low rate of calcium deposition in the increased osteoid. Establishing a normal vitamin D status is therefore of primary importance and a prerequisite before discussing specific treatment for osteoporosis (53,54). Analysis of dynamic histomorphometric indices shows a low bone formation rate in most patients, which seems characteristic of HPN-associated metabolic bone disease (53,55). The results of a study of markers of bone turnover also demonstrated a low rate of bone formation (56).

The pathogenesis is multifactorial, being due to general and life-style elements, underlying disease, and PN-related factors (53,54). Age, menopause, reduced physical activity, lower sunlight exposure, alcohol and tobacco abuse, may also be involved. Intestinal malabsorption of calcium and vitamin D, metabolic acidosis due to intestinal losses of bicarbonate, as well as D-lactic acidosis, chronic inflammation, malnutrition, and drug toxicities, such as chronic corticosteroid administration, are all factors attributable to the underlying disease. Aluminium toxicity as a consequence of the highly contaminated amino acid solutions derived from caseine hydrolysis was the first reported PN-related pathogenetic factor. This no longer occurs with modern crystalline amino acid solutions. PN-induced hypercalciuria has been reported by cross-sectional studies which showed a positive correlation with the amount of infused amino acids, glucose, sodium and calcium. On the contrary, urinary calcium was negatively correlated with intravenous phosphate load. Calciuria 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 acid, can induce bone calcium reabsorption. A few studies suggested an impairment of PTH secretion due to iv 25-vitamin D infusion or an altered response to PTH due to iv calcium infusion. Deficiency or toxicity of micronutrients may interfere with bone metabolism; vitamin K, vitamin C, copper, fluoride, boron and silicon deficiency, and vitamin A, cadmium, strontium and vanadium toxicity, are all implicated. A direct role of PN in inducing the release and/or regulating the activity of cytokines known to impair bone metabolism has also been suggested.

Optimisation of parenteral mixtures for the prevention of metabolic bone disease is based on control of the nutrient infusion (7,53,54). Aluminium contamination should be less than 25 µg/L. The amounts of minerals given should aim to maintain both the normal serum concentrations and their 24-hour urinary excretion. A Ca : P ratio of 12 mEq (6mmol) to 32-45 mmol has been reported to decrease the renal calcium losses. Amino acids and sodium should not be added in amounts greater than losses because of the risk of sodium induced hypercalciuria. Acetate-containing mixtures are useful to avoid acidosis and to help maintain serum bicarbonate in the normal range. Abnormal vitamin D nutritional status should be corrected and then maintained to avoid osteomalacia. Restitution of MBD with iv biphosphonates (clodronate or pamidronate) has been described (57,58). Only anecdotal reports have been provided on recombinant PTH, whereas impressive early data suggest that intestinotrophic hormones, like growth hormone and glucagon-like peptide-2, may improve bone mineral density (53).

10. Indications for intestinal transplantation

The treatment options for irreversible intestinal failure (IF) are lifelong HPN or intestinal transplantation (ITx). The defining component of any ITx is the small intestine (jejunoileum). On the basis of the transplanted organs, three 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) multivisceral transplant, including stomach, pancreas, duodenum, (or some combination thereof) together with the jejunum and ileum with or without liver. (59)

Survival rates on HPN are still reported to be greater that after ITx, even though data from the International Transplant Registry show that both patient and graft survival have steadily improved over time. The most recent data from experienced centres indicate a roughly similar 1 year survival rate (60). Deaths related to HPN complications accounted for 5–20% of the total deaths in adults and 23–42% in children, whereas almost all the deaths after ITx were related to the treatment (sepsis 46.0%, graft rejection 11.2%, post-transplant lymphomas 6.2%, technical reasons 6.2%, graft-thrombosis 3.2%) (60). Graft failure requiring HPN or retransplantation may occur in about 25% of ITx recipients. A few studies, using non-specific tools, have compared the quality of life on HPN and after ITx. The results show that quality of life is improved after successful ITx (60).

On the basis of data on safety and efficacy, HPN is still considered the primary treatment for CIF. The USA Center for Medicare and Medicaid Services has approved the payment for ITx when one of the following conditions: categorized as HPN-failure and/or life-threatening states occur (33):

1a) Impending (total bilirubin above 3–6mg/dL / 54-108 \( \mu \)mol/L, progressive thrombocytopenia, and progressive splenomegaly), or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis) due to IF/PN associated liver disease (IF/PNALD)

1b) CVC-related thrombosis of ≥ 2 central veins

1c) 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

1d) Frequent episodes of severe dehydration despite intravenous fluids in addition to HPN

The American Society of Transplantation position-paper on paediatric intestinal transplantation considers as candidates for intestinal transplantation also those patients with a high risk of death or with a very poor quality of life on HPN (61). These conditions have been interpreted by the ESPEN Home Artificial Nutrition & Chronic Intestinal Failure special interest group (ESPEN HAN & CIF group) as follows (60):

2. High risk of death attributable to the underlying disease
   2a) Intra-abdominal invasive desmoid tumours
   2b) Congenital mucosal disorders
   2c) Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel < 10 cm in infants and < 20 cm in adults)

3. IF with high morbidity or low acceptance of HPN
   3a) Need for frequent hospitalization, narcotic dependency or inability to function
   3b) Patient’s unwillingness to accept long-term HPN

The above criteria for ITx are based on retrospective analyses of national and international registries, individual centre experience, and case reports (33). There is no doubt that patients developing liver failure are otherwise destined to die on HPN, and should be referred for combined liver-small bowel transplantation in a timely fashion. Indeed, the annual rate of death on the waiting list for ITx is higher than that on the waiting list for any other solid organ transplantation. This is mainly due to death occurring in patients waiting for combined small bowel and liver transplantation. Late consideration of ITx and lack of clarity of referral criteria have, historically, been part of the reason for this waiting list mortality (33). Also those with intra-abdominal invasive desmoids and congenital mucosal disease may eventually be at increased risk of death. The reasons in support of the other indications have been questioned (33). Evidence on the life-threatening nature of major CVC-related complications are weak. Recurrent episodes of dehydration may cause chronic renal failure requiring combined intestinal and renal transplantation, but it is not known at what point renal failure becomes a concern. Furthermore, many patients who undergo ITx develop renal failure, mainly due to the immunosuppressive treatment, whose degree is greater that that occurring after any other solid organ transplantation. Ultra-short bowel is a risk factor for the development of
IF/PNALD rather than death on HPN. The efficacy of ITx in improving the patient’s quality of life is not yet definitely proved. The ESPEN HAN & CIF group has evaluated the appropriateness of the above criteria carrying out a multicentre prospective survey in Europe, comparing 2 groups of patients on HPN for irreversible IF: a group of “non-candidates” for ITx, having neither indications nor contraindications for ITx, and a group of “candidates” who had an indication without a contraindication for ITx (60,62,63). The results: a) confirmed HPN as the primary maintenance therapy for IF; b) indicated IF/PNALD or intra-abdominal desmoids as the only conditions placing patients at significantly increased risk of death on HPN and being therefore clear indications for a timely life-saving ITx; c) indicated that CVC-related major complications as well as ultra-short bowel and congenital mucosal disease were not conditions posing a high risk of death on HPN, but could be indications for a preemptive/rehabilitative ITx, in a case-by-case approach to selected patients; d) The risk of death on HPN was greater in the early years of treatment and the causes of death on HPN were mainly underlying disease-related in the early years and mainly HPN-related in the late years of HPN, suggesting that in the early years of HPN a life-saving ITx could be required for some patients who are at higher risk of death related to their underlying disease. The results also strongly supported the recommendation, previously made by a special working group at the Xth International Small Bowel Transplantation Symposium held in 2007, for early referral to expert intestinal failure centres for all patients with IF, to devise the most appropriate treatment strategy (41). It was also recommended that: a) collaboration between care givers and intestinal rehabilitation centers should be initiated if PN requirements are anticipated to be more than 50% at 3 months from initiating therapy; b) IF programmes should include intestinal rehabilitation and ITx, or should have an active collaborative relationship with a centre that performs ITx; c) national registers for IF patients should be established and that participation of all prescribers of PN solutions should be expected.

11. Summary

- HPN metabolic complications are still frequent but they can be significantly decreased through present knowledge, expertise and continued attention.
- Most of the metabolic complications are multifactorial and interrelated.
- Nutrition support team input, education and a complete, but non-exclusive, HPN adapted to the type of intestinal failure, are together able to lower the rates of metabolic complications.
- Further understanding is needed, especially in HPN associated complications involving the kidneys, bone and liver, in order to prevent, ameliorate and cure.
- An early referral to an expert intestinal failure centre is recommended for all patients with intestinal failure, to devise the most appropriate treatment strategy, including medical treatment, home parenteral nutrition, non-transplant surgery, and a life-saving intestinal transplantation when indicated.

12. References:

1. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1SA-138SA.
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