

Review article: the management of long-term parenteral nutrition

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SUMMARY

Background

Home parenteral nutrition (HPN) is currently the management of choice for patients with chronic intestinal failure.

Aim

To summarise the major issues in delivering long-term parenteral nutrition (>3 months) and assess outcome as per complications, mortality and quality of life. To assess the evidence for the therapeutic use of trophic factors such as teduglutide and to review evolving therapeutic options in the treatment of chronic intestinal failure.

Methods

A literature search using PubMed and MEDLINE databases was performed.

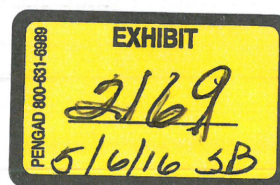
Results

Safe delivery of HPN relies upon individualised formulations of parenteral nutrition administered via carefully maintained central venous catheters by trained patients or carers, supported by a skilled multidisciplinary team. Early diagnosis and treatment of complications including catheter-associated blood stream infection (reported incidence 0.14–0.83 episodes/patient-year on HPN) and central venous thrombosis (reported incidence 0.03 episodes/patient-year) is important to minimise mortality and morbidity. There is a significant variation in the reported incidence of both hepatobiliary complications (19–75%) and advanced liver disease (0–50%). Five-year survival rates in large centres are reported between 60% and 78% with survival primarily related to underlying diagnosis. Long-term survival remains higher on HPN than with intestinal transplantation. The role of intestinal lengthening procedures is yet to be validated in adults.

Conclusions

Home parenteral nutrition delivered by skilled nutrition teams has low incidences of catheter-related complications. Most deaths relate to the underlying disease. Therapies such as teduglutide and small bowel transplantation appear promising, but home parenteral nutrition appears likely to remain the bedrock of management in the near term.

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INTRODUCTION

Parenteral nutrition (PN) was first pioneered in the late 1940s for patients intolerant of, or not receiving adequate nutrition via the enteral route.^{1, 2} This was an essential medical development, as it had been recognised, over a decade earlier, that malnutrition was associated with a poor clinical outcome.³ As practice evolved, an increasing number of malnourished patients received PN in the hospital setting, and it was not until the 1970s that patients could be managed at home on a long-term basis.⁴

Currently, PN has become the mainstay of managing patients with intestinal failure (IF), a term first coined in 1981 as 'a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients'.⁵ IF can be further subclassified into three types to take into account the duration or severity of the disease process⁶:

Type 1 IF is self-limiting IF that occurs following abdominal surgery, whereby patients require fluid, electrolyte, enteral and/or parenteral nutritional support for a limited period of time, before making a full recovery without complication.

Type 2 IF occurs in severely ill patients, who develop septic, metabolic and nutritional complications following gastrointestinal surgery. These patients need multidisciplinary input and nutritional support to permit recovery.

Type 3 is chronic IF requiring long-term nutritional support; usually home parenteral nutrition (HPN), but also surgical procedures such as intestinal lengthening and transplantation.

Type 1 IF is relatively common: the recent National Confidential Enquiry into Patient Outcome and Death (NCEPOD), into the care of hospital patients receiving PN support, identified that 93% of patients in hospitals throughout the UK received PN for <30 days, with the majority of these patients needing nutritional support as a result of postsurgical complications.⁷ By contrast, and fortunately, the more severe types 2 and 3 IF are less common. The annual British artificial nutrition survey (BANS) reported that 624 adult patients with IF were receiving HPN in 2010.⁸

METHODS

A PubMed search was performed looking for English language only papers. The following search terms were used alone or in combination: (total) parenteral nutrition, (T)PN, intravenous nutrition, (total) parenteral nutrition AND hepatic/liver/bone/renal/metabolic complications, intestinal failure, intestinal transplantation,

short bowel syndrome AND trophic factors/GLP-2, IGF-1, EGF, (total) parenteral nutrition AND central venous line/catheter/ (total) parenteral nutrition AND line/ catheter sepsis/thrombosis/ mechanical complications/ problem, (total) parenteral nutrition AND outcome/wean/ quality of life/survival, fistuloclysis, intestinal adaptation, autologous intestinal reconstruction AND Bianchi/ STEP. Long-term parenteral nutrition was defined as a period of >3 months.

INDICATIONS FOR LONG-TERM PN

A significant proportion (around 50%) of patients with type 2 IF will go on to develop type 3 IF and require long-term PN.⁶ Some patients will develop type 3 IF *de novo* without preexisting type 2 IF; for example, patients with dysmotility (e.g. systemic sclerosis) or radiation enteritis, who have not undergone previous intestinal surgery, may become dependent on HPN after a prolonged period of nutritional impairment that cannot be managed via the enteral route. In the UK, Crohn's disease, intestinal ischaemia and surgical complications account for the bulk of underlying pathologies of patients requiring HPN (Figure 1).⁹ Data from other European and Canadian centres would seem to suggest similar aetiologies,^{10, 11} whereas a diagnosis of cancer forms a principle indication for HPN in the USA (42%) and Japan (40%).^{12, 13} Patients with active cancer received PN for the indications of malignant small bowel obstruction, short bowel syndrome or high output fistulae.¹⁴

PARENTERAL NUTRITION FORMULATIONS

Parenteral nutrition requirements – protein, calories, electrolytes, vitamins and micronutrients and fluid – are tailored to the individual patient's need. Historically, PN feeds consisted of multiple bottles of different nutrients, with trace elements added as necessary to minimise degradation or precipitation; this meant that the patient had to connect multiple bottles of PN per day.¹⁵ Modern nutritive mixtures can now be compounded in single bags (called 'all-in-one') or, sometimes, in 'bipartite' bags (the second compartment for a lipid emulsion is opened and mixed with other compounds before infusion). PN formulations contain both essential and non-essential amino acids with a reduced infusion volume achieved using amino acids with nitrogen contents above 18 g/L. The primary energy source in PN formulations can be derived either from a combined carbohydrate and fat emulsion administered together or from separate glucose and fat PN formulations administered on different days.¹⁶

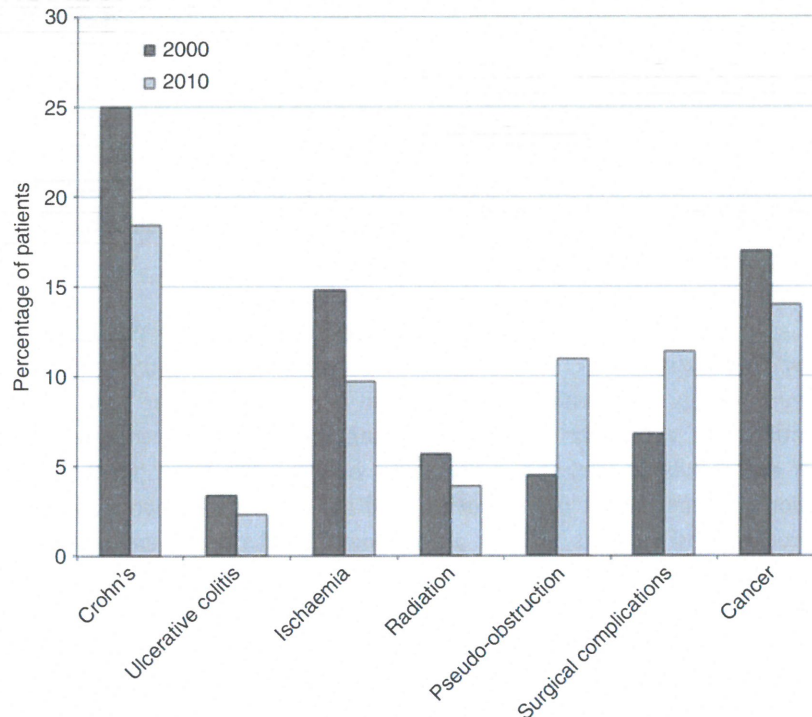


Figure 1 | The changing aetiology of type 3 Intestinal failure in the 21st century. Data adapted from the BANS report 2010/11 (used with permission).

Lipid emulsions were initially from soybean oil, which contains relatively high levels of omega-6 essential fatty acids and may be associated with hepatotoxicity (see below).¹⁷ Newer preparations containing long and medium chain triglycerides with a more physiological balance of omega 3 and 6 fatty acids have since been created.¹⁸ An example of such a preparation is SMOFlipid, an emulsion containing soya bean, medium chain triglycerides, olive and fish oil, yielding an improved ratio of omega 3 and 6 fatty acids, which, in the acute, post-operative setting, has been associated with a better hepatic tolerance and reduced length of hospital stay.¹⁹ Further evidence is needed to assess the advantages and disadvantages of alternative lipid emulsions in longer term HPN.

Electrolytes can be delivered either in commercially available carbohydrate and amino acid solutions or may be added to PN formulations to meet individual requirements. Commercial preparations of appropriate amounts of trace elements and multivitamins can also be added to lipid, glucose or electrolyte preparations. Drug additions are not recommended given the complexity of PN solutions, although heparin is sometimes added to glucose-based PN formulations to reduce the thrombotic risk of hyper-osmolar solutions.^{20, 21}

Stability and storage

Stability of the PN formulation is paramount, as degradation of components can result in lack of sufficient nutrient provision or even in the production of potentially toxic degradation products. PN formulations should be designed to minimise the risk of precipitation, destabilisation and degradation. Precipitation may be affected by solution pH, type of amino acids and phosphates, trace element concentrations and temperature.²¹ Once compounded, the stability of the PN solution is prolonged significantly by refrigeration.²² Fat emulsions can also be destabilised by the addition of electrolytes, which may neutralise the negative charge on the emulsion surface, leading to precipitation and creation of a cream layer.²³ Furthermore, lipid emulsions are thermodynamically unstable; destabilisation of lipid emulsions is characterised by formation of increasing sizes of lipid droplets and sizes above 5 μm may lead to embolic complications.²³ Therefore, PN mixtures should be visually inspected for lipid emulsion coalescence, as well as calcium phosphate precipitates, prior to use.²¹

The addition of vitamins to PN mixtures may accelerate chemical degradation, including vitamin C oxidation, vitamin B1 reduction and vitamin A and E photodegradation.

tion, each of which will reduce shelf life.²⁴ Because of this, some patients will opt to add vitamins themselves to their HPN bags immediately before use, to increase their PN bag shelf life and reduce the frequency of PN deliveries to their homes. Vitamin C oxidation can be minimised using ethyl vinyl multilayered bags, which prevent oxygen influx,²⁵ whereas photodegradation can be minimised by covering bags and giving sets from sunlight and/or administering HPN at night and away from windows.²⁴

Timing and frequency of PN infusion

The amount of intravenous energy and protein that a patient requires is determined by a number of factors, such as body mass index and metabolic rate, and is balanced against any nutrition that the patient may absorb via the oral or enteral route. Most patients will eat as much as their disease or their faecal losses will allow. Fluid and electrolyte requirements, on the other hand, are principally determined by gastrointestinal losses. The patient with a high output proximal small bowel stoma or fistula will have excessive fluid losses and such patients usually have to receive nightly intravenous infusions. On the other hand, the patient who still has his/her colon in continuity with small bowel will usually have lower intravenous fluid requirements due to the ability of their colon to absorb water and electrolytes and consequently will be able to have at least one night/week without the need for PN.

Shorter infusion durations are associated with lower rates of thrombophlebitis in animal models²⁶ and shorter infusion periods may, of course, also improve patients' quality of life (QoL). Consequently, infusion times are reduced to the minimum tolerated and interference with daily living limited by nocturnal administration where possible.

INTRAVENOUS FEEDING CATHETERS

Establishing a suitable and reliable long-term intravenous feeding catheter is imperative for HPN delivery. Expert practitioners achieve best safe catheter insertion in an aseptic environment. Image guidance with real time ultrasound has been shown in several meta-analyses to be associated with both reduced procedure failure rates (RR: 0.14–0.32) and reduced complication rates (RR: 0.22) and is recommended by the National Institute of Clinical Excellence.^{27–30} Around 2% chlorhexidine is preferred for skin preparation prior to procedure as this demonstrated lower catheter-related infection rates (2.7 per 100 catheters) than either alcohol- or iodine-based solutions (7.1 and 9.3 per 100 catheter insertions $P = 0.02$).³¹ There is

currently no evidence to support the use of preprocedural antibiotics. A meta-analysis of five RCTs and 530 catheter insertions has demonstrated an increased risk of bloodstream infections in catheters with more than one lumen (odds ratio, 2.58; 95% CI, 1.24–5.37; number needed to treat, 19); therefore, most centres would advocate single lumen catheters where possible.³²

Vascular access

Achieving long-term vascular access requires placement of a central venous catheter (CVC) in either the subclavian or internal jugular vein.¹⁶ CVCs are usually placed using the Seldinger technique, positioning the catheter tip between the lower third of the superior vena cava and the atrio-caval junction, a site that is associated with a lower incidence of venous thrombosis ($P \leq 0.0005$).³³ CVCs are best tunnelled or implanted subcutaneously for long-term use to minimise the risk of displacement: 'Hickman' or 'Broviac' single lumen CVCs are tunnelled subcutaneously to an external site and secured in place with an internal cuff, while 'portacaths' are implanted and terminate in a subcutaneous reservoir. The choice between tunnelled lines and ports will be determined by patient choice and nursing staff experience: ports will certainly be less attractive if the patient requires frequent access due to the repeated skin puncture required.¹⁶

Peripherally inserted central venous catheters (PICCs) and peripheral midline catheters are also used for PN administration, but the higher risk of displacement and/or thrombosis inherent to these lines usually limits their use to 2–3 months.^{34, 35} Furthermore, PICC lines also tend to be unsuitable for long-term HPN as patients find them difficult to self-access as they are sited in the antecubital fossa or upper arm. Some practitioners advocate the use of arteriovenous fistulae to administer long-term PN, with recent experience suggesting very low infection, but high occlusion rates.³⁶

When standard neck central venous access approaches have failed due to venous thrombosis and/or stenosis, the femoral approach can be considered although the risk of bacterial contamination is high.³⁷ Beyond this, translumbar, transhepatic and transcatheter catheter placements have been described.^{38, 39} Patients with threatened loss of vascular access should be considered early for intestinal transplantation (ITx) as loss of access may preclude ITx.

Catheter care

Aseptic care of CVCs for patients with IF is mandatory. Any patient with type 2 IF requiring PN could progress

to type 3 IF, and therefore maintaining sustainable venous access is vital. Stringent adherence to catheter care protocols reduces CVC sepsis and thrombosis, so prolonging CVC viability.⁴⁰ These protocols are key to the success of all HPN programmes.

Catheter training and care exemplifies the importance of the multidisciplinary IF team, with the patient at the centre, in achieving a successful HPN programme. The core of any IF team consists of medical doctors with an interest in nutrition, nursing staff with extensive experience of PN, dieticians and clinical pharmacists.¹⁶ In addition, the team receives dedicated input from psychology, biochemistry, microbiology, occupational therapy and physiotherapy colleagues. Telephone and videoconferences have been explored as ways of streamlining lines of support for patients and their carers to ensure that catheter care is optimised.^{41, 42} Limited available evidence from retrospective studies suggests that PN management by dedicated teams with clear management protocols is associated with lower catheter complications rates and perhaps lower overall costs.^{43–45}

COMPLICATIONS OF LONG-TERM PN

Catheter-related problems

Catheter infection. Central venous catheter-related sepsis rates are a surrogate measure of overall quality of catheter care.⁴⁵ Complications in patients with type 3 IF can be devastating with sepsis-related mortality being reported to be as high as 30% in one French series, half of which originate from infected CVCs.⁴⁶ CVC-related sepsis rates have recently been variably reported as 0.14–0.83 episodes/patient-year.^{47–51}

As outlined above, maintaining low sepsis rates requires careful catheter care protocols, with multiple studies reiterating the importance of a multidisciplinary nutrition support team in reducing CVC-related sepsis.^{45, 52–54} The patient is key to minimising CVC-related sepsis rates at home. While patients accessing their line more frequently during the week may be at higher risk than those who receive PN less frequently,⁵⁵ with approximately 20% of patients on HPN are responsible for around 75% of the total number of CVC-related sepsis episodes.⁴⁷ It remains to be seen if this increased risk is in part linked to the bacterial skin and/or nasal ecosystem and/or to patient behaviour.⁵⁶ Antimicrobial (taurolidine) flush solutions and antibiotic lock techniques have been proposed for patients with recurrent CVC infections.^{57, 58} A recent randomised study of 30 patients found taurolidine lock to be highly effective in

reducing subsequent CVC infection with a mean infection-free survival of 175 days compared with 641 days with the introduction of taurolidine locks ($P \geq 0.0001$).⁵⁹ The use of antimicrobial locks should not, however, be considered a substitute for meticulous catheter care.

Patients with CVC infections usually present with symptoms and signs such as pyrexia and tachycardia during infusion. However, this may not always be the case and a high index of suspicion for CVC sepsis is required in a patient with IF who may display other features of infection; in a retrospective case series of 37 line infections, 13/37 episodes of catheter-related sepsis did not present with a pyrexia and; while most patients displayed an elevated C-reactive protein, less than a third had a raised blood white cell count.⁶⁰ Other pointers to CVC-related sepsis may be a low albumin or raised bilirubin.⁶⁰

As catheter maintenance is crucial to HPN patients and repeated catheter removal/re-insertion can lead to loss of venous access, it is recommended to attempt salvage of an infected tunnelled CVC wherever possible.⁴⁰ Clearly, if the patient is too unwell with CVC-associated sepsis with signs of shock, then the catheter should be removed immediately. Otherwise, if CVC-related sepsis is suspected, then line use should be discontinued and peripheral and central cultures taken while antimicrobial therapy (as per local policy) is commenced pending culture results. A recent systematic review demonstrated that Coagulase negative *Staphylococcus*, *S. epidermis epidermis* or other staphylococci was the causative agent in 378/759 (50%) episodes of CVC-associated sepsis, with *Staphylococcus aureus*, gram-negative and polymicrobial infections accounting for the majority of the remainder.^{47, 60–62} Small retrospective studies have shown that catheter salvage can be obtained in up to 95% of CVCs in the context of a coagulase-negative staphylococcal infection using standard antibiotic protocols, compared with 65% of catheters infected with other organisms.⁶⁰ Catheter salvage is rarely, if ever, possible in the presence of fungal line sepsis.

Catheter infection is not limited to the catheter lumen, but can occur within the catheter exit site and/or subcutaneous tunnel. Exit site infections manifest as erythema, tenderness and sometimes discharge and can usually be successfully treated with a combination of systemic antibiotics together with antimicrobial dressings. Tunnel infections, however, usually require line removal.

Catheter occlusion

Central venous catheters may be occluded by fibrin and/or lipid deposits, with an incidence in the HPN population

of 0.07 episodes/year.^{55, 63} Such deposits often act as a one-way valve allowing PN infusion, but preventing blood withdrawal. Complete occlusion can result if a sluggish line remains unattended, often necessitating line removal.⁶⁴ Fibrin occlusions can be resolved by locking the catheter with urokinase or recombinant tissue plasminogen activator,^{65–67} while lipid occlusions can be minimised by flushing the CVC with saline before and after lipid infusion and treated, once developed, using a 70% ethanol line lock.⁶⁸ Endoluminal brushing of occluded CVCs has been shown to be more effective at catheter clearance than urokinase locks, although these brushes are no longer available in the UK.⁶⁴

Central venous thrombosis

Catheter-associated central vein thrombosis may occur at a rate of between 0.01 and 0.03 episodes per catheter year,^{63, 69, 70} and is positively correlated with CVC-related sepsis episodes.⁷¹ There is no clear evidence that all patients requiring HPN should receive prophylactic anticoagulation to prevent line thrombosis, unless at underlying high risk.^{16, 72–74} The role of heparin flushes to prevent catheter-related thrombosis remains unclear, and may be associated with an increased risk of line infection; furthermore, long-term heparin administration carries the inherent risk of osteoporosis and hair loss, as well as the risk of lipid precipitation if mixed with a lipid emulsion – therefore, currently saline flushing is recommended.¹⁶

Patients with diagnosed venous thrombosis may be considered for thrombolytic therapy or thrombectomy if diagnosed early and all patients should be screened for thrombophilic risk and receive anticoagulation therapy (low molecular weight heparin or warfarin depending on the patient's intestinal absorptive ability).⁴⁰ If venous thrombosis is associated with CVC sepsis, then the line will likely have to be removed; otherwise, the decision to remove the catheter depends on patency: if intravenous infusion is impossible or induces pain or swelling, then the nonfunctioning catheter has to be removed, but if flow is unimpeded, the catheter can be maintained as CVC lifespan will not necessarily be impaired if the patient is anticoagulated.⁷⁵

Mechanical problems

Mechanical problems due to catheter displacement or fracture can lead to malfunction. This can be assessed using a radio-opaque dye study and salvaged by repositioning or repair.⁷⁶ Tunnelling catheters cuffs to at least 2.5 cm reduces the risk of displacement,^{40, 77} but exit

site sutures increase the risk of catheter contamination and are not advised. Complete catheter fracture has rarely been reported and warrants emergency removal of all parts.^{78, 79}

METABOLIC COMPLICATIONS

Renal complications

Patients with short bowel syndrome on long-term PN are at risk of nephrolithiasis. This is particularly true for patients with a short bowel and retained colon (jejunocolonic anastomosis), who are at increased risk of calcium oxalate stones, with almost a quarter of developing associated symptoms,⁸⁰ although asymptomatic decline in renal function is not uncommon.⁸¹ Clearly, all patients with a short bowel are at risk of dehydration, which compounds the risk of nephrolithiasis, but in patients with a jejunocolonic anastomosis, unabsorbed fatty acids in the short bowel will preferentially bind to calcium rather than oxalate; the latter is then absorbed in the colon leading to high urinary levels and an increased risk of calcium oxalate stone formation.⁸⁰ Patients with a short bowel and a retained colon, who are able to eat, should therefore consume a diet low in oxalate.

Liver disease

Hepatobiliary complications occur in patients on long-term PN with a reported incidence of between 19% and 75%.^{17, 82–85} The incidence of advanced liver disease (fibrosis or cirrhosis) varies between 0% and 50% of patients in retrospective cohorts on long-term PN, with an associated reported mortality rate of up to 22%.^{17, 82–85} This discrepancy in the incidence in severe liver disease between different patient cohorts may reflect an increased use of parenteral lipid predisposing to higher rates of severe liver disease.¹⁷ Patients with ultra-short bowel (<50 cm) are at greatest risk of severe liver disease, which this may, of course, reflect their greater calorie requirement.¹⁷

The term intestinal failure-associated liver disease (IFALD) has broadly replaced the use of PN-associated liver disease. The aetiology of IFALD is broad and not limited solely to PN, but often has multiple aetiological contributing factors.⁸⁶

Nonnutritive causes of IFALD

Patients receiving PN with abnormal liver function test should be assessed and treated for nonnutritive-related abnormalities such as drugs, sepsis, biliary obstruction, bacterial overgrowth, hepatotoxic medications and

underlying intrinsic liver disease, while evaluating nutrient-related factors.⁸⁶ Sepsis is a common cause of liver function test abnormalities in IF and should be actively sought and treated.^{87, 88} Biliary stone formation is common in patients needing long-term PN, with up to 38% of patients having ultrasonographic evidence of cholelithiasis after 2 years.⁸⁹ Stone formation is significantly more likely in patients who have minimal oral intake, which likely relates to TPN-associated alterations in bile acidification as well as reduced gallbladder contraction.^{90, 91} Various pharmacological treatments have been proposed to prevent biliary stone formation with limited clinical benefit, including cholecystokinin, pulsed amino acids, nonsteroidal antiinflammatory drugs, metronidazole and cisapride.^{92–96} Prophylactic cholecystectomy has been proposed at the time of the last intestinal resection particularly in patients with an intestinal remnant <120 cm and an absent ileocaecal junction.⁹⁷

Nutrient-related causes of IFALD

Both parenteral nutrient toxicity and parenteral nutrient deficiency have been implicated as possible causes of IFALD. Nutrient toxicity has been documented as a result of excess calories (either lipid or glucose based), phytosterols, manganese and aluminium toxicity. Nutrient deficiencies identified as causes of IFALD include essential fatty acids, choline, taurine and carnitine.^{98–102}

Care should be taken to ensure that patients receiving PN receive the correct daily amount of both calories (25–35 kcal/kg) and protein (0.8–1.5 g/kg) as both malnutrition and overfeeding can lead to steatosis.^{100, 103} Steatosis is the commonest initial histological finding in liver disease associated with PN, followed by later by the development of persistent intrahepatic cholestasis, fibrosis and cirrhosis.¹⁷ A recent retrospective histological study demonstrated a 58% incidence of steatosis in 36 predominantly adult patients who underwent a liver biopsy while on TPN for abnormal liver function tests.¹⁰⁴ Cholestatic complications have long been noted to be associated with higher lipid contents and, particularly, a parenteral lipid intake >1 g/kg of body weight per day.^{17, 98} Lipid emulsions containing a mixture of long-chain and medium-chain triacylglycerol, high monounsaturated fatty acid content emulsions and fish oil emulsions may reduce the risk of cholestatic complications compared with soybean-based emulsions.^{105, 106} Maintaining oral/enteral nutrition and cyclical administration of PN have both been shown to attenuate liver dysfunction and are routinely recommended wherever possible.¹⁰⁷

Pharmacological treatments

Pharmacological treatments for cholestasis including ursodeoxycholic acid, parenteral choline and taurine have a limited evidence base in adult patients needing HPN, although have been explored in the paediatric population.^{108–111} Orally ingested methionine is converted to choline and taurine via hepatic trans-sulphuration pathways; however, when methionine is administered parenterally to the systemic circulation rather than to the portal circulation, it is transaminated to mercaptans, reducing the synthesis of these metabolites. Deficiencies of both taurine and choline have been documented in small ($n \leq 50$) retrospective studies of patients receiving long-term HPN and are associated with increased biochemical markers of liver function.^{101, 102, 112} A study of 10 adult patients with short bowel syndrome receiving taurine supplementation did not show an improvement in cholestasis, although a significant improvement in AST (from $2.3 \times$ ULN to 1.3 ULN $P \geq 0.02$) was seen.¹¹² Parenteral choline supplementation perhaps shows the most promise in the adults on HPN, with a small study of 15 patients suggesting significant improvements in liver enzyme function (ALT/AST/alkaline phosphatase) and hepatic steatosis (non-invasively measured by liver computed tomography).¹⁰¹

Osteopathy

Metabolic bone disease has long been associated with HPN administration.¹¹³ Historically, PN formulations containing high levels of aluminium were a significant cause of bone disease until aluminium was removed from PN formulations in the 1980s.^{99, 114} Most cases of PN-associated metabolic bone disease now relate to abnormalities in the handling of calcium, phosphorus, vitamins D and K as well as underlying medical conditions such as Crohn's disease.^{115, 116} Metabolic bone disease remains a significant problem with 41–46% of HPN patients reported to have established osteoporosis on bone densitometry.^{115, 117}

Patients needing HPN should undergo surveillance for metabolic bone disease, and appropriate measures taken to correct vitamin D deficiency and address any evidence of osteopaenia or osteoporosis. Adequate administration of calcium and phosphate in TPN solutions is essential for skeletal health,¹¹⁸ while metabolic acidosis should be excluded in patients with a short bowel, as this can impair vitamin D metabolism and directly affect bone-buffering systems.¹¹⁶ General measures such as hormone replacement therapy in postmenopausal women and regular exercise are also recommended, although their

benefits in patients on long-term PN have yet to be evaluated. Bisphosphonate therapy may have to be administered parenterally if there is a question of impaired drug absorption in a patient with IF. The role of glucagon-like peptide 2 (GLP-2) in attenuating bone loss has been evaluated in patients with short bowel; however, recent evidence suggests no significant reduction in bone resorption after 2 months of therapy.^{119, 120}

OUTCOME OF LONG-TERM PN

Weaning from Long-term PN

The amount of functioning small bowel is clearly paramount in determining whether a patient will ultimately require long-term PN support; in general, patients with <75–100 cm of healthy small bowel to an end-enterostomy tend to require long-term parenteral fluid and/or protein-energy support.^{46, 121} The presence of a retained colon (jejunocolonic anastomosis) may allow patients to remain nutritionally autonomous with shorter lengths (sometimes <60 cm) of small intestine.^{46, 121} However, the length of residual small bowel only offers a relatively crude prediction of nutritional autonomy and, long-term PN dependency will also, of course, be determined by the presence of intestinal disease.^{46, 121} Although it may be difficult to predict exactly whether an individual patient with IF will need long-term PN support, plasma citrulline

levels may be a useful biomarker of small bowel mass and function, reflecting absorptive capacity.¹²² In an observational study of 57 patients, a plasma citrulline level of <20 $\mu\text{mol/L}$ predicted the development of permanent IF with a sensitivity of 92% and specificity of 90%.^{122, 123}

A retrospective European study assessing 124 patients receiving HPN demonstrated that the probability of weaning patients from HPN is <6% if not successfully undertaken in the first 2 years following the last digestive tract modification, ostensibly because the chance of intestinal adaptation thereafter is minimal.⁴⁶ Current work evaluating the role of trophic factors aimed at promoting intestinal adaptation that holds some promise; these include both nutrient (e.g. enteral delivery of saturated fatty acids,^{124, 125} dietary carbohydrates,¹²⁶ glutamine¹²⁷ and ornithine¹²⁸) and nonnutrient factors (e.g. growth hormone,^{129–136} epidermal growth factor,¹³⁷ insulin-like growth factor,^{138–140} keratinocyte growth factor,¹⁴¹ leptin¹⁴² and GLP-1¹⁴³ and -2.^{144–147} Growth hormone (Table 1) and GLP-2 (Table 2) have perhaps been studied in the most detail. Growth hormone was first proposed as a therapeutic modality by Byrne in 1995 with an open-label trial. This appeared to demonstrate a benefit to intestinal adaptation in 10 short bowel syndrome patients on long-term PN.¹³¹ The use of growth hormone in intestinal adaptation has been the subject of a Cochrane review, which includes five RCTs

Table 1 | Trials of growth hormone \pm glutamine in short bowel syndrome

Factor	Patient numbers	Design	SB length (cm), mean (range)	Outcomes ($P \geq 0.05$)	Reference
Growth hormone (0.05 mg/kg)	12	Double-blind 2 \times 3 week crossover	48 (ND)	Increased weight Increased lean body mass	129
Growth hormone (0.09 mg/kg)	61	Open (variable length of therapy)	ND (0–183)	No control group	130
Growth hormone (0.14 mg/kg)	47	Open (up to 4 weeks therapy)	50 (0–240)	Short-term improvement in protein absorption Decreased faecal losses	131
Growth hormone (0.6 mg/kg)	37	Open	45 (15–100)	No control group	132
Growth hormone (0.1 mg/kg)	41	Double-blind 4-week treatment	ND	Reduction in PN volume	133
Growth hormone (0.024 mg/kg)	10	Double-blind 2 \times 8 week crossover	130 (90–170)	Increased body weight Increased lean body mass	134
Growth hormone (0.63 mg/kg)	8	Double-blind 2 \times 6 week crossover	71 (55–120)	Increased body weight Increased lean body mass	135
Growth hormone (0.14 mg/kg)	8	Double-blind 2 \times 4 week crossover	100 (30–150)	No significant change in energy and nitrogen absorption	136