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e-SPEN guideline

ESPEN guidelines on chronic intestinal failure in adults

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SUMMARY

Background & aims: Chronic Intestinal Failure (CIF) is the long-lasting reduction of gut function, below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth. CIF is the rarest organ failure. Home parenteral nutrition (HPN) is the primary treatment for CIF. No guidelines (GLs) have been developed that address the global management of CIF. These GLs have been devised to generate comprehensive recommendations for safe and effective management of adult patients with CIF.
Methods: The GLs were developed by the Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. The GRADE system was used for assigning strength of evidence. Recommendations were discussed, submitted to Delphi rounds, and accepted in an online survey of ESPEN members.
Results: The following topics were addressed: management of HPN; parenteral nutrition formulation; intestinal rehabilitation, medical therapies, and non-transplant surgery, for short bowel syndrome, chronic intestinal pseudo-obstruction, and radiation enteritis; intestinal transplantation; prevention/treatment of CVC-related infection, CVC-related occlusion/thrombosis; intestinal failure-associated liver disease, gallbladder sludge and stones, renal failure and metabolic bone disease. Literature search provided 623 full papers. Only 12% were controlled studies or meta-analyses. A total of 112 recommendations are given: grade of evidence, very low for 51%, low for 39%, moderate for 8%, and high for 2%; strength of recommendation: strong for 63%, weak for 37%.
Conclusions: CIF management requires complex technologies, multidisciplinary and multiprofessional activity, and expertise to care for both the underlying gastrointestinal disease and to provide HPN support. The rarity of the condition impairs the development of RCTs. As a consequence, most of the recommendations have a low or very low grade of evidence. However, two-thirds of the recommendations are considered strong. Specialized management and organization underpin these recommendations.

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Abbreviations

A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
AuSPEN	Australasian Society of Parenteral and Enteral Nutrition
AVF	arteriovenous fistula
BMD	bone mineral density
CDC	Centers for Disease Control and Prevention
CDDS	color doppler duplex sonography
CIF	chronic intestinal failure
CIPO	chronic intestinal pseudo-obstruction
CRBSI	catheter-related bloodstream infection
CRI	catheter-related infection
CRVT	catheter-related vein thrombosis
CT	computed tomography
CTE	controlled tissue expansion
CVC	central venous catheter
DEXA	dual-energy X-ray absorptiometry
EFA	essential fatty acid
EFAD	essential fatty acid deficiency
ELT	ethanol locking therapy
ESPEN	European Society for Clinical Nutrition and Metabolism
GH	growth hormone
GLP-2	glucagon-like peptide-2
HAN&CIF	Home Artificial Nutrition and Chronic Intestinal Failure
HPEN	home parenteral and enteral nutrition
HPN	home parenteral nutrition
ICU	intensive care unit
IF	intestinal failure
IFALD	intestinal failure-associated liver disease
ITx	intestinal transplantation
IVS	intravenous supplementation
LCT	long-chain triglyceride
LILT	longitudinal intestinal lengthening and tailoring
LMWH	low molecular weight heparin
MBD	metabolic bone disease
MCT	medium-chain triglyceride
MMC	migrating motor complex
MRI	magnetic resonance imaging
ORS	oral rehydration solution
PICC	peripherally inserted central venous catheter
PN	parenteral nutrition
PPI	proton-pump inhibitors
PUFA	polyunsaturated fatty acids
QoL	quality of life
RCT	randomized controlled trial
RE	radiation enteritis
SBS	short bowel syndrome
SCFAs	short chain fatty acids
SRSB	segmental reversal of the small bowel
STEP	serial transverse enteroplasty
SVC	superior vena cava

1. Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) has recently published the recommendations on the "definition and classification of intestinal failure in adults" [1], devised by its two "special interest groups" devoted to intestinal failure (IF), "the home artificial nutrition and chronic intestinal failure group (HAN&CIF)" and the "acute intestinal failure group". The recommendations comprise the definition of IF, functional and pathophysiological classifications for both acute and chronic IF and a clinical classification for chronic IF (Table 1), endorsing a common language to facilitate communication and cooperation among professionals in clinical practice, organization, management, and research.

After reviewing the original definition from Fleming and Remington [2] and the proposed changes from other authors, IF was defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth". The term "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning) was proposed to define the reduction of gut absorptive function that doesn't require IVS to maintain health and/or growth [1]. According to the definition, two criteria must be simultaneously present to diagnose IF: a "decreased absorption of macronutrients and/or water and electrolytes due to a loss of gut function" and the "need for IVS". This implies that the definition of IF precludes IVS as being considered synonymous with IF, and so excludes patients receiving IVS associated with normal intestinal absorptive function, such as those with disease-related hypophagia, anorexia nervosa, impaired swallowing or dysphagia, or those who refuse otherwise effective enteral nutrition.

The "functional classification" was based on onset, metabolic, and expected outcome criteria, as originally proposed by Shaffer [3]:

- Type I – an acute, short-term and usually self-limiting condition.

This is a common feature, occurring in the perioperative setting after abdominal surgery and/or in association with critical illnesses, where patients require IVS over a period of days or a few weeks.

- Type II – a prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and IVS over periods of weeks or months.

This is an uncommon clinical condition accompanied by septic, metabolic and complex nutritional complications, most often seen in the setting of an intra-abdominal catastrophe. It is often an acute event, occurring in a previously healthy subject (e.g. mesenteric ischaemia, volvulus, or abdominal trauma) or complicating intestinal surgery and necessitating massive enterectomy and/or resulting in one or more enterocutaneous fistulae. Less frequently, it may occur following a complication of type III chronic IF (see below), representing "acute on chronic" IF. These patients often need the facilities of an intensive care or high dependency unit and always need to be managed by a multi-professional specialist IF team during their stay in the hospital.

- Type III – a chronic condition, in metabolically stable patients, who require IVS over months or years. It may be reversible or irreversible.

Chronic intestinal failure (CIF) may evolve following type II acute IF, may be the result of progressive and devastating

Table 1
ESPEN recommendations: definition and classification of intestinal failure.

Definition

Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.

The reduction of gut absorptive function that doesn't require any intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency" (or deficiency).

Functional classification

On the basis of onset, metabolic, and expected outcome criteria, IF is classified as:

- Type I – acute, short-term, and often self-limiting condition
- Type II – prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
- Type III – chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible.

Pathophysiological classification

IF can be classified into five major pathophysiological conditions, which may originate from various gastrointestinal or systemic diseases:

- Short bowel
- Intestinal fistula
- Intestinal dysmotility
- Mechanical obstruction
- Extensive small bowel mucosal disease

Clinical classification of chronic Intestinal failure

On the basis of the energy and the volume of the required intravenous supplementation, IF is categorized into 16 combinations

IV energy supplementation[b] (kcal/Kg body weight)	Volume of IV supplementation[a] (mL) ≤1000 [1]	1001–2000 [2]	2001–3000 [3]	>3000 [4]
0 (A)	A1	A2	A3	A4
1–10 (B)	B1	B2	B3	B4
11–20 (C)	C1	C2	C3	C4
>20 (D)	D1	D2	D3	D4

[a] Calculated as daily mean of the total volume infused per week = (volume per day of infusion × number of infusions per week)/7.
[b] Calculated as daily mean the total energy infused per week = (energy per day of infusion × number of infusions per week)/7/Kg.

gastrointestinal or systemic benign diseases, the main clinical feature of congenital digestive diseases, or the end stage of intra-abdominal or pelvic cancer. Intravenous supplementation is required for a long period or for the rest of the patient's life. Such patients are metabolically stable and they and/or their relatives are trained to become independent in managing IVS at home (home parenteral nutrition, HPN).

The "pathophysiological classification" of IF has identified five major conditions, which may originate from various gastrointestinal or systemic diseases: short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction, and extensive small bowel mucosal disease. In the case of a short bowel, an enterocutaneous fistula, or extensive small bowel disease, the primary mechanism of IF is the malabsorption of the ingested food, due to a reduction or bypass of the absorptive mucosal surface. In the case of intestinal dysmotility or an intestinal mechanical obstruction, the primary mechanism is the restriction of oral/enteral nutrition as a result of feed-related exacerbation of digestive symptoms or of episodes of mechanical or non-mechanical intestinal obstruction. Besides these primary mechanisms, several concomitant pathophysiological mechanisms may contribute to the severity of IF in the individual patient. These consist of increased intestinal secretion of fluids and electrolytes in obstructed or dilated segments, intestinal loss of fluids and electrolytes with vomiting or gastric drainage, disease-related hypophagia, accelerated gastrointestinal transit time, small bowel bacterial overgrowth, and increased metabolic demand related to concomitant sepsis and inflammation.

A short bowel may occur as a result of extensive surgical resection or of congenital diseases of the small intestine. The clinical condition associated with the remaining small bowel in continuity (even though the total small bowel length including that bypassed may be normal) of less than 200 cm is defined as short bowel syndrome (SBS). Depending on the anatomy of the remnant bowel, three categories of SBS are identified: end-jejunostomy with no colon in continuity, jejunocolic anastomosis with no ileo-cecal valve and a part of the colon in continuity, and jejunoileal anastomosis with both the ileo-cecal valve and the entire colon in continuity.

Intestinal fistulas are abnormal communications between two parts of the gastrointestinal tract, between the gut and the other organs (eg the bladder), or between the gastrointestinal tract and the skin (enterocutaneous fistulas, EC). Most of the EC fistulas form in the early post-operative period after abdominal surgery, but they may also form spontaneously secondary to underlying pathology, such as Crohn's disease or radiation enteritis. EC fistulas are among the most common causes of type II IF.

The term intestinal dysmotility is used to indicate the presence of disorders of the propulsion of the gut content in the absence of fixed occluding lesions. Acute intestinal dysmotility is the primary pathophysiological cause of type I IF due to post-operative or acute critical illness-associated ileus, and a frequent concomitant cause of type II IF, due to the impaired gastrointestinal motility associated with systemic or intra-abdominal inflammation. Permanent intestinal dysmotility is termed chronic intestinal pseudo-obstruction (CIPO), where the modifier "pseudo" is used to underline the absence of occluding lesions. CIPO may be congenital or acquired, due to a variety of diseases.

Mechanical obstruction of the intestinal lumen results from a physical abnormality affecting the intestine, which may be intraluminal, intrinsic or extrinsic, of benign or malignant origin. It may be an acute event encompassing a feature of type I IF. It may also be a prolonged feature, leading to type II or III IF, as in patients with extensive adhesions ("frozen abdomen"), or in those with peritoneal carcinomatosis associated with late-stage intra-abdominal malignancy.

Extensive small bowel mucosal disease indicates a condition characterized by an intact or almost intact, although inefficient, mucosal surface, that may be of congenital or acquired origin.

The "clinical classification" of CIF is aimed to facilitate communication and cooperation among professionals through a more objective categorization of patients and is to be used in clinical practice, management/administrative organization, epidemiological surveys and clinical research. It has been devised on the basis of the requirements for energy and the volume of the intravenous supplementation. Sixteen categories were defined. The clinical classification was not intended to be a "severity classification of CIF". The panel highlighted that classifications carry no implications for the level of optimization of care required by the patients, which must be the same for all the patients regardless of their classification.

2. Chronic intestinal failure

Chronic intestinal failure may be the consequences of severe gastrointestinal or systemic benign diseases, or the end stage of intra-abdominal or pelvic cancer. Treatment with HPN for CIF due to end-stage malignant disease is controversial. In Europe, HPN patients with cancer greatly differ among countries, varying from 8% to 60% of the total population on HPN. This wide range may be due to different medical and social attitudes toward palliative care. Overall, the scientific society guidelines have not recommended HPN for patients with a short life expectancy due to malignancy (generally considered inappropriate if this is less than 2–3 months) [4]. Due to the controversial aspects of managing CIF in patients with cancer, the present GLs are limited to "CIF due to benign disease", where the term benign means the absence of end-stage malignant disease.

CIF is the rarest organ failure. In Europe, the prevalence of HPN for CIF due to benign disease has been estimated to range from 5 to 20 cases per million population. CIF due to benign disease has been included in the 2013 Orphanet list of rare diseases.

Table 2 shows the mechanisms of CIF and the underlying disease from which they originated as reported by a European cross-sectional survey on patients on HPN for CIF due to benign disease [5]. SBS was the main mechanism, accounting for about 75% and 50% of cases in adults and children, respectively. Intestinal dysmotility was present in about 20% of both age categories. Extensive mucosal disease accounted for about 5% in adults and 25% in children, the latter mainly due to congenital mucosal disease. EC fistulas represented the cause of CIF in a few cases in adults.

Reversibility of CIF and weaning from HPN after 1–2 years may occur in 20%–50% of patients, depending on the characteristics of the CIF. In patients with SBS, CIF may be reversible because of the intestinal adaptation process and/or intestinal rehabilitation programs based on medical and surgical treatments [6]. The probability of weaning off HPN has been reported to be about 50% in adults and up to 73% in children and is more likely to occur in SBS with partial or total colon in continuity. Complete weaning off HPN in patients with SBS is relatively unlikely (<10%) to occur after 2–3 years have elapsed since the most recent intestinal resection. In patients with CIPO, the reversibility of CIF is lower than that reported in SBS, having been reported in 25–50% in adults and 25–38% in children. Intestinal rehabilitation and weaning from HPN in CIF due to EC fistulas depends on the possibility of performing a reconstructive surgery to recover bowel continuity and intestinal absorptive surface. Reversibility of CIF due to extensive mucosal disease rarely occurs.

Patients with CIF due to benign disease have a high probability of long-term survival on HPN (about 80% in adults and 90% in children at 5 years) [6]. Overall, about two-thirds of patients may have partial or total social and working rehabilitation as well as a good family life [7]. On the other hand, CIF may be associated with life-threatening complications and the condition itself may be highly disabling and impair quality of life (QoL) [7]. Treatment of CIF is based on complex technologies and requires multidisciplinary and multiprofessional activity and expertise. The outcome of patients with benign CIF, in terms of reversibility, treatment-related morbidity and mortality, and survival probability is strongly dependent on care and support from an expert specialist team. Patients with irreversible CIF are destined to need life-long HPN or intestinal transplantation (ITx). On the basis of data on safety and efficacy, HPN is considered the primary treatment for CIF, whereas ITx is reserved for those patients at risk of death because of life-threatening complications related to HPN or to the underlying gastrointestinal disease [6].

Table 2
Pathophysiology and underlying diseases of patients on long-term home parenteral nutrition for chronic intestinal failure due to benign disease (no cancer) (adapted from 5).

	Adults (n. 688)	Children (n. 166)
Short bowel syndrome (No. %)	**514 (74.7%)**	**87 (52.4%)**
• Mesenteric ischemia	35.8%	
• Crohn's disease	29.0%	
• Radiation enteritis	9.7%	
• Surgical complications	7.8%	
• Familial polyposis	4.1%	
• Volvulus	2.3%	25.3%
• Intestinal malformation		48.3%
• Necrotizing enterocolitis		14.9%
• Others	13.6%	11.5%
Motility disorder	**124 (18.0%)**	**38 (22.9%)**
• CIPO primary	56.4%	71.0%
• Radiation enteritis	16.1%	
• Scleroderma	5.6%	
• Hirschprung's disease	1.6%	15.7%
• Others	20.1%	13.1%
Extensive parenchymal disease	**35 (5.1%)**	**41 (24.7%)**
• Coeliac	17.1%	
• Immunodeficiency	14.3%	7.3%
• Crohn's disease	14.3%	9.8%
• Lymphangectasia	11.4%	12.2%
• Radiation enteritis	9.0%	
• Tufting enteropathy	5.7%	24.4%
• Autoimmune enteropathy	5.7%	7.3%
• Intractable diarrhea	2.9%	17.2%
• Microvillus atrophy		9.8%
• Others	20.0%	12.2%
Intestinal fistulas	**15 (2.2%)**	**0**
• Surgical complication	60.0%	
• Crohn's disease	26.6%	
• Others	13.3%	

ESPEN and other scientific societies have devised guidelines (GLs) for HPN [4,8–12] and central venous catheter (CVC) management [13], as well as for SBS [14,15]. No GLs have been developed to globally address management of CIF. The aim of the present GL is to generate comprehensive recommendations for safe and effective management of adult patients with CIF due to benign disease.

3. Methods

The working group included gastroenterologists, surgeons, endocrinologists, anesthesiologists, and dietitians with long-term expertise in IF and HPN. The GLs were developed according to the ESPEN method [16]. All working group members are authors of this guideline document. The experts followed the GRADE method, which is based on determinations of grade of evidence (GOE) and

strength of recommendation; the methodology is described elsewhere [17,18].

In February 2014, the topics to be included in the GLs and the questions for the recommendations within each topic were defined. The GLs were devised between March 2014 and July 2015, through email exchanges, a two-day live meeting held in Nice, France, in February 2015, followed by three Delphi rounds [19].

A systematic literature search was conducted in PubMed. Any pertinent publication retrieved from the references of the selected papers as well as chapters from specialized books were also considered. The GOE was determined by a number of factors, starting with the number and type of research studies [17]. Grading from High to Very Low was used to rate the quality of the underlying evidence and the level of certainty for effect (Table 3) [18]. Highest quality evidence resulted from consistent results or meta-analysis of multiple randomized controlled trials, with the next highest level defined by at least one well-designed randomized controlled trial. Moderate and low-level evidence came from controlled trials that were not randomized, from cohort- or case-controlled studies, or from multiple time-series trials. Very low-level evidence was from expert clinical experience or from descriptive studies. The grade was then decreased if there were limitations to study quality, inconsistencies in findings, imprecise or sparse data, or high likelihood of reporting bias. The grade was increased if there was high consistency of findings or strong evidence of association (Table 3).

The strength of recommendation was based on a consensus discussion, which included expression and deliberation of expert opinions, risk-benefit ratio of recommendation, costs, and a review of supportive evidence, followed by Delphi rounds and votes until agreement was reached (Table 4).

Literature search provided 623 full papers: meta-analysis 16, randomized controlled trials 58, comparative studies 44, prospective studies 30, case-control studies 6, observational studies 243, scientific society GLs 33 or position papers 2, reviews 113, expert opinion 66, animal studies 12. The low percentage of controlled studies may be considered to be a direct consequence of the rarity of CIF, a factor that impairs the feasibility of well-designed investigations.

A total of 112 recommendations were devised. On July 29th 2015, the final list of recommendations was sent to all 2755 ESPEN members with an e-mail address on file to ask for approval/disapproval or no opinion of every statement, and in case of disapproval to provide justification and any supporting paper. Fifty-four members completed the survey. The rates of approval are reported in Table 5.

A rate of approval equal or greater than 80% was reported in 82.1% of the recommendations. For only 4 questions the approval rate was lower that 70%, this was related to a high percentage of responders who expressed no opinion. The final disapproval rate ranged from 0 to 11%. In no cases was the disapproval supported by a literature reference. Thus, only minor changes, not requiring further submission to ESPEN members, were made to a few statements according to the received comments.

Table 4
Strength of recommendation.

Strength of recommendation	
Strong	We recommend/do not recommend
Weak	We suggest/do not suggest

4. Recommendations

Table 6 lists the statements along with their GOE and strength of recommendation. The GOE is very low for 51% of the recommendations, low for 39%, moderate for 8%, and high for only 2%. The strength of the recommendation is strong for 63% and weak for 37% of them. Notwithstanding the high percentage of recommendations with a very low or low grade of evidence, due to the lack of RCTs, the strength of the recommendations was considered strong for two-thirds of them. This highlights how CIF management requires complex technologies and multidisciplinary and multiprofessional activity and expertise dedicated to the care of both the underlying gastrointestinal condition and the HPN support.

4.1. Management of home parenteral nutrition for benign chronic intestinal failure

1. **We recommend that the aims of an HPN programme include provision of evidence-based therapy, prevention of HPN–related complications such as catheter-related infections and metabolic complications and ensure quality of life is maximized.** (Grade of evidence: **very low**)
2. **We recommend regular audit of therapy and outcomes against standards to ensure safety and efficacy of an HPN programme.** (Grade of evidence: **very low**)

The aim of a safe and effective HPN programme for CIF has been considered in national strategic planning of IF services [20]. The principles used in the planning for an Intestinal Failure and HPN service in England included:

- Provision of consistent and high care standards throughout the country
- Foster equity of access for IF/HPN patients throughout the country
- Allow access for patients to high quality and clinically safe services as close to their homes as possible
- Be patient centered and use resources appropriately and effectively
- Reflect on models of care and ensure that the framework of services remains relevant to patients
- Develop and sustain mechanisms that demonstrate value for money in the provision of HPN and IF services through audit and outcome reporting

To identify the ultimate aim of the HPN therapy, a set of expected and desirable results is needed for HPN patients [21]. A set of outcome indicators has been developed that allows goals of

Table 3
Grades of evidence [18].

Level	Definitions of evidence
High	Further research is unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Table 5
Approval, disapproval, and no opinion rates by 54 ESPEN members who evaluated the 112 recommendations.

Recommendations n. (% of total)	Approval (% of responders)	Disapproval (% of responders)	No opinion (% of responders)
43 (38.4)	90–96	0–5	1–10
40 (43.7)	80–89	0–10	7–18
16 (14.3)	70–79	0–11	13–23
3 (2.7)	60–69	0–7	26–33
1 (0.9)	50–59	2	48

treatment to be defined. The indicators were developed by an expert panel of health care clinicians in Europe and were subdivided into patient outcomes and therapy outcomes [22]. The top scoring outcome indicator for clinicians was prevention of catheter-related infections.

Patient priorities and concerns were sought in a survey of HPN patients with underlying benign disease in nine centres over eight countries [23]. This cohort identified incidence of catheter-related infections, survival and quality of life (QoL) as the most important indicators of their care.

The aims of a safe and effective HPN programme must therefore focus on therapy outcomes. It is important that catheter-related infections (CRI) are diagnosed early and treated effectively to minimize the associated risks [24,25]. All HPN-related complications including catheter obstruction, central venous thrombosis, liver disease, and osteoporosis, should be recognized as part of regular surveillance and treated early within an experienced multidisciplinary team to prevent later irreversible complications.

To measure and provide evidence of the safety and efficacy of the HPN service there should be regular audit of outcomes and scrutiny of results concerning HPN-related major complications, including re-admission rates. Furthermore, a recognized instrument for measuring QoL should be used regularly to monitor HPN patients [26].

Accreditation programmes for HPN providers must also ensure regular audit against these quality measures.

3. **We recommend that patients selected for an HPN programme have confirmed intestinal failure that despite maximal medical therapy would lead to deterioration of nutrition and/or fluid status.** (Grade of evidence: **very low**)
4. **We recommend that prior to discharge, patients are metabolically stable, able to physically and emotionally cope with the HPN therapy, and have an adequate home environment.** (Grade of evidence: **very low**)

Criteria for selection into an HPN programme do not need an evidence base to inform recommendations. Long-term HPN in this setting is a life-preserving therapy and is based on experience and expert opinion.

All patients who are considered for entry into an HPN programme should have documented prolonged IF which, if untreated, would lead to deteriorating nutritional and/or fluid status and should have undergone an adequate trial of enteral nutrition, if feasible (except, for example, in the case of extreme short bowel). They should be managed by a clinician and multidisciplinary nutrition support team that have an interest and experience in IF [8,27].

To optimize safety and efficacy, evidence-based procedures and protocols should be used to educate patients and carers (including hospital and home care provider staff) on catheter care and for monitoring the nutritional, metabolic, and clinical status of the patient [28,29]. Patients who are in a hospital without adequate experience or expertise to manage the medical/surgical and nutritional requirements of such patients should be transferred to a recognized IF centre.

The patient and/or carers must be physically and emotionally able to undertake HPN training and demonstrate self-care competency prior to discharge. The ability of the patient to cooperate with therapy should also be taken into account when assessing for HPN. Psychological assessment may be necessary for some patients. The home situation must be stable and have adequate facilities for safe administration of HPN.

5. **We recommend that HPN patients have access to infusion pumps or devices with specified safety features together with ancillary products, safe compounding and delivery systems** (Grade of evidence: **very low**)

It is recognized that not all health care domains have access to pumps for HPN patients. Electronic pumps with appropriate delivery sets should be used where possible to manage and monitor the delivery of HPN [4,8,10].

The growing number of HPN patients has encouraged the development of portable infusion pumps. One study found that the individual who meets the criteria for home therapy was also the same individual who welcomed independence. An ambulatory pump further enabled these individuals, whose lifestyle had already been greatly compromised, to achieve desired independence [30]. If an ambulatory pump is not available (or appropriate because of the patient's condition), a standard volumetric pump with an intravenous stand is an alternative. The range of other sterile consumable products or accessories required for use by the patient at home will vary, dependent on the pump in use and individual patient requirements. The pump should have the following features:

- Intuitive and easy to operate
- Easy to clean
- Battery backup
- Variable audible alarm control or alternative (e.g. light, vibrate function)
- Programmable mode options that include ramp-up/ramp-down and continuous infusion modes
- Option to “lock out” those infusion modes not required and control the panel lock to prevent accidental or child tampering
- Standard safety features including air-in-line alarm, upstream and downstream occlusion alarms, free-flow protection device, variable pressure delivery options [31].
- Availability of a variety of pump-compatible sets with different line lengths
- In-line filtration can be an option [32,33].
- Compliant with ECRI Institute safety recommendations [34].
- Service and maintenance contract provided

Parenteral nutrient admixtures can be compounded in single bags, dual chamber bags or 3 in 1 bags (contain separate compartments for lipid emulsion/glucose/amino acid to be opened and mixed before infusion). Vitamins and trace elements can be added prior to infusion in the home setting. Dual and triple chamber bags have advantages for HPN patients as they have a longer shelf life. Some triple chamber bags do not require refrigeration which provides advantages for HPN patients while traveling. Stability is also markedly prolonged by refrigeration [35]. This requires a dedicated refrigerator for HPN solution storage. Bags made of phthalate-free multi-layered ethyl vinyl acetate minimize oxidation of parenteral

Table 6
Complete list of statements on chronic intestinal failure due to benign disease (absence of end stage cancer disease).

#	Statement	Grade of evidence	Strength of recommendation
	Management of home parenteral nutrition for benign chronic intestinal failure		
1	We recommend that the aims of an HPN programme include provision of evidence-based therapy, prevention of HPN–related complications such as catheter-related infections and metabolic complications and ensure quality of life is maximized.	Very low	Strong
2	We recommend regular audit of therapy and outcomes against standards to ensure safety and efficacy of an HPN programme.	Very low	Strong
3	We recommend that patients selected for an HPN programme have confirmed intestinal failure that despite maximal medical therapy would lead to deterioration of nutrition and/or fluid status.	Very low	Strong
4	We recommend that prior to discharge, patients are metabolically stable, able to physically and emotionally cope with the HPN therapy, and have an adequate home environment.	Very low	Strong
5	We recommend that HPN patients have access to infusion pumps or devices with specified safety features together with ancillary products, safe compounding and delivery systems.	Very low	Strong
6	We recommend that patient/caregiver training for HPN management be patient-centred with a multidisciplinary approach, together with written guidelines. HPN training may take place in hospital or at home.	Very low	Strong
7	We recommend regular contact by the HPN team with patients, scheduled according to patients' clinical characteristics and requirements.	Very low	Strong
8	We recommend that laboratory testing be done on a regular basis using appropriate tests and timing relative to PN infusion.	Very low	Strong
9	We recommend that quality of life for HPN patients be regularly measured using validated tools as part of standard clinical care. Quality of care should be assessed regularly according to recognized criteria.	Very low	Strong
10	We suggest that HPN patients be encouraged to join non-profit groups that provide HPN education, support and networking among members. This may be beneficial to patient consumers of HPN with respect to quality of life, depression scores, and catheter infections.	Very low	Weak
11	We recommend that CIF patients be cared for by a multidisciplinary team with skills and experience in intestinal failure and HPN management.	Very low	Strong
	Parenteral nutrition formulation		
12	We recommend that the protein and energy requirements for CIF patients be based on individual patient characteristics (e.g. intestinal absorptive capacity as estimated by gastrointestinal anatomy and/or underlying disease) and specific needs (e.g. acute illness, protein malnutrition), and that the adequacy of the regimen is regularly evaluated through clinical, anthropometric, and biochemical parameters.	Very low	Strong
13	We 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.	Very low	Strong
14	We cannot make a recommendation at this time on addition of insulin to HPN admixtures due to lack of evidence-based data regarding insulin prescription for HPN patients who have hyperglycaemia.	Very low	Strong
15	We suggest, in patients totally dependent on HPN, a minimal supply of 1 g/kg/week of intravenous lipid emulsion containing EFA, to prevent EFA deficiency.	Very low	Weak
16	We suggest that most patients on long-term HPN for CIF without ongoing metabolic complications be safely treated with provision of no more than 1 g/kg/day of intravenous soybean-based lipid emulsion.	Very low	Weak
17	We recommend regular monitoring of signs and symptoms of dehydration, fluid balance, laboratory tests, and 24-h urine output as well as a timely adjustment of fluid supplementation to prevent chronic renal failure in patients on HPN.	Very low	Strong
18	We recommend that the HPN formula be adjusted with the aim of normalizing laboratory tests related to fluid, electrolytes and mineral balance in patients on HPN.	Very low	Strong
19	We recommend regular monitoring of acid-base status in patients on long-term HPN (serum concentration of chloride and bicarbonate), because either metabolic acidosis or metabolic alkalosis can occur.	Very low	Strong
20	We suggest that clinical signs and symptoms as well as biochemical indexes of vitamin deficiency or toxicity be regularly evaluated at clinical review.	Very low	Weak
21	We suggest that baseline serum vitamin concentrations be measured, according to laboratory availability, at the onset of HPN and then at least once per year.	Very low	Strong
22	We suggest that vitamin doses in HPN are adjusted as needed.	Very low	Weak
23	We suggest that the route of vitamin supplementation be selected according to the characteristics of the individual patient.	Very low	Weak
24	We suggest that clinical signs and symptoms as well as biochemical indexes of trace element deficiency or toxicity be regularly evaluated at clinical review.	Very low	Weak
25	We suggest that baseline serum trace element concentrations be measured, according to laboratory availability, at the onset of HPN and then at least once per year.	Very low	Weak
26	We suggest that trace element doses in HPN are adjusted as needed.	Very low	Weak
27	We suggest that the route of trace element supplementation be selected according to the characteristics of the individual patient.	Very low	Weak
28	We do not suggest the routine addition of individual amino acids (glutamine, cysteine, taurine) in the parenteral formula to decrease complications in adults on HPN.	Low	Weak
	Intestinal rehabilitation strategy-medical		
	Short bowel syndrome		
29	We recommend that SBS patients be advised to consume regular whole food diets, and are encouraged to compensate for malabsorption by hyperphagia.	Low	Strong

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Table 6 (*continued*)

#	Statement	Grade of evidence	Strength of recommendation
30	We suggest that dietary counselling be guided by an expert dietitian, based on the subjective experience of the patient, and ideally supported by objective metabolic balance measurements, in order to ensure high compliance.	Low	Weak
31	We recommend that SBS patients with a preserved colon consume a diet high in complex carbohydrates and low in fat whereas the fat:carbohydrate ratio seems of less importance in patients without a colon.	Low	Strong
32	We suggest a diet with a high content of medium-chain triglycerides that confers a marginal benefit on overall energy absorption compared to a diet containing regular long-chain triglycerides in SBS patients with a preserved colon.	Low	Weak
33	We recommend in SBS patients consuming a low fat diet or where the long-chain triglycerides have been replaced by medium-chain triglycerides that attention is paid to the potential deficiency in essential fatty acids and fat-soluble vitamins.	Low	Strong
34	We don't recommend the addition of soluble fiber (e.g. pectin) to the diet to enhance overall intestinal absorption.	Low	Strong
35	We suggest that lactose not be excluded from the diet of SBS patients unless intolerance has been documented on a clinical basis, such as a clear association between lactose ingestion and increase of diarrhea or of stoma output.	Low	Weak
36	We suggest the addition of oral isotonic nutritional supplements in borderline (i.e. B1 category of clinical classification) SBS intestinal failure patients at risk of malnutrition.	Low	Weak
37	We suggest the use of enteral tube feeding in combination with oral feeding in patients with CIF with a low-level of HPN dependence (i.e. B1 category of clinical classification) and in whom the expected gain with tube feeding could allow them to wean off HPN.	Low	Weak
38	We suggest, in patients with CIF treated with enteral tube feeding, the use of polymeric isotonic enteral diets.	Low	Weak
39	We don't recommend the addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process.	Low	Strong
40	We suggest that SBS patients use salt liberally and restrict the administration of oral fluids in relation to meals.	Low	Weak
41	We suggest that patients who have borderline dehydration or sodium depletion use an isotonic high sodium oral rehydration solution to replace stoma sodium losses.	Low	Weak
42	We suggest limiting the oral intake of low sodium, both hypotonic (e.g. water, tea, coffee, or alcohol) and hypertonic (e.g. fruit juices, colas) solutions in order to reduce output in patients with net-secretion and a high output jejunostomy.	Low	Weak
43	We recommend the use of H2-receptor antagonists or proton pump inhibitors in reducing faecal wet weight and sodium excretion, especially during the first 6 months after surgery, mainly in those SBS patients with a faecal output exceeding 2 L/day.	Moderate	Strong
44	We suggest that in the individual patient, H2-receptor antagonists or proton pump inhibitors are also effective in reducing faecal wet weight and sodium excretion in the long-term.	Very Low	Weak
45	We suggest, especially in the short-term after intestinal resection, the use of octreotide for patients with high-output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments.	Low	Weak
46	We recommend careful monitoring of patients treated with octreotide, to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects and potential negative interference with the process of intestinal adaptation during long-term use.	Low	Strong
47	We recommend oral loperamide to reduce wet weight and sodium faecal excretion in SBS patients with an ostomy.	Moderate	Strong
48	We recommend loperamide be preferred to opiate drugs, such as codeine phosphate or opium, because it is not addictive or sedative.	Moderate	Strong
49	We recommend that in SBS patients with a high ostomy output, the use of loperamide be guided by objective measurements of its effect.	Moderate	Strong
50	We recommend that SBS patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who suffer from symptoms of bacterial overgrowth, benefit from occasional antibiotic treatment.	Very low	Strong
51	We do not recommend the routine use of antibiotics in SBS patients with a preserved colon, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to short-chain fatty acids, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation.	Very low	Strong
52	We recommend that patients with CIF due to SBS be carefully informed of the potential benefits and risks associated with growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of quality of life improvement, the expected duration of treatment, the expected effects after cessation of the treatment, the potential adverse effects and risks of the treatment, the cost-effectiveness of the treatment, and the need to undergo careful and regular monitoring.	Low	Strong
53	We suggest that, for those carefully selected SBS patients who are candidates for growth factor treatment, the GPL2-analog, teduglutide, be the first choice.	Moderate	Weak
54	We recommend evaluation of the efficacy of growth factor treatment according to standardized protocols measuring fluids, electrolytes and, whenever possible, energy balance.	Low	Strong
55	We recommend that intestinal growth factors are only prescribed by experts who are experienced in the diagnosis and management of SBS patients and who have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks, and cost-effectiveness.	Low	Strong
56	We recommend drugs be prescribed on an individual basis to patients with SBS following a careful evaluation of the absorptive capacity of the remnant bowel, knowledge of the physiochemical characteristics of the drug, and an evaluation as to if the drug can be titrated according to an	Very low	Strong

Table 6 (*continued*)

#	Statement	Grade of evidence	Strength of recommendation
	objectively measured effect or according to measurements of plasma concentrations. The use of parenteral and transdermal routes and the use of suppositories should also be considered in SBS patients with limited intestinal absorption.		
	Chronic intestinal pseudo-obstruction		
57	We recommend that a specific diet not be prescribed but that patients with CIPO be encouraged to eat according to individual tolerance.	Very low	Strong
58	We suggest trying enteral tube feeding as a first step in patients with chronic gastrointestinal motility dysfunctions who are not able to meet their energy needs with oral nutrition alone and continue to lose weight, before using HPN.	Very low	Weak
59	We recommend that HPN not be delayed in malnourished CIPO patients with chronic gastrointestinal motility dysfunctions when oral/enteral nutrition is obviously inadequate.	Very low	Strong
60	We recommend attempting a trial with prokinetics in patients with chronic gastrointestinal motility dysfunctions.	Very low	Strong
61	We recommend using antibiotic therapy to treat intestinal bacterial overgrowth and to reduce malabsorption in patients with chronic gastrointestinal motility dysfunctions.	Very low	Strong
62	We suggest periodic antibiotic therapy to prevent intestinal bacterial overgrowth in patients with chronic intestinal motility dysfunction who have frequent relapsing episodes.	Very low	Weak
	Radiation enteritis		
63	We recommend that the nutritional regime in chronic radiation enteritis patients follows the same criteria adopted for the HPN of patients with other causes of CIF.	Very low	Strong
64	We suggest trying enteral tube feeding in patients with radiation enteritis if oral nutrition including use of oral nutritional supplements is inadequate.	Very low	Weak
65	We recommend HPN not be delayed in malnourished radiation enteritis patients, if oral nutrition/ enteral tube feeding is obviously inadequate.	Very low	Strong
	Intestinal rehabilitation strategy-non-transplant surgery		
66	We recommend that, in patients with SBS, during intestinal resection, bowel length be conserved to the fullest extent possible to avoid dependence on HPN.	Low	Strong
67	We recommend that, in patients with SBS, restoration of intestinal continuity, be realized whenever possible, to decrease HPN dependency.	Moderate	Strong
68	We recommend that, when considering non-transplant surgery in patients with SBS, bowel lengthening procedures be considered in selected patients.	Very low	Strong
69	We recommend that, in patients with SBS, management is performed through a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome.	Low	Strong
70	We suggest to avoid surgery in CIPO patients, whenever possible, due to the risk of postoperative worsening of intestinal function and need for subsequent reoperation; venting ostomy (either endoscopically or surgically), however, can diminish symptoms in selected patients.	Very low	Weak
	Intestinal transplantation		
71	We recommend HPN as the primary treatment for patients with CIF and the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, to maximize the opportunity of weaning off HPN, to prevent HPN failure, and to ensure timely assessment of candidacy for intestinal transplantation.	Very low	Strong
72	We recommend assessment for candidacy for intestinal transplantation, when one of the following indications exists. 1. Failure of HPN: • Impending (total bilirubin above 3–6 mg/dL (54–108 μmol/L), progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of intestinal failure-associated liver disease (IFALD). • Central venous catheter-related thrombosis of two or more central veins (internal jugular, subclavian, or femoral). • Frequent central line sepsis: two or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock and/or acute respiratory distress syndrome. • Frequent episodes of severe dehydration despite intravenous fluid in addition to HPN. 2. High risk of death attributable to the underlying disease • Invasive intra-abdominal desmoid tumors • Congenital mucosal disorders (i.e., microvillus inclusion disease, tufting enteropathy). • Ultra short bowel syndrome (gastrostomy, duodenostomy, residual small bowel <10 cm in infants and <20 cm in adults) 3. Intestinal failure with high morbidity or low acceptance of HPN • Need for frequent hospitalization, narcotic dependency, or inability to function (i.e., pseudo-obstruction, high output stoma). • Patient's unwillingness to accept long-term HPN (i.e., young patients)	Very low	Strong
73	We recommend that patients with impending or overt liver failure due to IFALD and those with an invasive intra-abdominal desmoid tumor be listed for a life-saving intestinal transplantation (with or without liver transplantation).	Very low	Strong
74	We suggest that patients with central venous catheter related thrombosis of two or more central veins (internal jugular, subclavian or femoral) be listed for a life-saving intestinal transplantation on a case-by-case basis.	Very low	Weak
75	We do not recommend listing for a life-saving intestinal transplantation of patients with CIF having any of the indications for assessment of candidacy other than IFALD-related liver failure, intra-abdominal desmoids or CVC-related multiple vein thrombosis.	Very low	Strong
76	We suggest that patients with CIF with high morbidity or low acceptance of HPN might be listed for a rehabilitative intestinal transplantation on a careful case-by-case basis.	Very low	Weak

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Table 6 (*continued*)

#	Statement	Grade of evidence	Strength of recommendation
77	We recommend that, whenever possible, patients listed for intestinal transplantation undergo the procedure while they are in stable clinical condition, as represented by being able to stay at home and not requiring hospitalization while waiting for transplant. For patients listed for a combined intestinal and liver transplantation, mechanisms to prioritize patients on the waiting list for liver transplantation should be adopted in order to minimize the risk of mortality while on waiting list and after transplantation.	Very low	Strong
	Prevention/treatment of CVC-related complications		
	CVC-related infection		
78	We recommend that the choice of central venous catheter type and location of exit site be made by a multidisciplinary HPN team, along with an experienced specialist as well as the patient.	Low	Strong
79	We recommend that access to the upper vena cava is the first choice for CVC placement, via internal jugular vein or subclavian vein.	Moderate	Strong
80	We suggest that right-sided access is preferable to a left-sided approach with respect to risk for thrombotic complications.	Low	Weak
81	We recommend that the tip of the catheter be placed at the level of the right atrial-superior vena cava junction.	Moderate	Strong
82	We recommend that the exit site of the catheter should be easily visualized and accessible for patients doing self-care and that the preferred site be marked by clinicians experienced with HPN.	Low	Strong
83	We recommend that tunnelled central venous catheters or totally implanted devices are used for long-term HPN.	Very low	Strong
84	We do not recommend the use of PICC lines for expected long-term HPN, because of the higher risk of thrombosis and issues related to self-administration of HPN.	Low	Strong
85	We recommend that central venous catheter-related infections are diagnosed according to current guidelines on catheter-related infections.	Very low	Strong
86	We recommend that central venous catheter-related infections be managed according to current guidelines on long-term intravascular catheters and as described in the comments section. A conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections. Catheter removal should be the first choice in case of tunnel infections or blood cultures positive for virulent bacteria; catheter removal is mandatory for port abscesses, complicated infections, persistent hemodynamic instability, or blood cultures that are positive for fungi.	Moderate	Strong
87	We recommend, for prevention of central venous catheter-related infections: • education of staff and patients/caregivers • implementation of an adequate policy of hand washing and disinfection by patients and staff • handwashing and disinfection by patient and caregivers before touching central venous catheter as well as after catheter care • disinfection of the hub connector every time it is accessed • use of tunnelled single-lumen catheters whenever possible • use of chlorhexidine 2% for antisepsis of hands, catheter exit site, stopcocks, catheter hubs and other sampling ports • regular change of i.v. administration sets	High	Strong
88	We do not recommend, for prevention of central venous catheter-related infections: • use of in-line filters • routine replacement of catheters • antibiotic prophylaxis • use of heparin lock	Low	Strong
89	We suggest, for prevention of central venous catheter-related infections: • performing site care, including catheter hub cleaning on at least a weekly basis • changing catheter dressings at least once weekly • avoiding catheter care immediately after changing or emptying ostomy appliances • disinfecting hands after ostomy care	Very low	Weak
90	We suggest that catheter locking with taurolidine may be used to prevent central venous catheter-related infections.	Low	Weak
91	We suggest the creation of arterio-venous fistulae to prevent central venous catheter-related infections in carefully selected patients.	Very low	Weak
92	We do not recommend catheter locking with 70% ethanol to prevent central venous catheter-related infections, because its use is associated with systemic toxicity, catheter occlusion and catheter damage.	High	Strong
93	We recommend in patients who repeatedly present with central venous catheter-related infections, re-education of the patient and/or caregiver and/or use of an antimicrobial catheter lock.	Low	Strong
	CVC-related occlusion/thrombosis		
94	We recommend: • treating HPN patients with central venous catheter-related venous thrombosis with anticoagulation; • the duration of this treatment be chosen on an individual basis • the decision to maintain the catheter be dependent on individual factors (e.g. necessity of a central line, lack of infection, clinical outcome)	Low	Strong
95	We recommend, for the primary prevention of central venous catheter-related venous thrombosis, insertion of the catheter using ultrasound guidance and placement of the tip at the superior vena cava-right atrium junction.	Low	Strong
96	We do not recommend routine thromboprophylaxis with drugs (heparin, warfarin) as primary prevention of central venous catheter-related venous thrombosis for all adults on HPN based on the risk/benefit balance.	Low	Strong
97	We suggest flushing catheters with saline to prevent central venous catheter occlusion.	Low	Weak
98	We suggest irrigation of the catheter with saline as the first attempt to restore catheter patency in intra-lumen catheter occlusion.	Low	Weak

Table 6 (*continued*)

#	Statement	Grade of evidence	Strength of recommendation
99	We suggest using fibrinolytic drugs for the treatment of acute catheter occlusion likely caused by blood clotting.	Low	Weak
	Prevention/treatment of intestinal failure-associated liver disease		
100	We recommend for prevention of intestinal failure-associated liver disease that: • sepsis is prevented and/or managed, if present • attempts are made to preserve small intestinal length and retain the colon in continuity with small bowel; • oral/enteral intake is maintained; • PN is cycled; • PN overfeeding is avoided; • the dose of soybean-oil based lipid is limited to less than 1 g/kg/day	Low	Strong
101	We suggest for treatment of intestinal failure-associated liver disease: • to re-consider all the measures to prevent intestinal failure-associated liver disease • to revise the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω6/ω3 PUFA ratio • to revise any potential inflammatory/infective foci	Low	Weak
	Prevention/treatment of gallbladder sludge and stones		
102	We suggest for the prevention/treatment of gallbladder sludge to maintain/resume oral feeding.	Very low	Weak
103	We recommend for the treatment of gallbladder sludge and stones to perform cholecystectomy and/or endoscopic procedures in case of biliary complications as for the general population.	Low	Strong
	Prevention/treatment of intestinal failure-associated renal failure and stones		
104	We recommend for the primary prevention of renal failure and of renal stones, regular monitoring of renal function and fluid balance as well as a timely adjustment of fluid supplementation in order to avoid episodes of dehydration in patients with CIF.	Low	Strong
105	We recommend for the primary prevention of renal failure, that acute and chronic infections as well as acute and chronic dehydration are addressed by the relevant clinical intervention.	Low	Strong
106	We suggest for the primary prevention of renal stones a low oxalate and low fat diet, in addition to an increase of oral calcium, to reduce the risk of oxalate stone formation in patients with SBS with a colon in continuity.	Low	Weak
107	We suggest avoiding metabolic acidosis and giving citrate supplementation, to reduce the risk of uric acid stones.	Very low	Weak
108	We recommend treating renal failure and renal stones in patients with CIF according to the standards for these conditions.	Very low	Strong
	Prevention/treatment of intestinal failure-associated metabolic bone disease		
109	We recommend that for routine purposes diagnosis of metabolic bone disease is based on a combination of bone densitometry scanning and biochemistry.	Low	Strong
110	We recommend that the HPN population is routinely monitored for metabolic bone disease by bone densitometry scanning and biochemistry.	Low	Strong
111	We recommend that general risk factors for developing osteoporosis be promptly addressed, as well as factors with a possible negative impact on bone health, i.e. chronic inflammation, infections, drugs and other relevant factors related to the underlying disease, in all patients on long-term HPN.	Very low	Strong
112	We recommend as the primary step for treatment of metabolic bone disease to optimize the program for parenteral nutrition with the required supplements of vitamin D, calcium and phosphate. Further, medical treatment may be useful to increase bone mineral density and lower fracture risk.	Low	Strong

nutrition (PN) components [36] and covering bags and giving sets can minimize photo-degradation [37].

The stability and compatibility of parenteral nutrition admixtures compounded for patients requiring nutritional support is paramount to HPN patient safety. The most significant pharmaceutical issues associated with mixing PN formulations affecting their safety involve the stability of lipid-injectable emulsions and the compatibility of calcium and phosphate salts. Factors affecting the functioning of the emulsifier include temperature, pH, type of amino acid mixture, concentration of amino acids, electrolytes (calcium and magnesium) and degree of dilution. Home parenteral nutrition admixtures should be visually inspected for lipid emulsion coalescence as well as calcium phosphate precipitates prior to use [38].

Delivery of HPN admixtures to patients should be in strong containers under known temperature/time conditions to ensure safe storage requirements are not exceeded in transit. Attention should be paid to these requirements in particularly hot or cold regions [39]. The ambient temperature of the HPN solution must be kept at 4–8 C° and air excluded from an all-in-one admixture [40]. The patient should be consulted about establishment of stock-holding and delivery schedules. These should, as far as possible, not require regular intervention by the patient (routine pattern deliveries). It should also be possible for patients to easily obtain replacement items contaminated during opening or other similar problems [41,42].

6. **We recommend that patient/caregiver training for HPN management be patient-centred with a multidisciplinary approach, together with written guidelines. HPN training may take place in hospital or at home.** (Grade of evidence: **very low**)

Qualitative research in education processes suggests that successful learning characteristics can be developed into a framework for teaching delivery of home infusions [43].

Contemporary reviews recommend that HPN patients be trained by a multidisciplinary team (medical, nursing, dietetic, and pharmacy clinicians with experience in an HPN programme) in the management of HPN as an inpatient in preparation for the home environment [28,44–47]. The patient will need to be stable on the HPN regimen before being discharged.

Initiation of HPN in the home is of interest to patients, health care providers, and third party payers and has been a growing trend

in North America [48]. Caution regarding this practice has been expressed including the need for careful patient selection. One recommendation is that initiation of HPN in the home setting should only be considered in patients who are clinically stable, have an appropriate indication for HPN, are able to be evaluated in the home, and are capable of safe administration of the therapy [48,49].

Prevention plays an important role in safe and effective care outside the hospital. In particular prevention of CVC-related infections can minimize re-admission rates and lead to savings of healthcare resources [25]. One retrospective study showed that HPN patients given detailed written and verbal training on aseptic management and avoiding and recognizing complications had a lower rate of complications than a comparison group that had standard instructions [50].

The training process may take from several days to weeks depending on the patients' ability to learn the techniques to ensure safe practice in the home. In a few instances, care in a residential care facility may be an option. The patient will also need to be stable on the HPN regimen prior to discharge.

Key criteria for patient HPN competency training

Training institutions will determine competency to self-manage HPN before discharge. A checklist of criteria for patients/carer(s) and trainers to sign-off as a written record of demonstrated competence may be helpful [51,52]. For example, the patient/carer(s) will be able to:

- demonstrate understanding of principles of asepsis and its importance together with sterile procedures for commencing and discontinuing HPN
- demonstrate safe delivery of HPN according to institutional protocol guidelines
- recognize specific problems and symptoms and respond appropriately; these commonly include mechanical problems with the lines or pumps and febrile episodes
- have a connected telephone for medical and nursing support, emergency services, and logistics planning and delivery
- live independently or have adequate care and support
- have a home environment that provides a clean space for sterile additions, HPN setup, and connection
- have access to a dedicated refrigerator, if needed, for HPN solution storage

7. **We recommend regular contact by the HPN team with patients, scheduled according to patients' clinical characteristics and requirements.** (Grade of evidence: **very low**)
8. **We recommend that laboratory testing be done on a regular basis using appropriate tests and timing relative to PN infusion.** (Grade of evidence: **very low**)

Practices across Europe, as based on the few published studies, appear to be similar. In Scotland, the HPN Managed Clinical Network set standards, approved protocols, conducted audits, measured outcomes, and encouraged multi-professional care of persons receiving HPN [53]. Due to the lack of published studies, the Scottish HPN Managed Clinical Network guidance, as well as that of National Institute for Health and Clinical Excellence [10], has been based on expert opinion rather than higher levels of evidence and recommends that initially the patient should be observed closely with the first clinic visit within 1–2 weeks of discharge from hospital. Thereafter, patients on HPN were to be seen every 3 months as an outpatient. The same guidelines stated that the patients' weight, haemoglobin, indices of inflammation such as white cell count and C-reactive protein, renal function, liver function, calcium and magnesium, micronutrients, vitamins and anthropometry should ideally be measured at each HPN visit. However, review of complications of Scottish patients on HPN for at least 3 months revealed few events of concern, causing the authors to indicate that there may be an argument for increasing the length of time between review appointments, without detrimental effect to patient safety [54].

Guidelines on HPN from the ESPEN state that the purpose of monitoring is to “secure and improve QoL” of persons on HPN [4]. They advise the monitoring of biochemistry and anthropometry at all visits; vitamins and trace elements at six-monthly intervals and investigations for metabolic bone disease annually. Wengler et al. studied monitoring practices for HPN across Europe and concluded that the majority of centers were similar to Scotland regarding 3-month monitoring intervals for stable patients [55]. This group also emphasized that responsibility for monitoring should be assigned to a designated person on the hospital HPN specialist team.

The ASPEN GLs have some similarities to ESPEN GLs such as annual bone densitometry [29]. However, they recommend slightly different intervals for monitoring other elements, with monthly to quarterly biochemistry and liver function tests, quarterly iron and folate, and quarterly-to-annual trace elements and annual vitamins.

The AuSPEN GLs [8] provide an outline of core monitoring to be assessed regularly in all patients on HPN including weight and height, oral intake, biochemistry studies, hematology screen, lipid screening in long-term patients, minerals including trace elements (every 6 months), listing of all medications, gastrointestinal loss assessment for stability and replacement, central venous catheter status and concerns, and functional status. Other than the frequency noted, these were usually recommended to be done every 3 months. Additional monitoring was recommended for some patients. This included glycemic monitoring in diabetics, annual bone mineral density studies, quality of life surveys, anthropometry, inflammatory markers, problem solving checklist, and INR for those on anticoagulants.

After hospital discharge following training of the HPN patient and family members, it is critical that the HPN team make contact with them on a regular basis, initially every few days, then weekly and eventually monthly as the patient gains confidence. The clinician who is in contact should be prepared to clarify confusing issues and also to follow weight, urine output, diarrhea or stoma output, temperatures before and within an hour of starting the TPN infusion, and general health. Monitoring of hydration status is particularly important to prevent hospitalization with dehydration by early provision of extra intravenous fluid, as shown by a recent large retrospective study [56]. If insulin is required, capillary blood sugars should be performed frequently and also recorded by the HPN team clinicians.

Patients whose infusion is cycled (<24 h) have wide variations in the degree of hydration, ranging from relative over-hydration when the infusion is completed to relative dehydration before starting the next infusion. In monitoring laboratory studies and body weight it is important that the timing of blood draws and weight assessment is consistent relative to stopping infusions to make results comparable from day to day.

It is important that the HPN team is able to learn about the patient's compliance from the patient and other caregivers, as well as from the supplier of the home infusion products. The supplier's employees should be able to report whether the orders are in line with the time elapsed. This information is critical for interpreting the results of laboratory testing, development of infections, and reliability of weight data.

The frequency of blood testing varies with the PN component of interest. There are no comparative studies documenting ideal timing of blood draws relative to time since the last infusion. Furthermore, there are no studies indicating the preferred interval between blood tests. Some blood tests are less indicative of nutritional status than are 24-h urinary excretion studies (for example magnesium) [57]. It is thus important that the proper laboratory test be performed and consistent timing relative to PN infusions be used to assess any individual person on HPN.

The use of disease-specific pathways for obtaining laboratory values and follow-up patient visits is recommended [28]. Electrolytes, including Na^+, K^+, Cl^-, HCO_3^-, plus studies of renal function (creatinine and blood urea nitrogen) should be measured frequently until stable, then at regular intervals. Assays of liver enzymes, bilirubin, albumin, and complete blood counts should also be monitored on a regular basis. Vitamin levels and trace element levels are typically done less frequently, often once or twice annually. Bone mineral densitometry should be done when HPN is initiated and at intervals thereafter [58]. All laboratory results must be reviewed and HPN prescription adjustments made as indicated.

9. **We recommend that quality of life for HPN patients be regularly measured using validated tools as part of standard clinical care. Quality of care should be assessed regularly according to recognized criteria.** (Grade of evidence: **very low**)

Quality of care

To know how patients should best be managed, interventions determined to be essential for good quality of care (also called 'key interventions') need to be identified and ranked according to their relative importance. A recent study on HPN patients with benign underlying disease used a two-round Delphi approach which is a technique that transforms opinion into group consensus [22]. The resulting set of most highly ranked key interventions was then transformed into quality indicators. The Donabedian paradigm provides a framework to assess the quality of care by working with these quality indicators related to structure, process, and outcome of health care [59]. 'Structure' refers to general administrative standards for the organization and people providing care; 'process' refers to the manner in which care is actually provided and administered and 'outcome' refers to a set of expected or desirable results for patients [21]. As a result, the quality of care can be reflected by measuring several factors in practice such as the number of catheter-related infections, the incidence of hospital readmission for the patient, the QoL, weight change, or the incidence of dehydration. The key interventions identified should be measured in current practice to know if further improvement is possible. These key interventions can also be used by auditors to know more about current quality of care. Those key interventions were measured in centers in 8 countries to compare patients' desired outcomes [23]. This cohort identified incidence of catheter-related infections, survival, and QoL as the most important outcome indicators for their care; however, there were significant differences between the participating centers. Outcome indicators should not be measured alone; for example, reporting the number of catheter-related infections should be monitored along with the linked process indicators (for example hand hygiene) which will help to drive quality improvement.

Quality of life

Traditional monitoring of HPN patients involves clinical and laboratory tests. In modern healthcare, the use of patient-reported outcomes, including assessment of QoL are recognized care quality indicators. Quality of life is not only affected by the treatment itself but also by the underlying disease, presence or absence of a stoma, and frequency of hospital readmission [7]. Studies acknowledge the difficulty of trying to identify the effects of the underlying illness, resulting in the need for HPN, and the HPN itself [60–62]. Use of different QoL instruments, scales, and lifestyle domains limit comparison among studies [63]. It is recognized that reporting QoL should be patient-based rather than the clinician's perspective. The HPN-QoL® is a treatment specific questionnaire for patients with benign underlying disease [26]. The HPN-QoL® is a 48-item questionnaire that focuses on physical, emotional, and symptomatic issues. The capturing of social and personal data to measure QoL has traditionally been used in clinical trials but rarely in routine practice. The HPN-QoL® can be used to monitor longitudinal change in QoL as well as on-off assessment and population studies. The QoL of an HPN patient is intrinsically linked to the quality of care and this questionnaire is able to identify issues that impact QoL that might be addressed by altering aspects of clinical care, for example the provision of an ambulatory pump and volume or frequency of infusions.

10. **We suggest that HPN patients be encouraged to join non-profit groups that provide HPN education, support and networking among members. This may be beneficial to patient consumers of HPN with respect to quality of life, depression scores, and catheter infections.** (Grade of evidence: **very low**)

The first known organization for persons on home parenteral and enteral nutrition (HPEN) was the Oley Foundation, started in 1983 by Lyn Howard and her HPN patient Clarence "Oley" Oldenburg in the United States [64]. Originally a social and outreach organization that allowed networking among local patients on these complex home therapies, it developed quickly into a national/international (including Canada) organization. The goal was "enriching lives of those requiring home IVS and tube feeding through education outreach and networking" [65] of patients/consumers, their families, clinicians, and the public in general. The current membership exceeds 14,000. Involvement of clinicians with HPN consumers offers the opportunity for patient education on evolving therapy, clinical guidelines and also for association with national professional groups, such as (for example) in the Unites States, A.S.P.E.N., American Vascular Association (AVA), and Intravenous Nurses Society (INS).

Persons on HPN and their families were the subjects of a 1993 study by Smith who interviewed 178 families identifying low QoL, low self-esteem, poor family coping skills, and depression as prominent characteristics [66]. Subsequently, the same researcher compared members of the Oley Foundation on HPN to individuals on HPN who were not members of a peer-support/education group [67]. This case-control study (matched for age, gender, duration of HPN, and diagnosis) showed that the 49 HPN patients affiliated with the Foundation had significantly fewer episodes of catheter infections, less depression, and better QoL life than the control group ($n = 50$). In addition, a qualitative study of the value of the Oley Foundation included 22 consumers of HPN or tube feedings. They identified Oley's programs, educational resources, and the competency, inspiration, normalcy, and advocacy gained from membership, as factors that helped individuals adjust to life with HPEN dependency [68].

HPN peer-support groups primarily designed for mutual support and networking, are active in several European countries and in Australia–New Zealand. The UK organization PINNT (Patients on Intravenous and Nasogastric Nutrition Treatment) was started more than 25 years ago by 4 people receiving this therapy [69]. PINNT is a non-profit organization and has collaborated in some

projects with the National Health Service of the UK and the National Institute for Health and Care Excellence (NICE). In addition, they have developed relationships with members of industry who provide products and services for parenteral and enteral nutrition. PINNT and its pediatric arm (Half-PINNT) are associated with regional groups in thirteen regions of the UK. Their aim is to promote greater understanding of the therapies amongst patients, potential patients, and the medical profession through networking and group meetings.

Other non-profit groups that support individuals on HPN exist around the world. Some of these are associated with the respective PEN organizations of their respective countries (Table 7). An additional important role is advocacy through government groups, non-government organizations, and elected officials to help improve the survival and QoL of recipients of HPEN.

An International Alliance of Patient Organizations for Chronic Intestinal Failure and Home Artificial Nutrition (PACIFHAN) is under development to promote international sharing of information and resources, to improve the QoL of patients on HAN, and to increase global awareness of CIF and HAN.

11. **We recommend that CIF patients be cared for by a multidisciplinary team with skills and experience in intestinal failure and HPN management.** (Grade of evidence: **very low**)

All contemporary HPN Guidelines recommend the expertise of a multidisciplinary nutrition support team for patients with HPN [4,8,10,11]. The core members of a multidisciplinary team are defined as surgical and gastroenterology specialists, nurse specialists, dietitians, and pharmacists. Additional disciplines may be required, for example, psychologists and social workers.

Comparative data to support the concept that an experienced multidisciplinary team improves safety, increases bowel rehabilitation, and decreases complications of long term IF and HPN is confounded by the fact that centers studying these factors are themselves experienced multidisciplinary centers with sufficient patient numbers to maintain expertise. However, in French-designated HPN centers, survival improved as the experience of the supervising clinicians improved [70].

Reports from specialist in-patient IF units managing complications such as enterocutaneous fistulas show that experienced multidisciplinary teams together with adherence to a standardized guideline can result in good patient outcomes [5,71,72].

An audit of a non-specialist general hospital working in conjunction with a specialist IF hospital showed that low complication rates could be achieved that were comparable to large tertiary referral specialist centers in the UK [73]. However the authors and others acknowledged the need to find a balance between sufficient volume of patients to develop skills, knowledge of the specialist team, and providing a locally accessible service for patients [53,74].

A large review of patients with CIF including those who had been referred for ITx found that small centers managing intestinal failure patients should establish links with IF programs early and not more than 3 months after starting PN [75] The review also recommended that national registries for IF patients be established to support multicenter studies and lead to adoption of universally accepted standards of care.

Complication rates for HPN patients have been studied for the last 30 years and those that have also examined the presence of experienced multidisciplinary teams have found that experienced teams invariably have lower complication rates and better outcomes [55,67,76,77]. The North American Home Parenteral and Enteral Nutrition Registry compared mortality rates in 407 HPN Crohn's patients managed in either large teaching programmes ($\geq$25 HPN patients) or smaller non-teaching programmes ($\leq$5 HPN patients). The average mortality rate per year was significantly higher in the smaller programmes [78]. This again suggests the importance of clinical experience for optimal survival [79]. Specialist nurses as part of the multidisciplinary team have been repeatedly shown to favorably influence rates of central line-associated blood stream infections [80,81].

A survey of IF management in Europe examined clinical outcomes, structure and organization of services, referral criteria, treatment procedures, and guidelines. Findings indicated that patients were being managed in specialist units in the setting of both surgical and medical gastroenterology but that organizational structures varied widely [82]. A multidisciplinary comprehensive IF programme in North America was evaluated after treating 50 patients with short bowel (children = 30, adults = 20). The organized multidisciplinary approach including surgical intervention led to partial weaning or discontinuation of PN support in 85% of patients [83].

A recent study sought patient views on safe and effective treatment for CIF patients receiving HPN. Participants across a number of countries scored highly the importance to them of discharge planning and education, care from the hospital doctor,

Table 7
Non-profit organizations for caregivers and patients on home parenteral nutrition and for clinicians.

- Aepannupa (Spain): http://www.aepannupa.org/
- Bowel Group for Kids Inc.: www.bgk.org.au
- Kinder and Schweiriger Ernaehrungssituation. V. - KISE Germany:
- http://www.kise.de/
- LaVie Par Un Fil (French Organization for HomePEN Families):
- http://perso.wanadoo.fr/lavieparunfil/
- Life by a Thread – Belgium: http://users.skynet.be/lavieparunfil/
- Lifeline Foundation and Parenteral Nutrition in Poland: http://www.idn.org.pl/liniazycia/toppage1.htm
- Norwegian Society of Clinical Nutrition and Metabolism: http://www.nske.no
- Oley Foundation: http://www.Oley.org
- Parenteral Nutrition Down Under (PNDU): http://www.parenteralnutritiondownunder.com
- PINNT (British Organization for HomePEN Consumers): http://www.pinnt.com/
- Polish Support Groups: http://www.apetytnazycie.org/, http://www.NaZywieniu.pl
- Short Bowel Survivor & Friends (Great Britain):http://www.shortbowelsurvivor.co.uk/
- South African Society for Parenteral and Enteral Nutrition: http://www.saspen.com/
- Swedish HPN-Association: http://www.hpn.se/english.php
- The Norwegian Association For Home Parenteral Nutrition: http://www.nifo.no
- Un Filo per la Vita (Thread for Life Italy): http://www.unfiloperlavita.it/

dietitian and nurse together with ongoing medical review [84,85].

4.2. Parenteral nutrition formulation

12. **We recommend that the protein and energy requirements for CIF patients be based on individual patient characteristics (e.g. intestinal absorptive capacity as estimated by gastrointestinal anatomy and/or underlying disease) and specific needs (e.g. acute illness, protein malnutrition), and that the adequacy of the regimen is regularly evaluated through clinical, anthropometric, and biochemical parameters.** (Grade of evidence: **very low**)

Protein intake in HPN admixtures is supplied as L-amino acids. All commercially available amino acid formulations for PN provide the nine essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) in amounts varying between 38% and 57% of total amino acids. Commonly used amino acid mixtures also provide nonessential amino acids comprising 43–62% of total amino acids [86].

Amino acid requirements in HPN must take into account the heterogeneous HPN patient population, some of whom will have ongoing high stoma losses or protein loosing enteropathy whilst others will have requirements more aligned with normal free-living people. The protein-sparing effects of the intestine, which facilitate gradual release of nutrients after bolus feeding are absent in HPN [87] and thus infusions over time rather than bolus protein infusions are the preferred delivery method. A small study showed that segmental reversal of the small bowel in adults with SBS allowed increased protein absorption and, as this type of surgery has been developed for intestinal rehabilitation, the consequences of changing protein requirements must be considered [88].

More fundamentally, it is commonly assumed that the weight of amino acids in a PN mixture equals the amount of protein they would provide if fed by mouth. A recent study showed that amino acid solutions provide 17% less protein substrate than the sum of their constituent amino acids [89]. Protein prescriptions must therefore take in consideration the lack of equivalence of amino acids to dietary protein into account.

Protein requirements must be assessed as individual requirements based on a formal nutritional assessment which includes disease-specific needs, medical condition, nutritional status, age, sex, and organ function. In healthy individuals, national and international guidelines have recommended that protein requirements are 0.8–1 g/kg/day which must be accompanied by adequate energy to allow optimal nitrogen utilization but have acknowledged that there is insufficient evidence to extend this to specialized medical care [4,10,90]. Administration of mixed essential and non-essential amino acids in HPN prescriptions must be based on the needs of the individual and be infused over time. Many stable patients on HPN are satisfactorily maintained on prescriptions that provide 0.8–1.4 g of protein (0.13–0.24 g of nitrogen)/kg/day [4,8,10]. Limited outcome data is available on the effects of adjusting amino acid doses for HPN patients.

Energy sources for HPN prescriptions can be derived either from a combined carbohydrate and fat emulsion administered together or from separate glucose and fat emulsion HPN prescriptions delivered on different days [4]. Determining energy requirements cannot be achieved by a single fixed formula and must be based on a formal nutritional assessment including disease-specific needs. Individual factors to be considered include medical condition, nutritional status, activity level, and organ function. An earlier small study measured energy expenditure by doubly-labelled water in patients receiving parenteral nutrition at home compared to those receiving it in the ICU. The results showed that septic patients had higher energy requirements but that HPN patients' energy requirements could be met by supplying 1.4 times the resting energy expenditure or about 30 kcal/kg/day [91]. HPN patients often have significant oral intake which may be at least partly absorbed and contribute to energy intake. Another small study examined the metabolic use of fuels using indirect calorimetry in HPN patients without cancer who received nocturnal glucose-based HPN and a self-selected oral intake [92]. The patients who ate were in positive energy and nitrogen balance with a normal adapted metabolic response to nutrient utilization. HPN energy requirements may also be modified depending on gut organ function and, in particular, gut anatomy. A cross-sectional survey of HPN patients in Denmark showed that preservation of substantial colonic function resulted in a reduction in HPN energy requirements of over 1200 kcals/day in patients with less than 100 cm of small bowel compared to similar patients who had no colon [93]. The colon has been shown to be an energy salvaging organ [94–96] and its preservation may make relative requirements for HPN less or sometimes unnecessary. Segmental reversal of the small bowel to slow peristalsis has been proposed in patients with SBS as a rehabilitation therapy. A small recent study showed a gain in macronutrient absorption and reduction to a median of HPN requirements to 3 infusions per week compared to prior requirements for 3.5 infusions per week [88]. Little evidence exists to guide energy prescription for HPN patients and individual assessment for requirements is essential. Many stable patients on HPN are satisfactorily maintained on 20–35 kcals total energy per kg per day [4,8,10]. Goals of treatment with HPN and regular re-evaluation should direct the energy requirement in an HPN prescription. Replenishment of body cell mass will differ from maintenance requirements.

13. **We 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.** (Grade of evidence: **very low**)
14. **We cannot make a recommendation at this time on addition of insulin to HPN admixtures due to lack of evidence-based data regarding insulin prescription for HPN patients who have hyperglycaemia.** (Grade of evidence: **very low**)

Free-living people have a wide range of fuel mixture from food in their diet and it has been shown that whole body glucose oxidation rapidly adapts to changes in glucose or carbohydrate intake [97]. Patients requiring HPN have a nutrient intake which is different from normal food intake. Many patients manage to sustain a variable and usually small oral intake but as PN carbohydrate is glucose, the intake of monosaccharide is greater compared with oral nutrition. In addition, HPN is often infused continuously overnight compared to bolus eating during the day. These factors, together with possible decreased insulin sensitivity from the primary disease process or co-existing Type 1 or 2 diabetes mellitus, mean that some patients on long-term PN have hyperglycaemia.

Hyperglycaemia is associated with adverse outcomes in patients with diabetes as well as non-diabetic patients when patients have hyperglycaemia whilst receiving PN in the hospital setting. This effect may extend into the community [98–100]. HbA1c, which gives a measure of the mean blood glucose level over approximately the past two months, is the essential baseline measure of long-term glycaemic control in almost all patients who experience elevated blood glucose levels on HPN. A

community recommendation for glycaemic control is that patients should have an HbA1c target between 48 mmol/mol and 58 mmol/mol (6.5% and 7.5%) and on-going review of treatment to prevent hypoglycaemia [101,102]. Glycaemic control can also be assessed by blood glucose measurements and may be used for checking hypoglycaemia symptoms. Blood glucose targets should be: fasting<7 mmol/L (<140 mg/dl), pre-infusion/meals between 4 and 7 mmol/L (100–140 mg/dl), during HPN infusion 7–10 mmol/L (140–180 mg/dl) [103,104].

There is limited data on strategies for managing hyperglycaemia in patients receiving HPN but the deleterious effects of unchecked hyperglycaemia are well documented. Options for medically managing hyperglycaemia range from decreasing the glucose load in the HPN prescription, prescribing oral hypoglycaemic medication, giving a daily dose of injectable insulin, or adding insulin to the HPN admixture. Hyperglycaemia, however, should be minimized by individualized PN prescriptions based on the patient's clinical condition, body composition, age and gender, level of activity, and ability to take oral nutrition. Relative proportions of lipid and carbohydrate may be considered to minimize hyperglycaemia. One group has suggested that the range may lie between 60% carbohydrate and 40% lipid to a maximum of 60% lipid and 40% carbohydrate (non-protein kcals) [104] but the metabolic consequences of this in HPN patients should be carefully considered (see elsewhere in Guideline).

Insulin protocols for management of hyperglycaemia in patients receiving PN have been proposed. One insulin-dosing schedule for hospitalized patients suggests using 1 unit of insulin for every 20 g of PN glucose but the dosing was two-thirds short-acting insulin in the PN and one-third NPH insulin subcutaneously in divided doses [105]. Another study recommended the use of a peak-less long-acting insulin analog in hyperglycaemic hospitalized PN patients [106]. There is little evidence regarding dosing protocols for longer term PN patients. All options have advantages and disadvantages. Many HPN patients cannot reliably absorb oral medications and both oral hypoglycaemic medications and separately-injected insulin rely on HPN subsequently being administered at full dose or hypoglycaemia becomes a risk. Inclusion of insulin in the PN admixture raises other issues: specific criteria for evaluating compatibility and stability studies of medication in PN are well recognized and should be met [107]. However a recent US study showed that insulin was a frequent non-nutrient inclusion in PN [108]. 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.

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 [109,110]. Earlier reports from 3 to 4 decades ago suggested approximately 50% loss of insulin from PN solutions by nonspecific binding to infusion material [111]. Since these reports, the purity and source of insulin and PN admixtures and bag materials have all changed. More recent reports of admixtures containing glucose, amino acids, and lipid in ethylene vinyl acetate bags suggest that insulin availability is much higher (90–95% available) [109,112]. It has also been shown that at 10 units/L insulin recovery was much greater from PN solutions containing multivitamins/trace elements than those without at every time point measured [112]. Insulin availability from multilayer bags does not seem to be reported in the literature. These findings, however, should not impact patients with consistent and stable HPN prescriptions in a community setting. Short-acting insulin may be cautiously added to HPN prescriptions after dosage requirements have been established. Any subsequent change in the PN formulation, volume, or bag size should initiate a closer evaluation of blood glucose over the next few days to determine if any insulin dose adjustment is needed.

15. **We suggest, in patients totally dependent on HPN, a minimal supply of 1 g/kg/week of intravenous lipid emulsion containing EFA, to prevent EFA deficiency.** (Grade of evidence: **very low**)

Patients on long-term PN on lipid-free or very limited lipid and high glucose admixtures may experience induction of hyperinsulinaemia which suppresses mobilization of essential fatty acids (EFA) from fat stores and induces EFA deficiency (EFAD) [113].

Essential fatty acids (linoleic acid and α-linolenic acid) cannot be synthesized by humans and external supplementation is necessary. Symptoms of linoleic acid deficiency include: dermatitis (scaling, thinning and dryness of skin) and alopecia [114], other clinical manifestations of EFAD include neurological or haematological side effects, and may even lead to death [115–117]. Patients on long-term PN are in the group at high risk of development EFAD [118] if not given an external source of EFA. The clinical signs of EFAD may develop within 2–6 months of fat-free PN [117].

According to a study by Mascioli et al., EFA ratios can be normalized by administration of soybean oil lipid emulsions in the amount of 1.2–2.4 g/kg body weight biweekly [119]. Although no differences were found in EFA status after introduction of the same amount of long-chain triglyceride (LCT) and medium-chain triglyceride (MCT)/LCT lipid emulsion in a crossover study [120], more studies are needed with second and third generation lipid emulsions.

Based on one observational study [121] and existing GLs [4], in long-term PN, the necessary minimum of lipid emulsion that should be administered to prevent EFAD is 1 g/kg/week. If patients take some oral diet in the form of fat, EFAD is rarely a specific problem [4].

Laboratory examination of EFA supplementation can be supported by the assessment of the triene:tetraene ratio (T:T ratio, the Holman index). A T:T value > 0.2 indicates EFA deficiency, even without appearance of clinical signs [122]. T:T ratio refers to the eicosatrienoic (mead) acid: arachidonic acid ratio. Omega 3 and omega 6 are preferred substrates over omega 9 for elongase and desaturase enzymes that regulate fatty acid metabolism. In the absence of EFAs, omega 9 is metabolized to mead acid, thus increasing the T:T ratio.

16. **We suggest that most patients on long-term HPN for CIF without ongoing metabolic complications be safely treated with provision of no more than 1 g/kg/day of intravenous soybean-based lipid emulsion.** (Grade of evidence: **very low**)

Lipids should be an essential component of parenteral admixture in patients on long-term HPN. Lipid emulsions serve as a source of EFA and non-protein energy. Moreover, they can be used as an immunomodulating component of PN. Considering intravenous fat emulsion recommendations, the need to cover EFA requirements must be balanced against prevention of intestinal failure associated liver disease (IFALD), which can be achieved by limiting the lipid dose [123].

The recommendation for long-term HPN is as follows: intravenous administration of energy sources should be composed of lipids as 15–30% of the total calories, and 30–50% of non-protein calories [4,8]. High percentage of lipid (e.g. 50% of non-protein energy), may be beneficial for patients with cancer cachexia

needing prolonged PN, because of abnormalities in energy substrate metabolism in this condition [124].

The optimal amount of lipids for patients on HPN is not precisely established. At least 1 g/kg/per week should be supplemented to avoid EFAD in patients totally dependent on IVS. Probably most of the patients who maintain some oral intake of fat can be safely treated with provision of 0.3–0.9 g of intravenous lipid per kg of body weight per day [113,120,125–129].

For long-term HPN treatment (>6 months), the amount of intravenous soybean oil lipid emulsion should not exceed 1 g/kg per day. Administration of soybean oil lipid emulsion in higher doses was associated with significantly increased risk of development of IFALD [130,131]. Infusion of parenteral lipid emulsions at rates of 0.8–1.5 g/kg body weight per day is safe, but should not exceed 2.6 g/kg per day (0.11 g/kg/h) because side effects have been reported for cases in which that threshold was exceeded [132]. Practitioners need to match the proper dose with the clinical situation and in accordance with established GLs.

17. **We recommend regular monitoring of signs and symptoms of dehydration, fluid balance, laboratory tests, and 24-h urine output as well as a timely adjustment of fluid supplementation to prevent chronic renal failure in patients on HPN.** (Grade of evidence: **very low**)
18. **We recommend that the HPN formula be adjusted with the aim of normalizing laboratory tests related to fluid, electrolytes and mineral balance in patients on HPN.** (Grade of evidence: **very low**)
19. **We recommend regular monitoring of acid-base status in patients on long-term HPN (serum concentration of chloride and bicarbonate), because either metabolic acidosis or metabolic alkalosis can occur.** (Grade of evidence: **very low**)

Patients on HPN, particularly those with SBS, are at risk for fluid and electrolyte imbalance, which can lead to acute and chronic renal failure [133,134]. Persistent volume depletion, chronic hyponatremia, metabolic acidosis, as well as oxaluria (particularly in those with colon in continuity) [135] and nephrolithiasis [44] cause various nephropathies that may underlie chronic renal disease. This may be intensified by oral intake of hyperosmolar fluids that increase the osmotic load in the shortened bowel, causing large net fluid loss that cannot be corrected by distal absorption. Oral diets with high simple sugar and salt intakes are major contributors to fluid loss into the intestine [136]. Intake of very low osmolality liquids, particularly those with little or no sodium and sugar content (water, coffee, tea, etc.) also result in the loss of more volume than was ingested. Many clinicians recommend drinking water to help with hydration, so those who are most familiar with SBS should be aware that this is likely to mislead patients [137,138].

The daily parenteral water requirement varies from 25 to 35 mL/kg (approximately 2.0–2.5 L) for the well-hydrated individual [8]. For patients on HPN who have normal renal function and are not on diuretics, the urine output should be at least 0.8–1 L per day [15]. There have been no randomized studies of optimal PN volumes for those on long-term treatment. For those who have severe diarrhea, high stomal excretion, or large fistula outputs, the volume requirements are often markedly higher and this can be accomplished by increasing the water component of the PN formula. The adequacy of the HPN volume may be assessed by measuring 24-h urine output.

A suspected diagnosis of volume depletion is based on clinical evaluation including postural increase in heart rate and decrease in blood pressure (>20 mm Hg systolic and >10 mm Hg diastolic) comparing supine and standing levels, dry mucous membranes, poor skin turgor, decreased urine output, rapid body weight loss, and decreased central venous pressure demonstrated by collapsed jugular veins [139]. This is accompanied by laboratory parameters including increases in hematocrit, serum osmolality and sodium concentration, increased urine osmolarity (>450 mosml/kg) [139], random urine sodium level, as well as increased blood urea nitrogen. While these laboratory studies may be diagnostically helpful, they may not be evident until after some of the physical changes have appeared. Blood urea nitrogen and creatinine levels as well as urine output and body weight should be monitored frequently, especially early in the HPN course, with decreasing frequency during a stable HPN course [140]. Additionally, with seasonal weather changes (hot humid summers) or excessive physical exertion, symptoms and laboratory changes should be monitored closely, as the parenteral fluid requirements may be increased.

Oral rehydration solution (ORS), originally used to treat cholera, has been introduced to decrease or even eliminate parenteral fluid requirements in SBS [141]. It is based on acceleration of co-transport of sodium with glucose [142,143]. Since water is absorbed as a result of solvent drag, this is an effective way of improving water absorption. Nightingale's studies indicate that the sodium loss in stomal effluent is approximately 100 mmol/L [144]. Compliance with this treatment is often difficult to achieve, and the clinician may need to suggest further dilution with water initially, possibly with a gradual increase in sodium, as tolerated.

While dehydration is more common than overhydration in HPN patients, those that have synchronous renal failure or chronic heart failure will likely require volume restriction for their PN. This is especially true when such patients undergo hemodialysis. These patients require extremely careful monitoring of clinical status. Edema and shortness of breath are found in such patients.

Parenteral nutrition fluid and electrolyte dosing recommendations (Table 8) are based on clinical experience, as there are no randomized studies available. It is important to consider underlying disease state and gastrointestinal anatomy for individual patients (including residual small intestinal length, segment that has been resected, presence of colon) as well as comorbidities. In determining what the electrolyte requirements are for a specific patient, it is important to understand the composition of gastrointestinal fluids [138].

Serum sodium concentrations are more commonly related to hydration rather than to amount of sodium in the PN formula. Hypernatremia is most commonly related to a deficit of free water [145], and hyponatremia occurs with excessive hydration using hypotonic fluids. A case study nicely demonstrated this when a young man on TPN was treated with multiple antimicrobials diluted in free water and developed hyponatremia [146]. Instead of minimizing the dilution or using saline for the diluent, the sodium in the PN was increased. When antibiotics were discontinued, the result was hypernatremia. Signs and symptoms of hyponatremia are primarily neurological, generally appearing with a serum sodium less than 125 mmol/L. Nausea and malaise occur early, then

Table 8
Fluid and electrolyte recommendations for parenteral feeding (from [4,138,139]).

	/kg/day[a]	/day (average adult)[a]
Water	25–35 mL [4]	1500–2500 mL
Sodium	1.0–1.5 mmol [4]	60–150 mmol [138,139]
Potassium	1.0–1.5 mmol [4]	40–100 mmol [139]
Chloride	1.0–1.5 mmol [4]	
Phosphate	0.3–0.5 mmol [4]	10–30 [139]; 25 mmol [4]
Magnesium	0.1–0.15 mmol [4]	4–12 [139]; 10 mmol [4]
Calcium	0.1–0.15 mmol [4]	2.5–7.5 [139]; 10 mmol [4]

[a] Adjustments may be needed for underlying disease, clinical case, medications and oral intake.

are followed by headache, obtundation, seizures, coma, and respiratory arrest [147]. The manifestations of hypernatremia are also neurogical including lethargy, altered mental status, restlessness, irritability, hyperreflexia, nausea, vomiting, fever, intense thirst, and labored breathing. In both situations, correction must be done cautiously.

Hypokalemia is unusual in those whose residual small bowel length is greater than 50 cm, although it can occur in those with extremely short bowel [15]. Insufficient or excessive potassium in the PN and/or diet is also a common cause of abnormal levels. In addition, medications can have a marked effect on potassium levels (i.e. loop diuretics, such as furosemide, and amphoteracin b cause hypokalemia). Furthermore, hypokalemia may result from hypomagnesemia in which case the magnesium must be corrected before the potassium level will improve [148]. Hyperkalemia can occur in patients on HPN with concurrent medications, such as potassium-sparing diuretics, octreotide, and heparin [149]. Finally, hemolysis is a relatively common cause of a falsely elevated potassium level in blood, and repeat testing should be done before treating the abnormality. Hypokalemia is a cause of abnormal cardiac rhythms, often expressed as palpitations. Fatigue, muscle weakness, and tingling or numbness are other symptoms associated with low potassium levels. Hyperkalemia is also associated with cardiac dysrhythmias. Potassium either intravenously or orally may be used in hypokalemia, although the protocol for intravenous potassium replacement in many hospitals is limited to 10 mmol/h, unless the patient is under cardiac monitoring. For hyperkalemia, treatment depends on the degree of elevation and the rapidity of the elevation. This may include parenteral insulin, IV fluids, a cation exchange resin and hemodialysis, as well as discontinuation of the cause for the elevation.

Hypophosphatemia occurs due to some medications, such as bisphosphonates, insulin, or PN [150]. In refeeding syndrome, circulating phosphorus shifts into cells, causing a precipitous drop in serum phosphorus [151]. This occurs during the course of refeeding with either parenteral or enteral formulas, and it can have potentially life-threatening outcomes. Cautious use of intravenous drugs may be effective in treating the hypophosphatemia of refeeding syndrome [152]. Most cases of hypophosphatemia occur in hospitalized patients. Hyperphosphatemia occurs most often in renal failure, but it also seen in excessive vitamin D or milk intake. It is often asymptomatic but it may present as anorexia, fatigue, nausea and vomiting, muscle cramping, tetany, and sleep disturbances. Treatment involves phosphate binding agents and correction of excess intakes of high phosphate foods.

In a critical review of the magnesium absorption literature, data from in vivo perfusion studies, in vitro gut preparations and tracer studies support that animal and human magnesium absorption occurs primarily in the distal ileum and colon [153]. The distal absorption sites make magnesium deficiency a common finding in SBS and inflammatory bowel disease involving the distal small bowel. While serum magnesium levels are measurable, it has been found that low urinary magnesium excretion is a more accurate reflection of total body magnesium depletion [154]. A case control study compared serum magnesium versus 24 h urinary Mg in 16 patents with IF and 16 age- and gender-matched controls before and after replacement of magnesium. In magnesium depletion, urinary Mg decreased before serum levels, and with replacement, the 24-h urine levels improved before the serum magnesium did. Thus, urinary magnesium was found to be a more reliable indicator of Mg status [57]. Oral replacement of magnesium is difficult, since the inorganic salts of magnesium quickly dissociate in fluid resulting in hyperosmolar intraluminal milieu that causes diarrhea. Organic forms of magnesium dissociate slower, so are less diarrheagenic and thus more effective for replacement. In a small randomized double-blind study of persons on HPN, magnesium gluconate was added to oral rehydration solution that was sipped slowly throughout the day. This approach resulted in more efficient replacement than equal bolus doses and hydration was improved concurrently [155]. Magnesium can also be increased in the PN solution or by giving supplemental intravenous magnesium.

It is recommended that the calcium, magnesium, and phosphate content of the HPN should maintain normal serum concentrations and 24-h urinary excretion [4].

Serum concentrations of chloride and bicarbonate should be routinely measured in patients on long-term HPN for CIF to monitor acid-base balance. Alteration of acid-base balance may occur through several mechanisms due to either the underlying gastrointestinal condition, the intravenous nutritional admixtures and electrolyte solutions, or the presence of impaired renal or respiratory function [156–161]. Gastric fluids contain large amount of acids, whereas intestinal fluids contain large amounts of bicarbonate. Loss of gastric fluids from vomiting or drainage tubes in the upper gastrointestinal tract can lead to metabolic alkalosis with hypochloremia. Hyperchloremic metabolic acidosis with normal anion-gap may occur due to high intestinal losses of bicarbonates, as in SBS patients with a high output ostomy, or because of administration of large amounts of sodium chloride with the PN solution, or with ORS to maintain hydration [162]. Maintenance of PN admixture chemical stability requires pH solution in low levels (ideal range 5.0–5.4). This is obtained by the addition of hydrochloric acid and acetic acid. Patients receiving a chloride-based formula are at increased risk of metabolic hyperchloraemic acidosis, which may be prevented by an acetate-based regimen that increases serum bicarbonate levels, acetate being converted to bicarbonate in a 1:1 M ratio [161,163,164]. Metabolic hyperchloremic acidosis can also be observed in patients who have undergone urinary diversion using the colon, due to increased intestinal absorption of chloride, and in patients on treatment with anti-proton pump inhibitors that reduce the excretion of chloride ions in the stomach thereby increasing net gut bicarbonate losses while decreasing gut chloride losses [156,161].

Metabolic acidosis with increase anion-gap may occur due to high D-lactic acid production by colonic bacterial fermentation of carbohydrate substrates in patients with a SBS with a colon in continuity, to L-lactic acidosis due to thiamine deficiency, or to PN admixture with high content of sulfur-containing amino acids (methionine, cysteine, cystine). D-lactic acidosis should be suspected in patients presenting symptoms like slurred speech, ataxia, and altered mental status, associated with normal L-lactate serum concentration [159]. Patients with thiamine deficiency can have peripheral and central neuropathies (dry beriberi), cardiovascular disease (wet beriberi), metabolic coma, Wernicke encephalopathy, Korsakoff syndrome, and optic neuropathy [158]. The oxidation of sulfur-containing amino acids leads to the production of H^+ and sulfate, an unmeasured anion that determines an increased anion gap. Moreover, sulfate is not reabsorbed from renal tubules and is excreted by the kidneys as sodium sulfate, leading to extracellular volume contraction and increased reabsorption of sodium chloride with the final result being the appearance of hyperchloremic acidosis [161].

High carbohydrate intravenous loads can increase oxygen consumption with a parallel increase of carbon dioxide production (glucose oxidation). This doesn't determine acid-base alterations in patients with normal respiratory function, but may cause respiratory acidosis in those with respiratory insufficiency [156,161].

20. **We suggest that clinical signs and symptoms as well as biochemical indexes of vitamin deficiency or toxicity be**

regularly evaluated at clinical review. (Grade of evidence: **very low**)

21. **We suggest that baseline serum vitamin concentrations be measured, according to laboratory availability, at the onset of HPN and then at least once per year.** (Grade of evidence: **very low**)
22. **We suggest that vitamin doses in HPN are adjusted as needed.** (Grade of evidence: **very low**)
23. **We suggest that the route of vitamin supplementation be selected according to the characteristics of the individual patient.** (Grade of evidence: **very low**)

An early report of laboratory analyses consisting of 63 individuals on HPN (40 with short SBS and 23 with intestinal obstruction) identified 24% to have subnormal vitamin A levels, 30% with low Vitamin D levels, and 45% who had decreased vitamin C levels. Vitamins B12 and folate were subnormal in only 7% and 0%, respectively. Given that fat-soluble vitamin levels may have been low prior to HPN, it is unfortunate that prior levels were not compared to post-HPN levels and that the length of time on HPN was not indicated [165]. Subsequently, similar results were reported from France where 27 patients on HPN were studied [166].

Because of parenteral multivitamin shortages in the United States, attention has turned to the length of time a patient on HPN could be maintained with only oral vitamins in the face of restricted parenteral products. A study of 6 patients with normal renal function and 2 with chronic renal failure during the time of an early multivitamin shortage reported the effects of decreasing intravenous vitamin doses from daily to 3 times weekly [167]. Blood testing for vitamins, which was not done prior to the shortages, was subsequently done every 6 months. Five patients with normal renal and hepatic function and both patients with renal failure had subnormal vitamin C levels with decreased dosing of vitamins.

A recent study of ten Brazilian adults with SBS (10–100 cm residual small bowel, one with no colon, one with entire colon, and 8 with left hemi-colon intact) who had been on HPN for 3–101 months (median 16 months) and who were hospitalized with only intermittent availability of parenteral vitamins indicated that vitamins A, E, and C were below the normal values [168]. Of these, 60% were only poorly to moderately compliant with the oral vitamins, while 40% were deemed to be highly adherent. Unfortunately, in this very small study the baseline stable vitamin levels observed during HPN were not indicated in the text nor were the outcomes of the 4 patients who were compliant compared to those who were not. In none of these studies were clinical signs or symptoms of deficiencies described. Thus, these appear to actually be subclinical findings. Furthermore, the number of patients included in the few reported studies was relatively small.

Clinical signs of night blindness and poor dark adaptation, both of which can be highly suggestive of vitamin A deficiency, may occur, but subclinical deficiency is more prevalent in patients on HPN [169,170]. However, marked visual complications may occur among patients who are not compliant with adding multivitamin products to their HPN. Serum retinol levels are measured most commonly among HPN patients to identify a risk for vitamin A deficiency [169].

Serum 25 hydroxyvitamin D is the primary circulating form of vitamin D. It has a half-life of 2–3 weeks. This is the proper measure for vitamin D nutritional status [171–173]. By contrast, serum 1,25-dihydroxyvitamin D does not reflect vitamin D nutritional status and is often normal or even elevated due to secondary hyperparathyroidism associated with vitamin D deficiency. The 1,25 form is useful in diagnosing disorders of calcium metabolism related to renal issues, but it should not be used as a part of standard vitamin D testing. The desired serum level is a matter of debate among bone metabolism experts [174]. Evaluation of serum 25-hydroxyvitamin D in 22 patients on HPN in Canada identified 15 whose levels were less than 50 nmol/L and considered to be vitamin D deficient by these authors [175]. A retrospective study of 25-hydroxyvitamin D levels measured over a minimum of 6 months found that five out of fifteen patients on HPN were consistently deficient (<27.5 nmol/L), 60% had variable levels between deficient and sufficient, and none had persistently sufficient levels [176]. Many individuals on HPN must receive vitamin D intravenously for successful use. The adequacy of 200 international units of vitamin D that is typically included in parenteral multivitamin formulas is not known. It can be supplemented by oral supplements in some patients [176], as well as by conversion of precursors in the skin when exposed to ultraviolet light.

Vitamin E deficiencies were identified in about 20% of 44 individuals on HPN, compared to 7% of a non-PN control group who had various degrees of malabsorption [177]. Among those on HPN who were not receiving lipids, plasma alpha-tocopherol was decreased in 33%. However, those on HPN who did receive lipids had normal levels of vitamin E. The frequency of testing alpha-tocopherol in patients who are on HPN is not identified in the literature.

Dietary intake of vitamin K is one of the primary determinants of vitamin K status. In addition, plasma lipids are a determinant of vitamin K status for the form of vitamin K ingested [178]. Patients on HPN because of SBS or severe distal small bowel disease often have a deficiency of Vitamin K [179].

Vitamin B12 is often deficient in those who have undergone a distal small bowel resection. It is also prominent in inflammatory bowel disease of the ileum [180], as is folate deficiency which, in part, is the result of medications used [181–183]. These possibilities make regular assessment of these vitamins of prime importance as long as the disease remains active while on HPN.

Ascorbic acid in parenteral multivitamin formulations varies between countries from 100 to 200 mg. In the United States the requirements were increased from 100 mg to 200 mg, and this has raised some concern about metabolism of intravenous vitamin C to produce oxalate, increasing the risk for oxaluria and renal complications [184]. This was shown in a prospective study where 24-h urine collections were done in 13 patients on HPN before and 1 month after the new 200 mg US FDA amended parenteral multivitamin formulation was supplied. Ten had significantly increased oxalate urinary excretion and in three this was well above the upper limit of normal, possibly putting them at risk for oxalate stones.

Laboratory frequency: existing guidelines

Initially, the Scottish Managed Care Network recommended that patients should have vitamin levels evaluated at every outpatient visit, typically every 3 months [185]. However, this recommendation was revised when it was noted that, of these patients, one-third did not meet the recommended testing interval and this did not compromise patient safety [54]. However, no specific suggestion for appropriate intervals for vitamin assays was made. The ASPEN guideline for vitamin testing was for annual intervals [186]. Although the AuSPEN practice guidelines for HPN were published in 2008, laboratory monitoring did not include suggested intervals for monitoring vitamins [8]. Subsequently the ESPEN guidelines published in 2009 advised that vitamin measurements should be done every 6 months [4]. However these authors did note that the Home Artificial Working group of ESPEN recommended that vitamins A, D, E, B12, and folic acid should be measured annually [55]. All of these recommendations were based on expert opinion since there were no evidence-based GLs available. This remains the case in 2015.

Parenteral vitamin products

In general, vitamin products used for HPN, as well as short-term hospital products, are produced as multiple vitamins. Although the formulations vary somewhat between countries, they are relatively similar with respect to the components. However, there are small differences regarding the amount of a few of the components.

Some vitamins tend to be deficient as a result of specific disease states. For example, patients with inflammatory bowel diseases frequently have lower levels of the fat-soluble vitamins because of disease involvement of the distal small intestine. While most multiple vitamin products provide sufficient vitamins, 25-hydroxyvitamin D levels are often very low and may need to be supplemented parenterally when this form is available [187] or with high dose oral products [176]. Additionally, when the distal small intestine is either severely diseased or in many cases resected, vitamin B12 is deficient and needs to be replaced. In contrast to adamant teachings of the mid-late1900's indicating that parenteral replacement was required, later studies now recognize that oral replacement can be achieved with high doses on a daily or near daily basis in many conditions including some patients who are on HPN. It is important that baseline vitamin levels be determined prior to starting HPN so that replacement vitamins can be given by using more than a single dose of multiple vitamins or, when available, specific parenteral vitamins can be used until resolution.

24. **We suggest that clinical signs and symptoms as well as biochemical indexes of trace element deficiency or toxicity be regularly evaluated at clinical review.** (Grade of evidence: **very low**)
25. **We suggest that baseline serum trace element concentrations be measured, according to laboratory availability, at the onset of HPN and then at least once per year.** (Grade of evidence: **very low**)
26. **We suggest that trace element doses in HPN are adjusted as needed.** (Grade of evidence: **very low**)
27. **We suggest that the route of trace element supplementation be selected according to the characteristics of the individual patient.** (Grade of evidence: **very low**)

Requirements for trace elements during illness and in patients on long-term HPN are still poorly defined. There is insufficient knowledge about how disease affects the metabolism of micronutrients or on the effects of differences in mode of delivery, bioavailability, and absorption as a result of artificial nutrition [188]. In addition, good markers of overall status are available only for a limited number of trace elements and few clinical laboratories are equipped to measure them, with the attendant difficulties in identifying deficits and monitoring supplementation.

The nine known essential trace elements are Cr, Cu, F, I, Fe, Mn, Mo, Se, and Zn. Since the first guidelines for essential trace element preparations for parenteral use were published by the Nutrition Advisory Group of the American Medical Association (NAG-AMA) in 1979 [189], the daily doses recommended for zinc, copper, manganese, chromium, and selenium in adults have been modified as new research information became available [190]. Both trace element deficiencies and toxicities have been reported in patients on HPN, the latter probably related to contamination in various PN components [191]. A recent study on autopsy tissues of eight patients who lived on parenteral nutrition for 2–21 years receiving the NAG-AMA 1979 formula, confirmed very high concentrations of copper, manganese, and chromium [192]. ESPEN guidelines also warned about the excess provision of manganese and copper, especially in patients with cholestatic liver disease [4].

A research workshop of experts in 2009 agreed to require some level of control of trace element contamination in all components of the parenteral formula, and to add 70–150 mcg/day of iodine to a basic adult PN formula and 1 mg of iron if stability and compatibility issues can be resolved for the latter. A case can also be made for the potential addition of molybdenum, boron, and silicon, depending on the amounts present as contaminants [190]. Also, they recommended that all the products should be labeled with a maximum allowable trace element level.

Recently, ASPEN developed a position statement for each micronutrient to address evidence-based data on its use and to provide recommendations (Table 9) for changes in the products available in the market [193]. Some pharmaceutical companies have changed the composition of the multitrace sources to meet these recommendations.

In a recent survey in Canada, the mean daily supplementation of Zn, Mn, Cu, and Se exceeded published recommendations [195]. In a study with 26 adult and adolescent HPN patients, the majority of patients had high levels of serum Mn and Cr, 22% of patients had high levels of copper, and the levels of Se and Zn were low in 38% and 10%, respectively [196].

The choices of trace element products vary from country to country, but in many countries only multitrace element preparations with fixed combinations are licensed, and individual trace element products may not be routinely available. This makes it quite challenging to manage the dosage of these micronutrients in many cases. Practical information on parenteral trace element use can be gleaned from case reports, some retrospective studies, and very few clinical trials [191]. A brief summary of the evidence on each trace element on dosage, measurement, and clinical studies in adults on HPN can be found below.

From 1979 to 2013, numerous case reports described Se deficiency in adults and children who used PN lacking in Se for periods ranging from months to years [191]. In contrast, the literature contains no report of Se toxicity in patients using PN. Parenteral doses of 60–100 mcg/day Se are sufficient for most adults yet do not maintain ideal levels in all patients. Plasma selenium concentration and glutathione peroxidase activity are commonly used as markers of selenium nutritional status. However, plasma selenium concentration fall independently of selenium status during the acute phase response and glutathione peroxidase activity is analytically problematic [197]. In the presence of a systemic inflammatory response, erythrocyte selenium concentration is the preferred marker of selenium status [198].

Balance studies indicate that copper requirements in total PN amount to 0.3 mg/day for adults [199]. This amount may have to be decreased in patients with cholestasis and increased in case of excessive prolonged gastrointestinal fluid losses. Long-term PN creates a potential for Cu toxicity, because hepatic Cu accumulation occurs with PN-associated liver dysfunction and cholestasis [191]. Copper contamination should be limited to less than 0.1 mg/day total in a typical adult PN formulation [193]. Blaszyk et al. performed liver biopsies on 28 long-term PN patients with cholestasis, and in 8 of the 28 patients, hepatic copper was >250 mcg/g (in the

Table 9
Recommended daily doses of trace elements for parenteral nutrition.

Trace elements	Dose (g)	Dose (mol)
Zinc	2.5–4 mg	38–61 mcmol
Copper	0.3–0.5 mg	4.7–9.6 mcmol
Manganese	60–100 mcg	1.1–1.8 mcmol[a]
Chromium	10–15 mcg[b]	0.2–0.3 mcmol
Selenium	60–100 mcg	0.2–0.8 mcmol
Iodine	70–150 mcg	0.5–1.2 mcmol
Iron	1 mg	17.9 mcmol

[a] Less than 1 mcmol/day [193,194].
[b] 0.14–0.87 mcg/day [193].

range for Wilson's disease) [200]. Several reports since the 1970s describe Cu-deficient patients who had no Cu added to their PN because of lack of availability or intentional omission because of cholestasis. In severe copper deficiency, serum copper and ceruloplasmin levels are low and reflect the copper status of the body, but are usually normal in marginal copper deficiency. Furthermore, ceruloplasmin is an acute phase reactant that increases in case of inflammation, pregnancy, and liver disease [199].

The accumulated scientific data point to a need to lower the recommended amount of parenteral Cr, and some people even think that it is not necessary to give extra Cr in patients on PN, due to the widespread contamination in PN components [191,201]. In humans, 3 reported cases of Cr deficiency in long-term HPN developed peripheral neuropathy, weight loss, and hyperglycemia. For parenteral Cr, concerns arise from the high levels found in sera and tissues and their effects on the kidneys [192]. Even in patients on short-term PN, high levels of chromium were detected in 94% of the patients, being the major contaminant in the amino acid solution with the trivalent ionic form [202]. Cr contaminants in PN solutions can increase the amount delivered by 10–100%. Reliable methods to assess Cr status in humans are limited. Although current adult multiple trace element products available provide 10–15 mcg/d of chromium, based on oral absorption in healthy individuals, the parenteral requirements may be as low as 0.14–0.87 mcg/day [193].

Many cases of Zn deficiency associated with the use of PN lacking in Zn were documented, mostly in the 1970s, before routine use of trace elements in PN [203]. Zn toxicity with PN has been documented only in instances of large dosage errors. In PN, the requirements have been estimated by balance studies to be 3 mg/day. Patients with enterocutaneous fistulae, diarrhea, and intestinal drainage may require up to 12–17 mg of Zn per liter of lost fluid [193]. Although circulating zinc levels fall in the deficient state, there are other causes of low circulating zinc levels (stress, trauma, infection) that make this measurement unreliable [203].

Fixed-dose multiple trace element formulations restrict prescribing options and make it difficult to adjust Mn levels without reducing the other essential trace elements. Mn toxicity may lead to neurotoxicity and liver complications. On the other hand, sustained inflammation in HPN patients may facilitate hypermanganesemia through cholestatic liver disease and thereby decrease Mn biliary excretion [204]. During the last two decades, elevated serum, plasma, red blood cell, and whole-blood Mn concentrations have been reported in patients receiving PN, both with and without liver dysfunction and usually with no symptoms [191]. High levels of Mn in brain were detected in a deceased woman after long-term PN involving Mn supplementation [205] and in the autopsies of 8 people on long-term HPN [192]. In a prospective study, patients on HPN were administered PN solutions providing scaling doses from 0 to 20 mcmol/day according to an on-off design. The optimal dose was 1 mcmol/d for adults according to the levels of Mn in whole blood and magnetic resonance imaging (MRI) [206]. In a sample of 16 patients on long-term HPN with a mean daily Mn supplementation of 400 ± 53 mcg/day, the mean whole blood Mn level was 1.38 ± 0.29 times the upper limit of normal and 81% of patients had high signals on T1-weighted images assumed to be Mn deposits in their basal ganglia. Two patients with positive MRI had Parkinson's disease, and multiple neuropsychiatric complaints were reported (depression, lack of concentration, memory disturbances, gait instability) [207]. Also a survey of 40 Australasian hospitals with data on 108 patients on HPN revealed that Mn doses were 5–6 times over current daily requirements [208]. In a longitudinal study including 15 patients on HPN, Mn levels in blood and brain (in MRI) significantly decreased after 1 year of Mn withdrawal in the PN [209]. Although the current Mn recommendations for adults on PN are 60–100 mcg/day, the scarcity of PN-associated Mn deficiency, plus the growing evidence for Mn toxicity, leads to the conclusion that it may be unnecessary for Mn to be prescribed routinely for long-term HPN patients [194]. ASPEN recommends that the dose of Mn in parenteral multiple trace element products be decreased to 55 mcg/d for adults [193]. Mn should be further decreased or withheld in patients with significant cholestasis or hepatic dysfunction, elevated whole blood Mn levels or in those with signs or symptoms of Mn toxicity [193]. Mn contamination should be limited to less than 40 mcg/d total in a typical adult PN formula [193]. Routine whole-blood measurement of Mn in combination with MRI is recommended to monitor potential accumulation [208].

The evidence favors an intravenous dose of around 1 mg of elemental iron per day in adult men and postmenopausal women [210]. Doses of 1.5 mg/day in menstruating women and 2.0 mg/d for those in the later stages of pregnancy or lactating can be supported. Continuous monitoring of iron status is recommended. PN poses an additional difficulty in that iron has poor compatibility with multinutrient "all in one" admixtures. Iron deficiency anemia is frequent in HPN affecting more than 50% patients on HPN (in a series of 55 patients) [211]. Serum ferritin is a reliable indicator of Fe deficiency when it is low, but it is also a positive acute phase protein that is increased in inflammatory conditions.

Daily iodine requirements in adults receiving PN are estimated to be 70–150 mcg, but most PN formulations do not contain iodine [212]. If chlorhexidine replaces iodine-containing disinfectants for catheter care, iodine deficiency may occur during long-term HPN, and periodic testing of thyroid functions may be prudent. This is especially important during pregnancy, in pre-term and newborn in which iodine is necessary for central nervous system development [212].

Boron may be beneficial for bone growth and maintenance, central nervous system function, and the inflammatory response, and silicon may be beneficial for bone maintenance and wound healing. Fluoride is not an essential element but amounts provided by contamination may be beneficial for bone strength. Fluoride toxicity may be a concern in PN [213]. Although Mo is an essential trace element only 1 case of Mo deficiency with long-term PN has been reported in the literature, probably because it is present as a contaminant in PN [191].

28. **We do not suggest the routine addition of individual amino acids (glutamine, cysteine, taurine) in the parenteral formula to decrease complications in adults on HPN.** (Grade of evidence: **low**)

Commercial amino acid formulations contain varying amounts of classically nonessential amino acids that may become conditionally essential under certain circumstances (e.g. cysteine, as acetyl-cysteine or cysteine HCL, taurine, and in one formulation glycyl-glutamine and glycyl-tyrosine dipeptide). L-Cysteine HCL (50 mg/ml as a 5% solution) and L-alanyl-L-glutamine dipeptide (200 mg/ml as a 20% solution) are also available in many countries for admixture into cysteine-free or glutamine-free complete parenteral nutrition [86].

Glutamine becomes a conditionally essential amino acid in severe stress conditions such as critical illness, surgery, and trauma, when endogenous utilization exceeds endogenous glutamine production. Glutamine added to PN at doses up to 0.57 g/kg/day in adults appears to be safe [214]. Very little information is available on the efficacy of glutamine-supplemented PN in home patients. In one study, 5 patients received glutamine at a dose of 0.285 g/kg for 4 weeks in their PN, and, in 3 out of 5 patients, glutamine administration was stopped because of elevations in liver enzymes [215].

In a randomized, controlled, 12-month cross-over study, 22 HPN patients received 6 months of PN containing glycyl-glutamine during the first or second 6-month study period (0.14–0.15 g/kg/day dipeptide, 10 g Gln). No differences were observed between study periods in infectious complications, nutritional status, intestinal permeability, plasma glutamine concentrations, or quality of life [216].

Cysteine is commonly believed to be a conditionally essential amino acid in preterm neonates, who have a relative inability to enzymatically convert methionine (the essential sulfur amino acid precursor to cysteine) in the liver. However, in adults there are no published studies on the clinical effects of cysteine added to PN.

Taurine, which can be synthesized via its amino acid precursor cysteine, is believed to be conditionally essential in premature neonates. It plays a role in brain development, bile acid metabolism, antioxidation, and retinal and cardiac functions, among other actions. Early studies in patients on long-term HPN showed low levels of taurine in plasma and within various blood cells [217,218]. The supplementation of taurine in adults on long-term HPN (10 mg/kg/d) normalizes plasma and blood cell taurine levels [219]. In a pilot study of adults on HPN for SBS, 32 patients were studied retrospectively and 10 of them with cholestasis were enrolled in a prospective study with taurine-supplemented HPN at a dose of 6 mg/kg. During the supplementation period the plasma levels of taurine increased, but not the level of the biliary taurine pool, and the levels of cholestasis enzymes and bilirubin did not change in the study group thus providing no benefit [220].

4.3. Intestinal rehabilitation strategy-medical

4.3.1. Short bowel syndrome

29. **We recommend that SBS patients be advised to consume regular whole food diets, and are encouraged to compensate for malabsorption by hyperphagia.** (Grade of evidence: **low**)
30. **We suggest that dietary counselling be guided by an expert dietitian, based on the subjective experience of the patient, and ideally supported by objective metabolic balance measurements, in order to ensure high compliance.** (Grade of evidence: **low**)
31. **We recommend that SBS patients with a preserved colon consume a diet high in complex carbohydrates and low in fat whereas the fat:carbohydrate ratio seems of less importance in patients without a colon.** (Grade of evidence: **low**)
32. **We suggest a diet with a high content of medium-chain triglycerides that confers a marginal benefit on overall energy absorption compared to a diet containing regular long-chain triglycerides in SBS patients with a preserved colon.** (Grade of evidence: **low**)
33. **We recommend in SBS patients consuming a low fat diet or where the long-chain triglycerides have been replaced by medium-chain triglycerides that attention is paid to the potential deficiency in essential fatty acids and fat-soluble vitamins.** (Grade of evidence: **low**)
34. **We don't recommend the addition of soluble fiber (e.g. pectin) to the diet to enhance overall intestinal absorption.** (Grade of evidence: **low**)
35. **We suggest that lactose not be excluded from the diet of SBS patients unless intolerance has been documented on a clinical basis, such as a clear association between lactose ingestion and increase of diarrhea or of stoma output.** (Grade of evidence: **low**)
36. **We suggest the addition of oral isotonic nutritional supplements in borderline (i.e. B1 category of clinical classification) SBS intestinal failure patients at risk of malnutrition.** (Grade of evidence: **low**)

In general, SBS patients should consume regular whole food diets, and they are to be encouraged to compensate for malabsorption by hyperphagia [221–223]. Oral sip feeds between meals may help to increase overall energy intake. However, when suggesting rigorous dietary measures, it is important recognize the psychosocial aspects of eating, and that a diet is only good if eaten.

In SBS patients with a preserved colon, unabsorbed long-chain fatty acids accelerate intestinal transit and reduce water and sodium absorption. They bind to calcium and magnesium, and they may increase oxalate absorption thereby predisposing patients to the formation of renal stones.

Short-term metabolic balance experiments have suggested that a higher carbohydrate (60%), lower fat (20%) diet is preferable in SBS patients with colon in continuity in order to increase overall absolute energy absorption [224]. Compared to a high fat, low carbohydrate diet, a reduction in faecal energy excretion of approximately 2.0 MJ/day (477.7 kcal) was seen in these patients. Colonic carbohydrate and fiber fermentation result in the production of short-chain fatty acids (SCFAs), which are easily absorbed in the colon - thereby providing up to 4.2 MJ/day (1003 kcal) in these SBS patients [225]. Thus, energy-wise, the preservation of at least half a colon is equivalent to retaining 50 cm of functional small bowel, which is important to consider in SBS patients with intestinal segments excluded from continuity. The rare condition of D-lactic acidosis may be seen in SBS patients with a preserved colon in relation to the intake of easy fermentable carbohyrates. In the habitual setting and in the long-term treatment of patients, these low fat, high carbohydrate diets may reduce appetite and overall energy intake, given that such diets are more voluminous, less palatable, and may lead to more production of gas, meteorism, and flatulence [224]. Another drawback of low fat diets is the lower provision of EFA [116] and fat-soluble vitamins [177]. However, a low fat diet may benefit the absorption of calcium, magnesium and zinc [226]. In patients with jejuno- or ileostomies, who consume a 10 MJ/day (2388 kcal) diet, the weight of the high carbohydrate, low fat diet was approximately 700 g/day higher than the iso-energetic, high fat diet and tended to increase stomal wet weight losses in the same magnitude [224]. Thus, in these patients, significantly higher fat intakes are possible but at the expense of an increased loss of divalent cations: calcium, magnesium, zinc, and copper. Altering the ratio between saturated and poly-unsaturated fatty acids had no consistent effect of divalent cation losses [227].

Theoretically, MCT should provide benefits in SBS patients since they are easily hydrolyzed, do not require bile salts, and are easily absorbed across the intestinal mucosa and transported via the portal vein to the liver. Again, short-term metabolic balance studies have suggested that medium-chain fatty acids may share the ability of SCFAs to be absorbed by the colon. Replacement of 50% of normal LCT in a 60% fat-rich diet by MCT resulted in an improvement in energy-absorption of approximately 1.5 MJ/day in SBS-patients with a preserved colon. No benefits in absolute energy absorption were detected in jejuno- or ileostomy patients [228]. MCT oils are commercially available, but they are expensive and unpalatable. Since they do not contain EFA, the replacement of dietary LCT may aggravate EFAD. However, the clinical significance of biochemical signs of EFAD in the absence of clinical manifestations is unclear. The absolute amount of MCT contained in many commercial enteral products is too low to provide a clinically meaningful benefit. In addition, some patients experience an increase in

diarrhoea. Therefore, although the physiological rationale is appealing, the arguments for the clinical use of MCT are weak, except as a concentrated energy supplement in the SBS patient on the borderline of needing PS with a preserved colon.

With complex carbohydrates being the most important dietary carbohydrate for SBS patients with a preserved colon in continuity, the benefit of soluble fiber supplements such as pectin (4 g TID for two weeks) for enhancement of intestinal absorption through increased production of SCFAs and effects on intestinal transit have been investigated. However, a pectin supplement did not increase macronutrient or energy absorption (1768 vs. 1477 kcal/d, $p = 0.15$); faecal wet weight (1582 vs 1689 g/d, $p = 1.00$) and urine production (1615 vs. 1610 mL/d, $p = 1.00$) remained constant [229]. One study of SBS patients with a colon in continuity reported beneficial effects of ispaghula husk and calcium on stool viscosity and consistency, which may ameliorate the sensation of urgency [230]. Some patients with an end ostomy will report benefit from the use of fiber supplements as they help to gelatinize the ostomy effluent.

In general, a diet containing 20 g/day of lactose was well tolerated in patients with SBS but should be carefully titrated in case of previous intolerance [231]. In addition to restricting dietary choices, avoiding lactose potentially could diminish calcium intake and aggravate the development of osteoporosis commonly seen in these patients.

37. **We suggest the use of enteral tube feeding in combination with oral feeding in patients with CIF with a low-level of HPN dependence (i.e. B1 category of clinical classification) and in whom the expected gain with tube feeding could allow them to wean off HPN.**(Grade of evidence: **low**)
38. **We suggest, in patients with CIF treated with enteral tube feeding, the use of polymeric isotonic enteral diets.** (Grade of evidence: **low**)

Following intestinal resection, SBS patients are typically advanced from complete parenteral support (i.e., PN and/or intravenous fluids and electrolytes) to enteral or oral feeding as tolerated. The aim of continuous enteral feeding is to provide a better distribution and maximum exposure of the available intestinal surface-area to nutrients while stimulating gastrointestinal secretions and endogenous hormonal secretions that are important to advancing intestinal adaptation. It is likely that enteral feeding increases the absolute intestinal absorption compared to voluntary oral intake and even accelerates adaptation in the immediate postoperative setting, but it is currently unknown whether it benefits the degree of adaptation achieved in the long-term after the transition to an oral diet. In patients with high jejunostomies, who have an impaired endogenous secretion of the gastric and ileo-colonic brake hormones [223,232], it is likely that an aggressive approach to enteral stimulation may, in fact, aggravate gastric hypersecretion and intestinal fluid and electrolyte losses. Gastric emptying and small intestinal transit of liquid is accelerated in patients with a jejunostomy, whereas it is slower, but not normal, in patients with a colon in continuity [232]. Diets with high simple carbohydrate content are likely to pull water into the lumen of the gastrointestinal tract due to the high osmotic load and the leaky epithelium of the jejunum, thereby precipitating net fluid, electrolyte, and nutrient losses.

For patients with SBS, who are believed to benefit from enteral feeding, studies suggest that elemental and polymeric diets are similar in terms of nutrient absorption and fluid and electrolyte loss [233,234]. Although an improvement in protein absorption was observed with a small-peptide-based diet in patients with high jejunostomy (90–150 cm of remnant jejunum) compared to a whole protein diet (14 vs. 11 g/d, $p = 0.01$), this did not improve overall energy absorption. In spite of the higher osmolality of the small-peptide diet (667 mOsm), the faecal excretions of energy, wet weight, and electrolytes remained constant [235]. Polymeric diets are less costly and less hyperosmotic than elemental diets and are generally well tolerated. Based on animal models of SBS where the animals had a preserved colon in continuity, it has been suggested that polymeric diets may also better enhance intestinal adaptation [236].

A study in 15 adults with SBS (3–130 months from last surgery, 4 without a colon in continuity) illustrated that continuous tube feeding for 7 days, alone or in combination with oral feeding, increased intestinal macronutrient absorption compared with oral feeding alone [237]. An energy gain of approximately 400 kcal/day was achieved by increasing the oral energy intake by approximately 4.2 MJ/day (1003 kcal). Thus, this treatment could be recommended in patients on the borderline with a low-level of HPN (e.g. A1 or B1 category of clinical classification) dependence and in whom the expected gain with tube feeding could allow them to wean off HPN. Results on changes in abdominal symptoms, patient preferences, and faecal wet excretions were not reported in the study. This study also did not examine longer-term tube feeding: many patients find it difficult to comply with long-term nasogastric feeding, although some patients only require nighttime drip.

39. **We don't recommend the addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process.** (Grade of evidence: **low**)

Animal studies have suggested positive effects of glutamine on intestinal absorption and morphology. However, in an 8-week, randomized, placebo-controlled, cross-over study in 8 SBS patients, no effects were found on bowel morphology, transit, D-xylose absorption, or stool losses [238]. The use of probiotics for rehabilitative purposes in SBS has not been evaluated. A few publications on selected cases have described the use of probiotics in SBS for treating D-lactic acidosis [239]. However, in children, cases of bacteremia with the ingested probiotic bacteria have been described in SBS patients depending on PN [240,241]. A systematic review of studies in children concluded that there is insufficient evidence on the effects of probiotics in children with SBS, and that the safety and efficacy of probiotic supplementation in this high-risk cohort needs to be evaluated in large definitive trials [242]. There are no data about supplementation with probiotics in adults with SBS.

40. **We suggest that SBS patients use salt liberally and restrict the administration of oral fluids in relation to meals.** (Grade of evidence: **low**)
41. **We suggest that patients who have borderline dehydration or sodium depletion use an isotonic high sodium oral rehydration solution to replace stoma sodium losses.** (Grade of evidence: **low**)
42. **We suggest limiting the oral intake of low sodium, both hypotonic (e.g. water, tea, coffee, or alcohol) and hypertonic (e.g. fruit juices, colas) solutions in order to reduce output in patients with net-secretion and a high output jejunostomy.** (Grade of evidence: **low**)

The aim of providing SBS patients with oral rehydration solution (ORS) is to optimise wet weight and sodium absorption. In the borderline SBS intestinal insufficiency or failure patient, this should secure intestinal autonomy, whereas in the IF patient, this should result in a reduction in the need for parenteral fluid and sodium support.

When discussing fluid and sodium absorption in SBS patients, it is important to understand the nature of the intestine as both a secretory and absorptive organ and the physiological mechanism utilized by the ORS therapy. Thus, mucosal fluid and electrolyte absorption should not only be acknowledged as an isolated exchange at the single cellular or mucosal-luminal interface but as a system influenced by mucosal endocrine cells, blood capillaries and lymphatics, extrinsic and intrinsic neurons, and mesenchymal cells of the lamina propria.

The intestinal fluid and sodium net absorption may be evaluated in the individual SBS patient by performing balance studies. However, only a few centres have the facilities, setup, analyses, resources, and willingness to perform these studies. A less elaborate alternative is the use of measurements of 24-h urine volume and urine sodium excretion. Twenty-four hour urine collections frequently indirectly reflect intestinal fluid and sodium absorption. Unfortunately, most physicians rely on even less reliable patient evaluations, such as a global clinical evaluation, body weight, and standard blood biochemistry, to assess the fluid balance of individual SBS patients. This may be inadequate and when instituting ORS, objective measurements of the effects are advised.

With the large patient heterogeneity within the spectrum of SBS, the provision of general, uniform and evidence-based advice regarding the use of ORS is impossible. In addition, since only a few patients relish ORS, and since long-term acceptance is poor, in most instances these solutions may only serve as rescue therapy in relation to incidental instability and fluid imbalance in patients with borderline intestinal insufficiency. Under normal circumstances, most SBS patients tend to prefer liberal use of table salt in relation to meals and on snacks, whereas others tolerate sodium chloride capsules (up to 7 g/24 h), even though they occasionally may cause nausea and vomiting [141].

In adult SBS patients, wet weight absorption (the difference between the weight of the oral intake minus the weight of faecal excretions) below 1.41 kg/d, sodium absorption of 50–100 mmol/d, urine production below 800–900 mL/day, and urine sodium excretion below 35 mmol/d are suggestive of inadequate intestinal water and sodium absorption [223,243,244]. In general, in situations of severe pre-renal dehydration in SBS patients, serum creatinine rises, the renin-angiotensin pathway is activated, and serum aldosterone concentration is elevated [245]. In these patients, parenteral fluid and sodium support is indicated to avoid clinical symptoms and biochemical signs of dehydration, fluid and electrolyte disturbances, and renal impairment. The role of ORS in these patients is unclear, and it is advisable to perform objective measurements of their effects in order to justify their long-term use.

In general, SBS patients try to and are advised to compensate for their malabsorption by increasing oral intake [221–223]. Therefore, when evaluating the effects of ORS, it would be prudent to compare the effects of these ORS as either “add-on” to habitual fluid and diet intakes or as “alternatives” to conventional oral fluid intakes.

SBS patients who are at particular risk of significant dehydration and electrolyte disturbances are those with a reduced length of jejunum ending in the stoma. Many of these patients tend to secrete more sodium and fluid than they consume orally [144]. Some of these patients even experience losses of water and sodium when they take nothing by mouth (“secretors”) [144]. In addition, in these patients, oral intake of food and beverages increases the stomal losses of fluid and sodium. Some of these patients are also subject to magnesium deficiency [246]. In a study of 14 patients with a jejunostomy and one patient with a jejuno-rectal anastomosis (jejunal length<150 cm), the sodium concentration of the stomal effluent (wet weight output range 1.32–8.25 L/d) averaged 88 mmol/L (range from 60 to 118 mmol/L) [144]. Similar findings were observed in the study by Jeppesen et al. [223]. Awareness of this is of importance when trying to improve intestinal fluid and electrolyte absorption by the use of ORS.

The use of ORS was introduced after the discovery that sodium and glucose transport was coupled in the small intestine, and that other solutes, such as amino acids, were also absorbed by active transport, again coupled with sodium ions. Initially, ORSs were demonstrated to be effective in restoring physiological water and electrolyte homeostasis in patients with cholera [247], but its use has now become more widespread to include any acute diarrhoeal disease.

Evidence from animal and human experiments shows that the epithelium of the jejunum is characterized by a low electrochemical gradient and it is believed that sodium absorption can only take place against a small concentration gradient. It appears that sodium fluxes, both from the lumen to plasma and vice versa, are about twice as great in the jejunum as in the ileum [248]. Differences in water movements in response to an osmotic gradient are even greater in the jejunum compared to the ileum. Intestinal sodium transport is an active process stimulated by the presence of glucose, galactose, and some aminoacids (solvent drag), whereas water movements are passive [249]. This is in contrast to findings in patients with a preserved ileum, where sodium absorption can take place against a steep electrochemical gradient even in the absence of glucose [142,250]. Thus, jejunal sodium and water absorption may be dependent on the sodium and glucose concentration of oral intakes as well as the osmolarity [251].

Perfusion studies at the duodeno-jejunal flexure and in the upper jejununal segments in animals and normal humans have explored the composition of the optimal ORS. From these experiments, it seems that the optimal concentration of glucose polymer for sodium and water absorption was around 10 mmol/l (180 mg), which corresponded to a glucose concentration of 60 mmol/L (1080 mg). In humans, maximal sodium absorption occurred with a mixture of 120 mmol/L (2160 mg) of sodium chloride and 30 mmol/L (540 mg) of glucose [252]. However, SBS patients with distal bowel resections are known to have gastric hypersecretion, rapid gastric emptying, and accelerated intestinal motility. Thus, the secretory response to and the assimilative conditions to ORS may be altered in these patients. In SBS patients with a preserved ileum, the presence of glucose may be of less importance and, since the colon has a large reserve capacity for the absorption of water and sodium, ORSs are rarely indicated in SBS patients with a preserved colon [253].

Due to malabsorption and large fluctuations in fluid balance, many SBS patients are at risk of, or live on the edge of, dehydration. In these situations, they often describe an “insatiable thirst”, and they are often tempted to compensate by increasing their oral beverage intake. However, since an increase in both hypotonic (e.g. water, tea, coffee) and hypertonic fluids (sodas and fruit juices) theoretically may stimulate fluid secretion or increase the fluid and sodium influx into the lumen of the jejunum due to the leakiness of the epithelium, this would further aggravate stomal losses. Thus, a vicious cycle of chronic dehydration and excessive beverage intake is believed to be generated [141,253–258]. In order to halt this, the general advice has been that the patients should restrict excessive habitual beverages and instead drink ORS [141]. However, studies on the true effects of fluid restriction per se and the supplementation of ORS in SBS patients so far have not been performed.

Publications on the true effects of ORS on water and sodium absorption in SBS patients are scarce, treatment-periods are short, patients are heterogeneous and the number of patients treated is low. Thus, many of the studies conducted are short-term “physiological experiments” testing various ORSs compared to water in the absence of other oral intakes rather than “clinical studies” in the

habitual environment of the patients, where an ORS would be used as “add-on” to habitual fluid and diet intakes or as “alternatives” to conventional oral fluid intakes [141,254,255,257–267].

Thus, in general, in these physiological experiments or short-term clinical case series in patients with intestinal insufficiency, sodium absorption could be improved by ORS compared to the oral intake of water, but effects on intestinal water absorption were minor. In patients with intestinal failure, improvements in both water and sodium absorption were achieved. However, it is difficult to evaluate the clinical relevance of these interventions, bearing in mind that, in general, in the habitual life of SBS patients, none of them are kept on oral water exclusively and most of the patients, who drink water, do this in relation to intake of sodium and glucose containing meals. Little is known on the ideal timing of oral fluid intake. In a single, randomized balance study, it has been shown that restricting fluid intakes from 1 h before to 1 h after the meals did not improve absorption of energy from macronutrients, electrolytes, or divalent cations in 10 SBS patients out of whom two received supplemental IVS [268]. Therefore, the advice to restrict fluid intake at meal time cannot be considered a general rule for patients with SBS.

43. **We recommend the use of H2-receptor antagonists or proton pump inhibitors in reducing faecal wet weight and sodium excretion, especially during the first 6 months after surgery, mainly in those SBS patients with a faecal output exceeding 2 L/day.** (Grade of evidence: **moderate**)
44. **We suggest that in the individual patient, H2-receptor antagonists or proton pump inhibitors are also effective in reducing faecal wet weight and sodium excretion in the long-term.** (Grade of evidence: **very low**)
45. **We suggest, especially in the short-term after intestinal resection, the use of octreotide for patients with high-output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments.** (Grade of evidence: **low**)
46. **We recommend careful monitoring of patients treated with octreotide, to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects and potential negative interference with the process of intestinal adaptation during long-term use.** (Grade of evidence: **low**)

Enterectomy is associated with gastric hypergastrinaemia and hypersecretion [269]. The aetiology of gastric hypersecretion presumably involves loss of secretion of hormonal inhibitors confined to the terminal ileum and colon. The sheer volume of the gastric hypersecretion may flush the upper bowel, minimize time for absorption and thereby contribute to total faecal losses. In addition, the associated hyperacidity may denature pancreatic enzymes and compromise bile salt function [270], which may further aggravate conditions for absorption.

The main treatments for gastric hypersecretion are H2-receptor antagonists and proton-pump inhibitors (PPIs), but the more potent effect of PPIs on acid suppression has favored their use. Frequently, the degree of absorption of PPIs is unknown in SBS with intestinal failure patients: in case of lack of effect of tablets and capsules, soluble forms or intravenous administration should be considered. H2-receptor antagonists and PPIs have also been suggested to delay gastric emptying rates, which possibly also could benefit intestinal absorption in SBS patients [271].

Several clinical case series [272–275] as well as double-blind placebo controlled studies [276,277] have demonstrated their effect on decreasing ostomy output and faecal excretions in patients with SBS. On average, the reduction in faecal wet weights and sodium excretions are in the range of 20–25%, whereas the effects on energy, marcronutrients, and divalent cation secretion are less pronounced. A large effect heterogeneity is seen among SBS patients. The largest absolute effects are seen in patients with faecal wet weight excretions exceeding 2 kg/day. Therefore, it is advised to adjust treatment and IVS according to objective measurements of the effects.

Somatostatin, a neurotransmitter produced by the hypothalamus, and a peptide hormone found in pancreatic D cells and widely distributed in neuroendocrine cells throughout the gastrointestinal tract has been suggested to possess beneficial effects in the treatment of chronic diarrhoeal conditions. It has been suggested to decrease gastric [278], biliary, and pancreatic secretions [279–281]. In addition, it may inhibit secretagogue-induced water and electrolyte secretion in the jejunum and the colon [282], stimulate sodium and chloride absorption in the ileum [283], decrease intestinal motility [284], and inhibit the release of hormones that may contribute to diarrhoea (e.g. VIP, GIP, gastrin) [285]. Although it has beneficial effects on intestinal absorption by reducing faecal wet weight losses in patients with diarrhoea, potential detrimental effects have also been suggested since somatostatin could inhibit glucose absorption and pancreatic enzyme secretion which would impair macronutrient absorption in patients with SBS. Furthermore, somatostatin reduces splanchnic blood flow [286] and it may reduce the use of amino acids for splanchnic protein synthesis thereby interfering with the physiological process of adaptation to intestinal resection [287,288].

Somatostatin and the somatostatin analog octreotide have been shown to reduce ileostomy diarrhoea and large volume jejunostomy output in several case series [288–297] and a single placebo controlled trial [298]. No significant changes in the net absorption of potassium, calcium, magnesium, phosphate, zinc, nitrogen, or fat were seen in relation to these studies. The largest absolute effects are seen in patients with faecal wet weight excretions exceeding 2 kg/day. Some patients with the highest stomal outputs had significant fluid retention in relation to octreotide treatment. Therefore, it is advised to measure effects objectively and reduce parenteral support accordingly.

Clonidine is an α2-adrenergic receptor agonist that also inhibits gastrointestinal motility by both central and peripheral action and increases intestinal sodium and water absorption and decreases bicarbonate secretion by direct activation of post-synaptic enterocyte α2-adrenoreceptors [299,300]. In a single open label study, an approximately 10% reduction of stomal wet weight and sodium output was demonstrated in relation to the placement of a 0.3 mg clonidine patch for a week in SBS patients with a jejunostomy [301].

47. **We recommend oral loperamide to reduce wet weight and sodium faecal excretion in SBS patients with an ostomy.** (Grade of evidence: **moderate**)
48. **We recommend loperamide be preferred to opiate drugs, such as codeine phosphate or opium, because it is not addictive or sedative.** (Grade of evidence: **moderate**)
49. **We recommend that in SBS patients with a high ostomy output, the use of loperamide be guided by objective measurements of its effect.** (Grade of evidence: **moderate**)

The use of anti-diarrhoeal medication is widespread in patients with SBS and aims to reduce the losses of water and electrolytes and to minimize the symptoms and consequences of diarrhoea. Eventually, this can also reduce the need for IVS. Apart from lessening of malabsorption and salt and water depletion, anti-diarrhoeals can also facilitate ostomy appliances, prevent accidental soiling and skin excoriation, and ease ostomy care. However,

the evidence for the use of anti-diarrhoeals in SBS patients is mainly obtained from patients with normal intestinal anatomy but with diarrhoea due to other causes. A few studies have also been performed in patients with an ileostomy or with minimal ileal resection. Therefore, generalization of the findings in these studies to patients with SBS may not be valid. Thus, it is recommended that objective measurements of the effects of treatments with anti-diarrhoeals should be performed before and in relation to treatments and subsequently discussed with the patient prior to instigating a potentially life-long treatment. Opiates increase duodenal muscle tone and inhibit propulsive motor activity. This may retard accelerated gastric emptying and prolong intestinal transit time which may benefit some SBS patients.

Some anti-diarrhoeals (mainly codeine, diphenoxylate, and opium) may have central nervous system side effects, e.g. sedation, and they may have potential for addiction. A mixture of codeine phosphate (8 mg/mL) in doses as high as 80–160 mg or a tincture of opium, 0.3–1.0 mL, both four times per day, is employed in some centres.

Loperamide is chemically related to, but more potent, lacks central opiate effects, is more gut-specific, and has longer duration of action than diphenoxylate [302]. Loperamide is believed to inhibit the peristaltic activity of the small intestine and thereby prolong intestinal transit time [303]. Prolonged transit would increase time for water and sodium absorption. However, it may also inhibit pancreatic and biliary secretions, which, in theory, could impair macronutrient absorption [304]. In general, loperamide, 4 mg given 3–4 times per day has been advocated, but since loperamide is circulated through the enterohepatic circulation, doses as high as 12–24 mg at a time have been suggested to be required in patients with resection of the terminal ileum.

The optimal timing, dose, and tolerability of all of these drugs may be highly individual. They are often used in combination, and may be provided 30–60 min before meals and at bedtime, although the scientific evidence for this practice is lacking.

Small, randomized placebo-controlled trials of loperamide have been performed but mainly in patients with an ileostomy or ileocecal resection and diarrhoea of less than 1.5 kg/day [302,305–307]. In general, treatment reduced faecal wet weight output by 15–30%. Similar effects were found in studies employing codeine where stomal wet weight outputs in general were below 1.3 kg/day in the patients studied [308,309]. Whether similar relative effects are obtained in patients with more pronounced diarrhoea still remains to be investigated. The main side effects in relation to anti-motility drugs were nausea, vomiting, abdominal pain, and distension.

50. **We recommend that SBS patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who suffer from symptoms of bacterial overgrowth, benefit from occasional antibiotic treatment.** (Grade of evidence: **very low**)
51. **We do not recommend the routine use of antibiotics in SBS patients with a preserved colon, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to short-chain fatty acids, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation.** (Grade of evidence: **very low**)

Very little is known about the presence of small bowel bacterial overgrowth in patients with SBS [310–315]. Consensus regarding the definition and indications for treatment is lacking. Therefore, trial-and-error approaches employing various antibiotics frequently have been used, but detrimental effects on energy salvage by fermentation in SBS patients with a colon in continuity should be avoided.

52. **We recommend that patients with CIF due to SBS be carefully informed of the potential benefits and risks associated with growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of quality of life improvement, the expected duration of treatment, the expected effects after cessation of the treatment, the potential adverse effects and risks of the treatment, the cost-effectiveness of the treatment, and the need to undergo careful and regular monitoring.** (Grade of evidence: **low**)
53. **We suggest that, for those carefully selected SBS patients who are candidates for growth factor treatment, the GPL2-analog, teduglutide, be the first choice.** (Grade of evidence: **moderate**)
54. **We recommend evaluation of the efficacy of growth factor treatment according to standardized protocols measuring fluids, electrolytes and, whenever possible, energy balance.** (Grade of evidence: **low**)
55. **We recommend that intestinal growth factors are only prescribed by experts who are experienced in the diagnosis and management of SBS patients and who have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks, and cost-effectiveness.** (Grade of evidence: **low**)

So far, the conventional pharmacological treatments in short bowel patients mainly have included anti-secretory and anti-diarrhoeal agents. However, over the past decades, it has become increasingly clear that mucosal nerve endings and endocrine cells within the gastrointestinal tract pass information via the enteric nervous system in response to the passing of luminal contents, thereby regulating the highly coordinated processes of nutrient assimilation. The neuro-endocrine feedback mechanisms often referred to as the “gastric, ileal, or colonic brake” may be disrupted by intestinal resection or mucosal disease. The attenuation of the meal-stimulated secretion of hormones may result in some of the pathophysiological features of SBS: accelerated gastrointestinal motility, gastric and intestinal hypersecretion, diminished intestinal blood flow, disturbed immunological and barrier functions, impaired mucosal replacement, and repair and adaptation. These observations have instigated the use of hormonal factors in the intestinal rehabilitation of SBS patients, with the aim of maximizing absorption in the remnant bowel, decreasing intestinal losses, and reducing the need for IVS. At this time, only two molecules have been approved for SBS patients, the growth hormone (GH) somatotropin (only in US) and the glucagon-like peptide-2 (GLP-2) analog, teduglutide (in US and Europe).

However, since the number of patients treated with these agents is still low, it is advised that these treatments should only be used under the guidance of a physician experienced in the management of SBS with an expectation that these patients need to be monitored closely during and potentially after their use. Since potential long-term complications are unknown, careful long-term monitoring is required. In addition, careful ongoing evaluation of the clinical benefits has to be prudent. For patients and healthcare providers, the issue of costs may also need to be addressed.

A number of animal and human studies evaluating the effects of GH on intestinal adaptation and absorption have demonstrated conflicting findings [316–323]. Methodological differences

Table 10
Randomized controlled studies on growth hormone in patients with short bowel syndrome.

Author (ref)	Study design	Intervention		Pts	SBS characteristics			Results							
		Drugs	Duration (days)	n. (with CD)	Time from last resection (yr)	Remnant small bowel (cm)	Colon in continuity (n/total)	Drop out (n.)	Δ HPN volume	Δ HPN energy (kcal)	HPN weaned (Pts n.)	HPN reduction (n. of day/ week)	Intestinal absorption	Δ body weight (kg)	Adverse events (% of pts)
Scolapio, 1997 [317]	DBRC crossover study vs. placebo	GH 0.14 mgr/ kg/day; Oral Gln 0.63 mg/kg/ day; HCLF diet	21	8 (7)	3–19 (12.9)	71 ± 23		0	Fixed				Stool volume, n.s. Fat and Nitrogen, n.s. Na increased ($p = 0.03$) K increased ($p = 0.007$)	+3.3 ($p < 0.01$ vs placebo)	Peripheral edema, 100%; carpal tunnel syndr, 25%; sleep disturbances,25%; generalized arthralgias, fatigue, nausea, vomiting, low-grade fever, headaches, 12.5% each one
Ellegard, 1997 [320]	DBRC crossover study vs. placebo	GH 0.024 mg/ kg/day; Habitual diet	56	10 (10)	>1	125 ± 29	5/10	0 (1 reduced the dose because of AEs)	Fixed				Water, energy, and protein, n.s.	GH: +4% ($p > 0.05$) Placebo: + 1.8% (n.s.)	Slight muscle stiffness, 20%; increased heart rate, 20%; light stiffness of joints, 30%; transient gynecomastia, numbness in hands, 10% each one
Szkudlarek, 2000 [318]; Jeppesen, 2001 [319]	DBRC crossover study vs. placebo	GH 0.12 mg/kg/ day; Oral Gln 28 ± 2.0 g/day; IV Gln 5.2 ± 2.2 g/day; Habitual diet	28	8 (6)	3–11 (7)	104 ± 37	4/8	0	Fixed				Energy and macronutrients, n.s.		Peripheral edema, 75%; hand pain,75%; gynecomastia, 12.5%
Seguy, 2003 [321]	DBRC crossover study vs. placebo	GH 0.05 mg/kg/ day; Habitual diet	21	12 (3)	>1	48 ± 11	9/12	0	Fixed				Energy ($p = 0.002$), carbohydrates ($p = 0.04$), nitrogen (0.004), increased	GH + 2.4 ($p < 0.003$) Placebo n.s.	Arthralgia and myalgia, 8%
Byrne et al., 2005 [322]	RCT	a) Oral Gln 30 g/day; GH placebo; Habitual diet	28	9 (1)	≥0.5	62 ± 31	8/9	0	−3.8 ± 2.4 L/wk	−2633 ± 1341/wk	none	2 ± 1	NM	−0.7	Placebo: peripheral edema, 44%; musculoskeletal complaints, 11% GH: peripheral edema, 94%; musculoskeletal complaints, 44%; GH was held for several days in 4 pts
		b) Gln placebo; GH 0.10 mg/kg/ day; Habitual diet	28	16 (2)	≥0.5	84 ± 50	15/16	1 (on GH treatment; due to illness	−5.9 ± 3.8 L/wk	−4338 ± 1858/wk	none	3 ± 2	NM	+1.2	
		c) Gln Oral Gln 30 g/day; GH 0.10 mg/kg/ day; Habitual diet	28	16 (5)	≥0.5	68 ± 33	13/16	unrelated to GH)	−7.7 ± 3.2 L/wk	−5751 ± 2082/wk	none	4 ± 1	NM	+1.8	
		a) vs b)							$p < 0.05$	$p < 0.001$		$p < 0.05$		n.s.	
		a) vs c)							$p < 0.001$	$p < 0.001$		$p < 0.001$		n.s.	

Pts = patients; SBS = short bowel syndrome; CD = Crohn's disease; Drop out = patients who discontinued the treatment; Δ = variation from baseline; HPN = home parenteral nutrition; DBRC = double blind randomized controlled.
RCT = randomized controlled trial; HCLF = high carbohydrate low fat; GH = growth hormone; Gln = glutamin; wk = week; NM = not measured; n.s. = not significant.

between the studies limit definitive conclusions on the clinical effects of the clinical use of GH, either alone or in combination with a high-carbohydrate low-fat diet and glutamine. The results of studies in humans are summarized in Table 10. High-dose GH treatment in SBS patients may have a positive effect on intestinal wet-weight absorption, but its use is often associated with significant side effects. Low-dose GH has been demonstrated to have a beneficial effect on intestinal energy absorption in a single study, but this effect may be partly due to a stimulatory effect on oral energy intake. Side effects seem to be lower with the lower dose. The positive effects of GH have mainly been described in SBS patients with a colon in continuity.

Glucagon-like peptide 2 [324,325] and the degradation-resistant analog, teduglutide, mainly increases intestinal wet weight absorption [326] and decreases the need for parenteral fluid support in SBS patients with intestinal failure [327–329]. Table 11 shows the results of studies on teduglutide in humans. The effects on energy absorption seem less predominant. Effects have been seen in both categories of SBS patients, those with and without a colon in continuity. The only study investigating the effects on QoL did not demonstrate any significant improvement, indicating the need for more studies [330].

Table 12 summarizes the results from the randomized controlled studies on intestinal growth factors in SBS in humans. The total number of enrolled patients is small. With both growth factors, the effects on intestinal functions quickly decrease and vanish after stopping the treatment. Therefore, life-long treatment is required. The duration of treatment in published studies was 56 days for GH and 364 days for teduglutide. Adverse events are mainly localized to the gastrointestinal tract with teduglutide and are mainly systemic and appear to be more frequent with GH. The number of HPN days off has been documented in only one study with GH and in all the studies with teduglutide. Careful patient surveillance for the risk of cancer must be performed. Overall, these data would be in favor of teduglutide as the current drug of choice for intestinal rehabilitation of SBS patients. However, both treatments are costly, and the cost-efficacy as well as the risk-benefit ratio need to be considered when the decision to treat a patient is considered. The high degree of patient heterogeneity and effect heterogeneity reported in the studies employing growth factors mandates careful monitoring of patients during treatment. A consensus on criteria to identify SBS patients who are candidates for growth factor treatment is required.

56. **We recommend drugs be prescribed on an individual basis to patients with SBS following a careful evaluation of the absorptive capacity of the remnant bowel, knowledge of the physiochemical characteristics of the drug, and an evaluation as to if the drug can be titrated according to an objectively measured effect or according to measurements of plasma concentrations. The use of parenteral and transdermal routes and the use of suppositories should also be considered in SBS patients with limited intestinal absorption.** (Grade of evidence: **very low**)

Pharmacotherapy in SBS patients remains a difficult clinical problem, as drug absorption from the gastrointestinal tract may be considerably impaired in such patients. The impairment of absorption of orally administered drugs shows significant inter-patient variability that depends on both the characteristics of patients (site and extent of resection, condition of the remnant bowel, presence of other systemic diseases, age and time from resection) and the physicochemical and pharmacokinetics characteristics of drugs (formulation and solubility, site, extent and rate of absorption, interaction with other drugs, etc) [331–334].

There is limited and dated literature regarding absorption of oral drugs in SBS [334–344]. Acid hypersecretion and rapid gastric emptying time, reduction of absorptive surface area and rapid intestinal transit time, disruption of enterohepatic circulation and metabolic activity of lactobacilli that are sometimes abundantly present in the gastrointestinal tract of such patients, are the main factors affecting the oral absorption of drugs in SBS patients. Absorption of orally administered drugs takes place throughout the whole gastrointestinal tract, from mouth to rectum, although the upper small intestine (duodenum and jejunum) plays the most important role due to its large surface area, high blood flow, and favorable pH for the absorption of most drugs. Total or terminal ileum resection results in more rapid intestinal transit and less time for absorption in the upper small bowel. Another consequence of terminal ileum resection is bile salt malabsorption and the disruption of enterohepatic circulation. Bioavailability and pharmacologic effects of fat-soluble drugs (i.e. warfarin, cyclosporine, digoxin, tacrolimus etc.) that are excreted in bile and have their action enhanced by enterohepatic circulation may be significantly decreased by the lack of bile salt absorption. Successful warfarin therapy has been reported in patients with jejuno-colic anastomosis and in patients with jejunostomy, with only 12–15 cm of jejunum; whereas the failure to achieve a therapeutic window was observed in patients with total duodenectomy with gastrojejunostomy. One factor that may influence warfarin treatment in these patients is the possibility of coexisting vitamin K deficiency. Due to the narrow therapeutic window of warfarin, alternative treatment with low molecular weight heparin should be considered an option when appropriate [331–344].

Omeprazole is commonly used in SBS patients to slow gastric acid hypersecretion secondary to loss of inhibitory enteral hormones. Proton pump inhibitors and H2 blockers, that increase gastric pH, may inhibit absorption of drugs that are weak bases, like antifungals and antiretrovirals In contrast, increasing gastric pH may raise bioavailability of digoxin, nifedipine, and alendronate [335–339]. Loperamide is commonly used in SBS patients, especially in those with jejunostomy, to reduce intestinal losses. It may be necessary to increase the dosage to obtain a significant reduction of faecal losses, suggesting a reduction of its bioavailability in such patients [302–307]. No data are available about absorption of loperamide from orodispersible formulations.

Oral antibiotics such as cephalosporin are well absorbed in SBS, the active concentration is decreased, but it reaches the therapeutic window. Conversely, penicillins and macrolides are poorly absorbed. If the infectious agent has a sensitivity restricted to poorly-absorbed antibiotics, the use of a liquid form or of an IV formulation may be necessary [331–344]. In SBS patients the potential for therapeutic failure due to reduction of drug bioavailability is more likely for poorly- or moderately-soluble drugs (i.e polar drugs), given in oily solution, suspension, or solid form.

Highly soluble or permeable drugs, given in instant-release form (i.e liquid, orosoluble), have more rapid absorption and good likelihood to achieve a therapeutic window in SBS patients. A case report described good oral absorption of amitriptyline, a tricyclic antidepressant, after crushing the solid formulation and allowing the powder to dissolve in the mouth of a patient with jejunostomy and only 40 cm of proximal small bowel [337]. To optimize oral pharmacotherapy in SBS patients it is essential to know the gastrointestinal anatomy of the patient, the absorptive capacity of the remnant bowel, and the physicochemical and pharmacokinetic characteristics of the drug. Drugs should be dosed by monitoring

Table 11
Randomized controlled studies on enteroglucagon-like peptide 2 analog (teduglutide) in patients with short bowel syndrome.

Author (ref)	Study design	Intervention		Pts	SBS characteristics			Results						
		Drugs	Duration (days)	n. (with CD)	Time from last resection (yr)	Remnant small bowel (cm)	Colon in continuity (n/total)	Drop out (n.)	Δ HPN volume	Δ HPN energy (kcal)	HPN weaned (Pts n.)	HPN reduction (n. of day/ week)	Δ Body weight (kg)	Adverse events (% of Pts)
Jeppesen, 2011 [327]	RCT	a) Placebo; Habitual diet	168	16 (7)	>1	77 ± 23	9/16	1 (for AE)	−130 mL/day	−58/day	none	none	0.2, n.s.	Abdominal pain 6%, nausea 6%
		b) Teduglutide 0.05 mg/kg/ day; Habitual diet	168	32 (10)	>1	58 ± 44	26/35	6 (for AEs)	−350 mL/day	−218/day	2 (after 6.5 and 25 yr of HPN)	none	1.2	Abdominal pain 24%, headache 24%, nausea 22%, nasopharyngitis 16%, vomiting 15%
		c) Teduglutide 0.10 mg/kg/ day; Habitual diet	168	35 (13)	>1	68 ± 43	19/32	5 (for AEs)	−350 mL/day	−107/day	1 (after 3.7 yr of HPN)	none	1.4	
		a) vs. b)							p = 0.08	p = 0.11			p = 0.31	
		a) vs. c)							p = 0.08	p = 0.11			p = 0.18	
Jeppesen, 2012 [329]	RCT	a) Placebo; Habitual diet	168	43 (8)	>1	69 ± 64	23/43	3 (for AEs)	−21 ± 25%	NM	none	23% of pts (1 in 6 pts; ≥ 2 in 3 pts)	−0.6	Edema 5%, abdominal distension 2%, abdominal pain 23%, nausea 19%
		b) Teduglutide 0.05 mg/kg/ day; Habitual diet	168	43 (10)	>1	84 ± 65	26/43	2 (for AEs)	−32 ± 19%	NM	none	53% of pts (1 in 13 pts; ≥ 2 in 8 pts)	1.0	edema 17%, abdominal distension 21%, abdominal pain 23%, nausea 29%; acute cholecystitis 2%; small intestinal stenosis 2%
		a) vs. b)							p = 0.03			p = 0.05	n.s.	
O'Keefe, 2013 [328]	RCT	b) Teduglutide 0.05 mg/kg/ day; Habitual diet	196 (after the 168 from Jeppesen 2011)	25 (7)	>1	63 ± 46	19/25	9 (for AEs)	- 52% at 364 day with respect to baseline	- 3511 kcal/ wk at 364 day with respect to baseline	1 (after 2 yr of HPN)	>1 in 68% of pts	NR	Headache 35%, nausea 31%, abdominal pain 25%, nasopharyngitis
		c) Teduglutide 0.10 mg/kg/ day; Habitual diet	196 (after the 168 from Jeppesen 2011)	27 (11)	>1	57 ± 28	18/27		- 36% at 364 day with respect to baseline	- 1556 kcal/ wk at 364 day with respect to baseline		>1 in 37% of pts	NR	25%, vomiting 17%, catheter sepsis 17%, urinary tract infection 17%

Pts = patients; SBS = short bowel syndrome; CD = Crohn's disease; Drop out = patients who discontinued the treatment; Δ = variation from baseline; HPN = home parenteral nutrition.
RCT = randomized controlled trial; wk = week; NM = not measured; NR = not reported; n.s. = not significant; Aes = adverse events.

Table 12
Summary of data from randomized controlled studies on intestinal growth factors in short bowel syndrome in humans.

	Growth hormone	Teduglutide
Number of studies	5	3
Total patients enrolled (n)	72	110
Duration of treatment (days)	21–56	168–364
Dosages (mg/kg/day)	0.024; 0.5; 0.10; 0.12; 0.14	0.10; 0.05
Time from surgery, at enrollment	>6 months	>12 months
Main adverse events (% of patients)	Peripheral edema (44–100%) Muscoskeletal pain (8–44%)	Abdominal symptoms (20–25%)
Drop out for adverse events	1 patient	5–20% of patients
Dosage reductions or delays	5 patients	
Effect on HPN requirement:	HPN reduction 1–5/day week per patient, reported in one study (0.10 mg/kg/day)	HPN reduction $\geq$ 1 day/week: 37–68% of patients HPN weaned off: 4/110 patients (3.6%)
Duration of effects after stopping the treatment	return to baseline shortly after cessation of therapy	return to baseline shortly after cessation of therapy

therapeutic efficacy and levels of plasma concentration, when available and appropriate.

4.4. Chronic intestinal pseudo-obstruction

57. **We recommend that a specific diet not be prescribed but that patients with CIPO be encouraged to eat according to individual tolerance.** (Grade of evidence: **very low**)

The main goals of chronic intestinal pseudo-obstruction (CIPO) management are to reduce the major symptoms by improving intestinal propulsion and maintaining adequate nutritional status. Nutritional management is fundamental and relies on dietary education, which may be sufficient for patients with mild and moderate symptoms. Up to two-thirds of patients with CIPO develop nutritional problems or specific nutrient deficiencies [345–347].

Dietary actions should be used as first-line management [348,349]. They are influenced by the disease phenotype and intended to provide orally sufficient micro- and macro-nutrients in line with the patient's needs. The oral intake of patients with CIPO is influenced by the extent of gastrointestinal disease [350]. For instance, patients with gastroparesis often complain of early satiety, bloating, and nausea and are likely to have more difficulty with oral intake than those with predominantly small bowel involvement [351]. Small and soft frequent meals (up to 6 to 8 meals per day) are usually well tolerated in patients with sufficient residual digestive function [347]. A low-fiber, low-residue diet is helpful in minimizing intestinal gas, cramps, and potential bezoar formation. Food with high concentrations of fat should be avoided in order to limit the delay in gastrointestinal transit [347,351]. Patients with CIPO may also be at risk of developing vitamin and trace element deficiencies, therefore, multivitamin preparations should be added to their diet. In order to meet an adequate caloric intake, hypercaloric formulae are available on the market and can be helpful if tolerated [347,351]. In infants, protein hydrolyzed formulae are better tolerated than whole-protein formula because they are emptied from the stomach as fast as breast milk and faster than casein or whole-protein formulae [352].

To summarize, oral intake should be fractionated and divided into 5 to 6 meals per day. The patient is asked to follow a low-lactose, low-fiber, low-fat diet to optimize gut motility and decrease the risk of bacterial overgrowth and gastric bezoar. Associated multivitamin and micronutriment supplementation is also needed (iron, folate, calcium, and vitamins D, K, and B12) in order to prevent specific deficiencies. However, studies on specific dietary management are lacking [351].

58. **We suggest trying enteral tube feeding as a first step in patients with chronic gastrointestinal motility dysfunctions who are not able to meet their energy needs with oral nutrition alone and continue to lose weight, before using HPN.** (Grade of evidence: **very low**)
59. **We recommend that HPN not be delayed in malnourished CIPO patients with chronic gastrointestinal motility dysfunctions when oral/enteral nutrition is obviously inadequate.** (Grade of evidence: **very low**)

In patients with severe gastrointestinal motility dysfunction who are not able to meet their caloric needs with oral nutrition alone and continue to lose weight, enteral nutrition is the next step. Before placing a permanent enteric feeding tube, it is appropriate to perform a 72-h trial of naso-enteric feeding in order to confirm that the patient is able to tolerate the formula and the rate of formula delivery [348,353,354]. Percutaneous endoscopic gastrostomy can be performed in patients who do not have significant gastroparesis. Alternatively, an artificial feeding device that bypasses the stomach is preferred. Temporary or permanent small bowel access can be achieved by endoscopic, surgical, and radiological placement [348,354,355].

After a trial period of tube feeding, it can be administered by gastrostomy or jejunostomy [355]. In cases of severe gastroparesis, a venting gastrostomy can be added to the jejunostomy [354]. Percutaneous endoscopic gastrostomy/jejunostomy is a dual system in which a jejunal tube is passed via a gastrostomy tube to the small bowel. The use of large diameter jejunal tubes allows both easy endoscopic tube placement and low incidence of tube migration. However, fluoroscopically-guided or surgical tube placement may be alternatively performed [355]. Data on enteral nutrition in CIPO patients are rare. In children, there are a few reports and recommendations [346,356–359]. The success of jejunal feeding in children with CIPO varies and is unpredictable on the basis of signs and clinical symptoms. It has been clearly shown that jejunal feedings are more likely to be successful in children with phase 3 of the migrating motor complexes in duodenum or jejunum as compared with those without phase 3 of migrating motor complexes, supporting the view that the absence of normal fasting motility is not compatible with enteral feeding and normal growth in children [358]. Once appropriate enteral access has been achieved and the caloric needs of the patient have been estimated, tube feeding can be initiated. If the tube is placed in the stomach, because children frequently complain of abdominal bloating and nausea during gravity feeds, continuous infusion through a peristaltic pump is required. In children with a tube placed in the small intestine, continuous feedings are necessary. Jejunal feedings in each child should be started with an elemental formula appropriate for the child's age, and the infusion volume should be progressively increased if the child is thriving and has mild or no symptoms [357–359].

To summarize, enteral nutrition is an option for patients whose motility disorder is mainly localized. It presents fewer complications than PN, but clinical experience suggests that enteral feeding is rarely tolerated by patients [346]. In the most severe cases, when small bowel function is diffusely affected, PN is necessary to satisfy nutritional requirements.

60. **We recommend attempting a trial with prokinetics in patients with chronic gastrointestinal motility dysfunctions.** (Grade of evidence: **very low**)

Treatment of CIPO can be disappointing and frustrating for the physician and the patient, and remains extremely challenging even in referral centers. The management goals of CIPO are improving gastrointestinal motor activity, relieving symptoms, and restoring nutritional status and hydration. Unfortunately, the treatment of CIPO is mainly supportive because so far there are no motility agents in the market able to restore normal gastrointestinal motor function, particularly in those patients with a generalized motility disorder. However, even if drugs stimulating intestinal contractions are helpful only in a minority of patients, a trial with prokinetics should always be attempted [345].

Motility agents: antiemetics and prokinetics

Although prokinetics are poorly effective, they are systematically used in CIPO, probably because of their ability to improve digestive motility on manometry findings. Their lack of clinical efficacy can be explained by the poor intestinal bioavailability of oral drugs. The main drugs used are metoclopramide, domperidone, erythromycin, octreotide, and neostigmine [360–367].

The anticholinesterase drug, pyridostigmine may also be used. In some patients, an improvement of symptoms related to bowel dilatation with few side effects has been reported [360].

The serotoninergic agent, cisapride is the only prokinetic agent that has been shown to improve enteral tolerance, but it is no longer available because of the risk of life-threatening cardiac arrhythmias, mainly due to its effect on QT interval [361].

Erythromycin and derivates possess potent motilin receptor agonist activity, eliciting gastric emptying and antroduodenal coordination, but treatment does not appear to be effective in the long term [362].

The use of metoclopramide and domperidone has been limited due to their neurologic and cardiac adverse effects [363].

Octreotide, a somatostatin analog that induces phase III migrating motor complex (MMC) in the small intestine, has been shown to benefit adults with scleroderma-associated CIPO. The prokinetic effect occurs at a subcutaneous dose of 50–100 mcg/day (a dose much lower than that used to inhibit peptide secretion in neuroendocrine tumors) [365–367].

The latest drug assessed was prucalopride, a highly specific serotonin receptor agonist with enterokinetic effects. To date, only a few data are available. It has been recently tested in seven CIPO patients and only 4 patients completed the study, 3 of whom experienced a pain improvement but without significant functional changes [364].

Analgesic drugs

Abdominal pain is one of the main symptoms of CIPO. This pain has many mechanisms, making treatment difficult. Due to pathogenic uncertainty, abdominal pain is managed empirically with classic analgesic drugs such as paracetamol, non-steroidal anti-inflammatory drugs, or opiates in the most severe cases. Tricyclic antidepressants may also be used. But, analgesic drugs can impair neuromuscular activity, inducing a worsening of gut propulsion and an increase of intestinal pain. Some peripheral opioid antagonists can be tried when opiates are necessary. However, there are no studies that have evaluated these strategies for CIPO patients [345,347,348].

61. **We recommend using antibiotic therapy to treat intestinal bacterial overgrowth and to reduce malabsorption in patients with chronic gastrointestinal motility dysfunctions.** (Grade of evidence: **very low**)
62. **We suggest periodic antibiotic therapy to prevent intestinal bacterial overgrowth in patients with chronic intestinal motility dysfunction who have frequent relapsing episodes.** (Grade of evidence: **very low**)

Intestinal bacterial overgrowth has often been described in digestive motility disorders [368] and it has been shown that improvement of digestive motility reduces bacterial overgrowth [369]. Sequential antibiotic therapy is very effective in treating intestinal bacterial overgrowth and in reducing malabsorption [369]. Correlation between bacterial translocation and absence of MMC activity has been demonstrated and can result in a worsening of digestive motility disorders [370]. A potential life-threatening consequence of bacterial overgrowth relates to bacterial translocation [371,372].

The rationale for the use of antibiotics is the treatment and prevention of small intestinal overgrowth due to intestinal stasis in CIPO patients. The treatment of bacterial overgrowth should be evaluated individually. Sequential antibiotic therapy is very effective in treating intestinal bacterial overgrowth and reducing malabsorption. It has also been shown to improve nutritional status and sometimes bloating. Bacterial overgrowth may lead to life-threatening bacterial translocation. Poorly absorbable antibiotics such as aminoglycosides and rifaximine are preferred, but alternating cycles with metronidazole and tetracycline may be necessary to limit resistance [373]. In clinical practice, the most commonly used antibiotics are metronidazole, amoxicillin-clavulanate, doxycycline, and norfloxacine.

4.5. Radiation enteritis

63. **We recommend that the nutritional regime in chronic radiation enteritis patients follows the same criteria adopted for the HPN of patients with other causes of CIF.**(Grade of evidence: **very low**)
64. **We suggest trying enteral tube feeding in patients with radiation enteritis if oral nutrition including use of oral nutritional supplements is inadequate.** (Grade of evidence: **very low**)
65. **We recommend HPN not be delayed in malnourished radiation enteritis patients, if oral nutrition/enteral tube feeding is obviously inadequate.** (Grade of evidence: **very low**)

Several studies in the last 20–25 years have reported that chronic radiation enteritis (RE) still occurs in up to one-fifth of all patients undergoing pelvic radiotherapy [374–376].

The damage of RE initiates in the mucosa, which presents cellular devitalization, and in the submucosa, which initially becomes edematous but subsequently is characterized by diffuse collagen deposition and progressive occlusive vasculitis. Fibrosis and vasculitis progress over time and result in the narrowing of the intestinal loops with dilation of the bowel proximal to the stricture, which then thickens the affected segments of the intestine and serosa. Severe stenosis, ulceration, necrosis, and perforation of the intestinal wall may sometimes occur.

Patients requiring HPN because of RE usually belong to the type III IF [1,377], usually as a result of structuring and/or fistulising disease, often with associated surgical complications. Concomitant diagnoses such as bacterial overgrowth or pancreatic insufficiency may contribute to symptoms and malnutrition and it is important to treat such complications wherever possible to promote enteral autonomy.

A multicentre survey in Europe in 1993 [378] reported that RE accounted for 8% of underlying disease of patients receiving HPN, with Spain, France, and Belgium registering the highest number of subjects. Radiation enteritis currently accounts for approximately 4% of new HPN registrants in the UK [379].

The overall survival probability of patients has been reported to be 83% (58-100), 78% (60-100), 62% (36-90), and 56% (41-90), at 1, 3, 5, and 10 years, respectively [70,378,380–388]. There are no prospective studies on HPN in patients with RE. In an early RCT comparing PN with elemental diets, Loiudice and Lang [389] reported improvements in nutritional assessment data, nitrogen balance, radiographic, and clinical parameters after therapy in patients on IVS. It is noteworthy that some patients can achieve a resumption of oral intake.

Although therapies, including corticosteroids, pentoxifylline, and hyperbaric oxygen, have received attention, the evidence for benefit of specific anti-inflammatory therapies to reverse and/or prevent progression of RE in the context of IF is limited [390]. Baticci and Bozzetti [391], reviewing their experience at the National Cancer Institute of Milan, first published that HPN and bowel rest for some months can achieve a spontaneous resolution of intestinal obstruction and allow the resumption of oral alimentation without surgical intervention. A further report of one case appeared in the American Journal of Surgery in 1983 [392]. Silvain et al. [387], and Scolapio et al. [386], showed that approximately one-third of patients were able to discontinue HPN and resume oral intake. Bozzetti et al. [393], reported that 5 out of 10 patients with subacute RE were able to achieve oral nutritional autonomy after 19 months (1-32) of HPN. A longer follow-up of the previous original series of the National Cancer Institute of Milan [380] including 3 additional patients confirmed that 54% of patients on HPN showed resolution of their intestinal obstruction without surgery, and overall 5-year survival was 90%.

4.6. Intestinal rehabilitation strategy-non-transplant surgery

66. **We recommend that, in patients with SBS, during intestinal resection, bowel length be conserved to the fullest extent possible to avoid dependence on HPN.** (Grade of evidence: **low**)
67. **We recommend that, in patients with SBS, restoration of intestinal continuity, be realized whenever possible, to decrease HPN dependency.** (Grade of evidence: **moderate**)
68. **We recommend that, when considering non-transplant surgery in patients with SBS, bowel lengthening procedures be considered in selected patients.** (Grade of evidence: **very low**)
69. **We recommend that, in patients with SBS, management is performed through a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome.** (Grade of evidence: **low**)

For patients with SBS, surgery can play an important role in preventing, mitigating and, in some cases, reversing IF. During intestinal resection, bowel length should be conserved to the fullest extent possible, to avoid dependence on PN. Once the patient is stabilized, ostomy reversal and recruitment of distal unused bowel should be prioritized whenever feasible. Following progression to IF, surgical management of SBS depends on the symptoms and anatomical characteristics of the individual patient.

Surgical options in patients with long-term IF fall into 4 main categories: operations to correct slow transit [394], operations to improve intestinal motility in cases of dilated bowel [395], operations to slow intestinal transit in the absence of bowel dilatation [396], and operations to increase mucosal surface area [397].

Operations to correct slow transit

Slow transit in SBS is relatively rare and should trigger a search for strictures, partial obstructions or blind loops, and enteroenteric fistulas [395]. These are often sequelae of the underlying disease leading to SBS, such as Crohn's disease or RE, and often require meticulous investigation to diagnose and treat appropriately [396].

Operations to improve intestinal motility in cases of dilated bowel

Rapid intestinal transit is a nearly universal clinical challenge in SBS and should elicit prompt investigation into underlying structural causes. Segmental bowel dilatation with poor peristalsis is a frequent finding in pediatric patients with SBS and it often results in clinical features of small bowel bacterial overgrowth [397,398]. Excessive intestinal dilatation is most easily managed by a simple tapering enteroplasty, in which a strip of intestine along the antimesenteric border of dilated bowel is removed using a mechanical stapling device [399]. This procedure is most applicable when bowel length is considered adequate and when loss of surface area is an acceptable tradeoff for better peristalsis. In cases where bowel length is critical, the longitudinal intestinal lengthening and tailoring (LILT) operation first described by Adrian Bianchi [400] accomplishes intestinal tapering without loss of surface area. In the LILT procedure, an avascular space is created longitudinally along the mesenteric border of a dilated loop of bowel. The bowel is then split lengthwise, taking care to allocate alternating blood vessels to each side. Each side of the split bowel is then tubularized, generating 2 “hemi-loops” that are anastomosed end to end in isoperistaltic fashion. When completed, LILT creates a loop of bowel that is twice the length of the original and half the original diameter; no new bowel is created. The decrease in bowel diameter accomplished without loss of surface area is likely more important than the gain in length. Bianchi's early personal experience with the procedure in 20 children resulted in 7 of 9 survivors attaining enteral autonomy from PN at a mean follow-up of 6.4 years [401]. LILT should be applied with extreme caution in patients with ultrashort bowel and in the presence of liver disease [401,402].

Tapering without loss of surface area is accomplished effectively and relatively simply by the serial transverse enteroplasty (STEP) procedure described by Kim et al. [403] in 2003. In the STEP procedure, the intestinal lumen is narrowed by firing a series of staples perpendicularly to the long axis of the bowel in a zig-zag pattern without interfering with the blood supply of the bowel. In a long-term study of 12 pediatric patients who underwent STEP, 8 (67%) patients remained alive and transplant-free at a median follow-up of 5.7 years. Of those 8 patients, 7 achieved independence from PN. In addition, the dilated segment showed an 87% increase in median length and a 67% decrease in mean internal diameter [404].

The choice of lengthening procedure between the Bianchi LILT and the technically simpler STEP remains somewhat unclear and until recently seemed related to surgeon preference. In a retrospective, uncontrolled, single-center study, Sudan et al. [405] reported outcomes of 64 patients who underwent a total of 43 LILT and 34 STEP procedures over a 24-year period. Overall survival was 91% at a median follow-up of 3.8 years. Enteral autonomy was achieved by 69% of PN-dependent patients, and liver disease was reversed in >80% of affected patients. Differences between the 2 procedures were small, although nonsignificant trends were

documented for a lower rate of weaning from PN, longer time to PN discontinuation, and a higher incidence of complications requiring reoperation after LILT than after the STEP procedure. Of note in this series, 14% of patients underwent intestinal transplantation at a median of 2.9 years. Transplantation was required more often following LILT than after the STEP procedure (18.6% vs 5%, respectively; $P = 0.03$), although this difference may be due in part to the longer follow-up time for patients receiving LILT (5.9 vs 1.7 years for STEP) [406].

Operations to slow intestinal transit in the absence of bowel dilatation

Of procedures designed to slow transit in the absence of bowel dilatation, segmental reversal of the small bowel (SRSB) shows the greatest promise [407]. SRSB creates an antiperistaltic segment of bowel approximately 10–12 cm in length, located ~10 cm proximal to an end-stoma or small bowel-colon anastomosis [398–408]. Of 38 patients undergoing SRSB over a 25-year period at a single center, 17 (45%) achieved complete independence from PN. Among patients who were not weaned, PN requirements were decreased by a median 3 days per week. A shorter interval between enterectomy and SRSB, an SRSB >10 cm, and an extended stay with the nutrition unit were significantly associated with enteral autonomy [409]. A case control study evaluated intestinal absorption in a large series of patients with segmental reversal of the small bowel in comparison to SBS patients without SRSB. Results showed that digestive absorption of nitrogen and lipids, and total absorption improved compared to patients with jejunocolonic anastomosis without the reversed segment. This improvement corresponded to a gain of 300 kcal per day [410]. Authors proposed an algorithm for management of SBS adult patients with jejunocolonic anastomosis. For high-risk patients, defined as an SBS patient at higher risk of death from the underlying disease or HPN complications, ITx should be rapidly proposed. In the other cases, when patients have more than 60 cm of postduodenal small bowel length, a jejunocolonic anastomosis should be performed and trophic factors can be considered in case of permanent HPN dependence. When patients have less than 60 cm of postduodenal small bowel length with: a) a dilated remnant small bowel, a Bianchi procedure or step procedure can be discussed in addition to jejunocolonic anastomosis; b) without dilated remnant small bowel, an SRSB should be performed during the jejunocolonic anastomosis [410].

Isoperistaltic colonic interposition, the relocation of a segment of colon to the small intestine while maintaining peristaltic directionality, has limited use because of the lack of data in adult SBS patients [411]. The largest available study included 6 infants who were followed for 24–84 months. Three patients achieved enteral autonomy from PN within 4 months of surgery. The remaining 3 patients were not weaned from PN, and all died, at an average of 20 months post-surgery [412].

Operations to increase mucosal surface area

Although the creation of neomucosa remains an elusive goal, use of sequential lengthening procedures and controlled tissue expansion (CTE) before bowel lengthening may have immediate, albeit limited, clinical application [413]. The theoretical basis for the strategy of CTE of non-dilated bowel in preparation for definitive intestinal lengthening was laid out in experimental work on pigs by the demonstration of mucosal hypertrophy and gain in length and diameter of partially obstructed intestine [414]. The Manchester experience with CTE, limited to only 10 cases, is nevertheless noteworthy for having reached the goal of performing LILT procedures in all 10 patients and, more important, for accomplishing enteral autonomy in 9 of the 10 patients. A more immediate application of these principles is the demonstration of the feasibility of repeat intestinal lengthening with the STEP procedure [415]. However, more recent experience from the Ann Arbor group suggests that redilation after prior lengthening may be an overall poor prognostic sign and merits caution [416].

To summarize, management of IF requires a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome. Although ITx remains a good option for patients with severe life-threatening complications, autologous intestinal reconstruction appears the better overall option [417]. The surgical approach should integrate the age of patient, intestinal status (dilated or non-dilated small bowel remnant), and experience of the center.

70. **We suggest to avoid surgery in CIPO patients, whenever possible, due to the risk of postoperative worsening of intestinal function and need for subsequent reoperation; venting ostomy (either endoscopically or surgically), however, can diminish symptoms in selected patients.** (Grade of evidence: **very low**)

Surgery plays a limited role in the management of CIPO patients, and should be avoided due to the risk of postoperative worsening and need for subsequent reoperation. Nevertheless, a surgery is often performed before and/or during CIPO management with an average of 3 procedures per patient. Main procedures used include intestinal resection, explorative laparotomy, and creation of venting or feeding ostomy. A study has recently shown that in half of cases, the surgery was performed in emergency situations, and that laparotomy was the most frequent procedure (>80%). In this study, the overall rate of postoperative mortality was 7.9% and the overall rate of morbidity was 58.2% [418]. Postoperative morbidity was significantly increased following intraoperative bowel injury, idiopathic CIPO, and emergency procedures. After the first surgery, the probability of reoperation was high (44% at 1 year and 66% at 5 years). Furthermore, surgical procedures should only be used after achieving nutritional status and bowel distension improvement.

The most frequent procedure appears to be the creation of venting ostomy: ileostomy, jejunostomy or even gastrostomy. These ostomies enable the aspiration of digestive secretions. Ileostomy seems to improve digestive symptoms by releasing a physiological brake (ileal brake) but, usually, its beneficial effect is not sustainable [354,419,420]. Chronic postprandial bloating, abdominal distension, and pain may be treated with a venting gastrostomy or jejunostomy. This simple intervention can substantially reduce the number of hospital admissions and emergency room visits in selected patients with intermittent obstructive symptoms [421]. Jejunostomies may also provide access to enteral feedings. In some patients with CIPO of the stomach and proximal small bowel, a gastrostomy–jejunostomy combination provides venting through gastrostomy and jejunostomy for feeding. However, extreme caution should be observed in selecting patients for these procedures with careful assessment of the symptoms and parts of the GI tract involved. There are reports of surgical procedures such as loop enterostomy and shortening of the gastrointestinal tract to relieve abdominal distension in patients with CIPO. These procedures are reported to improve QoL among these patients in combination with or without HPN. In some very severe CIPO cases which are highly HPN-dependent and refractory to medical treatment, subtotal enterectomy has been proposed. Despite a high postoperative morbidity, it has been shown to improve the QoL, increase oral intake, remove the need for suction gastrostomy, and decrease abdominal pain and vomiting in a small series of patients [422]. However, although many patients are HPN-

dependent because of malabsorption induced by the extensive resection of the small intestine, infusion frequency and volume may be reduced.

The last surgical option is ITx. That is indicated in case of life-threatening HPN-related or underlying disease-related complications [423,424]. A study assessing the long-term outcome of adult CIPO patients treated with HPN conducted in 51 patients has shown that lower mortality was associated with the ability to restore oral feeding at baseline and the onset of symptoms before the age of 20 years but in the case of systemic sclerosis, the mortality rate was higher [425]. Non-transplant or transplant surgery should be indicated only in a highly selected, well-characterized subset of patients, or in cases of life-threatening complications [347,426].

4.7. Intestinal transplantation

71. **We recommend HPN as the primary treatment for patients with CIF and the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, to maximize the opportunity of weaning off HPN, to prevent HPN failure, and to ensure timely assessment of candidacy for intestinal transplantation.** (Grade of evidence: **very low**)
72. **We recommend assessment for candidacy for intestinal transplantation, when one of the following indications exists** (Grade of evidence: **very low**):
    1. **Failure of HPN:**
        - Impending (total bilirubin above 3–6 mg/dL (54–108 μmol/L), progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of intestinal failure-associated liver (IFALD).
        - Central venous catheter related thrombosis of two or more central veins (internal jugular, subclavian or femoral).
        - Frequent central line sepsis: two or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock and/or acute respiratory distress syndrome.
        - Frequent episodes of severe dehydration despite intravenous fluid in addition to HPN.
    2. **High risk of death attributable to the underlying disease**
        - Invasive intra-abdominal desmoid tumors
        - Congenital mucosal disorders (i.e., microvillus inclusion disease, tufting enteropathy).
        - Ultra short bowel syndrome (gastrostomy, duodenostomy, residual small bowel <10 cm in infants and <20 cm in adults)
    3. **Intestinal failure with high morbidity or low acceptance of HPN**
        - Need for frequent hospitalization, narcotic dependency, or inability to function (i.e., pseudo-obstruction, high output stoma).
        - Patient's unwillingness to accept long-term HPN (i.e., young patients)
73. **We recommend that patients with impending or overt liver failure due to IFALD and those with an invasive intra-abdominal desmoid tumor be listed for a life-saving intestinal transplantation (with or without liver transplantation).** (Grade of evidence: **very low**)
74. **We suggest that patients with central venous catheter related thrombosis of two or more central veins (internal jugular, subclavian or femoral) be listed for a life-saving intestinal transplantation on a case-by-case basis.** (Grade of evidence: **very low**)
75. **We do not recommend listing for a life-saving intestinal transplantation of patients with CIF having any of the indications for assessment of candidacy other than IFALD-related liver failure, intra-abdominal desmoids or CVC-related multiple vein thrombosis.** (Grade of evidence: **very low**)
76. **We suggest that patients with CIF with high morbidity or low acceptance of HPN might be listed for a rehabilitative intestinal transplantation on a careful case-by-case basis.** (Grade of evidence: **very low**)
77. **We recommend that, whenever possible, patients listed for intestinal transplantation undergo the procedure while they are in stable clinical condition, as represented by being able to stay at home and not requiring hospitalization while waiting for transplant. For patients listed for a combined intestinal and liver transplantation, mechanisms to prioritize patients on the waiting list for liver transplantation should be adopted in order to minimize the risk of mortality while on waiting list and after transplantation.** (Grade of evidence: **very low**)

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 [6,75,427]. The presence of a specialist team has been reported to be a factor independently associated with a better outcome on HPN [6,75]. 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 [75,428,429]. The progress in intestinal rehabilitation therapy 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 of weaning off HPN, to prevent HPN-failure, and to ensure timely ITx when this is needed [6,75,427–429].

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 [430,431]. Those indications were based on retrospective analyses of national and international registries and individual center cohorts of patients. However, in subsequent years, the International ITx Registry [429], the United States Organ Transplantation report [432], and the individual ITx center reports [433,434] did not record the indications for ITx as previously categorized so that no information about the outcome related to them was obtained.

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 [5,435,436]. Two cohorts of patients on HPN for CIF were compared, one of candidates for ITx and a control group of patients with no indication for ITx. The 5-year survival rate on HPN was 87% in non-candidates. The 5-year survival rate for ITx candidates however was 74% in candidates with HPN-failure, 84% in those with high-risk underlying disease, 100% in those with high morbidity IF/low acceptance of HPN, and 54% in ITx recipients. These data compare well with those of the International ITx Registry that shows actuarial 5-year patient and graft survival of 58% and 50%, respectively, for patients transplanted since 2000 with a

1-year conditional survival (obtained excluding cases of graft failure or patient death during the first year after transplantation to minimize the effects of recipient status at the time of surgery) [429].

In the European survey, the analysis of the risk of death and the causes of death on HPN associated with each indication showed that only patients with liver failure due to IFALD (RR 3.2) or with invasive intra-abdominal desmoids (RR 7.1) had an actual statistically significant increased risk of death on HPN. In these patients, almost all (91.7%) of the deaths on HPN were related to an indication for ITx. A non-statistically significant increase of the risk of death on HPN was observed also for candidates because of multiple central venous catheter-related deep vein thrombosis (RR 2.1, $P = 0.058$). None of the other indications for ITx showed an increased risk of death on HPN, and only 35.8% of deaths that occurred in patients with these indications were related to the underlying disease or to HPN. These data indicate that only liver failure due to IFALD and invasive intra-abdominal desmoids can be considered indications for a straight referral for a life-saving ITx. CVC-related thrombosis of $\geq$2 central veins can be also considered for a life-saving ITx, in appropriately selected patients. For patients having none of the above indications, ITx has no life-saving role, but it might have a potential rehabilitative role on a case-by-case basis for adequately informed patients [436].

The Intestinal Transplant Registry shows that combined liver and ITx has the same patient survival probability of ITx without liver, but a higher probability of graft survival [429]. Furthermore, the decrease of liver fibrosis or the reversal of cirrhosis has been reported after successful engraftment of an isolated ITx in adults and successful isolated liver transplant has been reported in children with liver failure and SBS with prognostic features for full enteral adaptation and weaning from HPN after transplantation [429]. Knowing when hepatic fibrosis is progressing up to irreversible cirrhosis is a key issue for the timing for referral as well as for the type of transplantation. Today, serial liver biopsy remains the gold standard for assessing IFALD. Studies to find appropriate non-invasive markers of the progression of liver fibrosis are required.

Once patients have been listed, the priority criteria for combined liver-ITx is a matter of debate. Stratification of waiting times for liver-ITx is regulated by the models for adult and paediatric end-stage liver disease (MELD and PELD). However, deaths on the waiting list for combined liver-ITx were 8 times higher compared to isolated liver transplant without IF [431]. As a result, these scores were adjusted to incorporate a sliding scale of 10% mortality at 3 months [75]. Over time this has reduced time waiting for a transplant, increased the number of liver-ITx and narrowed the gap between the two groups in both paediatric and adult populations [437].

The data from the International ITx Registry revealed that transplantation while the recipient is waiting at home prior to transplant versus at hospital (that would indicate a better clinical status), younger recipient age, maintenance on rapamycin, and the presence of a liver component were the factors significantly associated with improved graft survival. There were no significant effects related to ITx center volume, sex, type of graft, surgical reconstruction with or without portal venous drainage or removal of native organs [429].

4.8. Prevention/treatment of CVC-related complications

4.8.1. CVC-related infection

78. **We recommend that the choice of central venous catheter type and location of exit site be made by a multidisciplinary HPN team, along with an experienced specialist as well as the patient.** (Grade of evidence: **low**)
79. **We recommend that access to the upper vena cava is the first choice for CVC placement, via internal jugular vein or subclavian vein.** (Grade of evidence: **moderate**)
80. **We suggest that right-sided access is preferable to a left-sided approach with respect to risk for thrombotic complications.** (Grade of evidence: **low**)
81. **We recommend that the tip of the catheter be placed at the level of the right atrial-superior vena cava junction.** (Grade of evidence: **moderate**)
82. **We recommend that the exit site of the catheter should be easily visualized and accessible for patients doing self-care and that the preferred site be marked by clinicians experienced with HPN.** (Grade of evidence: **low**)
83. **We recommend that tunnelled central venous catheters or totally implanted devices are used for long-term HPN.** (Grade of evidence: **very low**)
84. **We do not recommend the use of PICC lines for expected long-term HPN, because of the higher risk of thrombosis and issues related to self-administration of HPN.** (Grade of evidence: **low**)

The process of choosing a central venous catheter (CVC) for an adult to be started on HPN must include a multidisciplinary HPN team [27], an experienced Interventional radiologist [438] or surgeon, and most importantly, the patient. For those needing long-term HPN, tunneled central venous catheters (such as Hickman, Broviac or Groshong) or totally implantable devices (port) are the usual choices [4]. If a subcutaneous port is preferred, it should be determined whether the patient or caregiver will be comfortable accessing it. If this is not the case, it is important that a clinician who can access the port is easily accessible.

It is important that the exit site of the catheter can be easily seen by the patient who does self-care. Consideration must be given to proximity to wounds, prior exit sites, tracheotomies, stomas or fistulae. It is advised that the preferred exit site location be marked by an experienced HPN clinician pre-procedure with the patient standing, in order to insure location of the implanted catheter for best patient acceptance and optimal self-care [439]. The preferred exit site location is not documented in the literature.

The choice of single lumen versus multiple lumen catheter must also be made. The literature indicates that infections are more common when CVCs with more lumens than absolutely necessary are used [440,441]. No recommendation can be made regarding the use of a designated lumen for PN [441]. When there are multiple lumens, treating infections is more complicated. Additionally, the multiple lumen catheter is much more visible than a single lumen line, making it more difficult for patients to maintain a low profile.

Regardless of the type of catheter used, placement of the tip of lines using internal jugular and subclavian approaches should be near the junction of the superior vena cava (SVC) and right atrium to decrease the risk of thrombosis [442–444]. A retrospective analysis of data from patients randomized to receive a prophylactic anticoagulant versus placebo demonstrated that catheters with “adequate placement” of the tip had a relative risk of deep venous thrombosis of 0.26 compared to poorly placed tips [442]. A retrospective review of 428 randomly selected CVC catheters revealed only 2.6% of catheter tips at the SVC-right atrium junctions developed clot, while 5.3% of those at the mid-SVC and 41.7% placed in the proximal third of the SVC were associated with clot [444]. Those with a right-sided insertion had a lower risk of CVC-related thrombosis (relative risk = 0.39) compared to those placed on the left side [442].

Arterio-venous shunts were the earliest type of central venous access when HPN was first used. A recent retrospective review of practice in the Netherlands, where some hospitals have continued to use these shunts, indicates that there is a tendency for the development of blood clots, but infection rates are less common than in other access devices [445].

Some studies document that totally implantable devices are less frequently infected, but these data are primarily based on patients receiving chemotherapy rather than PN. In this case, catheters are usually accessed only a few days a month for drug infusions as opposed to nutrient infusions typically given five to seven days weekly. Furthermore, the nutrient formulation for PN is more favorable for growth of microorganisms than chemotherapy drugs. Very few comparisons have been made between catheter types used for HPN infusion, and these do not indicate fewer infections with subcutaneous ports [446].

Peripherally Inserted Central Venous Catheters (PICCs) are occasionally used, but are generally preferred only for those who will be on HPN for the short-term (<3 months) [4]. Most PICCs are easily dislodged and are difficult for the patient to use independently because arm movement is restricted. Central venous thrombosis is also more common with PICCs. The possibility that PICCs have a lower rate of catheter-related blood stream infections has been suggested, but not confirmed with consistent data. An RCT of PICC vs. non-tunneled subclavian catheters in 102 hospitalized patients documented a higher complication rate with PICC's, but this was primarily the result of central venous thrombosis rather than catheter infections [447].

When the SVC tract is obstructed, an alternate approach must be considered. Although the femoral vein is often used, it is associated with greater risks of catheter-related bloodstream infection and thrombosis [441]. An early multicenter blinded study in 16 ICUs randomized 289 patients to receive femoral vs. subclavian central venous catheters to analyze occurrence of complications. Infectious complications were 19.8% for femoral access and 4.5% for subclavian access and thrombotic complications were 21.5% vs. 1.9%, respectively [448]. A subsequent randomized, multicenter, evaluator-blinded, parallel-group trial compared femoral and internal jugular access used for short-term dialysis in 736 patients who were critically ill [449]. Analysis of a subgroup with high BMI's found that jugular catheters were associated with higher rates of colonization than femoral catheters (45.4 vs 23.7/1000 catheter days). However, overall analysis failed to find a significant difference between the vessels used. Thrombotic complications were not significantly different in this study. In another study that attempted to identify the best vessel to use for central venous access for chemotherapy through a subcutaneous port catheter, the authors found no difference between internal jugular, subclavian, and cephalic veins for access with respect to early complications [451]. There were fewer failed attempts to access the subclavian vein ($P = 0.001$) [451]. However, a Cochrane systemic review [452] found that there were no significant differences between femoral and internal jugular central venous access routes in catheter colonization, catheter-related bloodstream infection (CRBSI), and thrombotic complications, but fewer mechanical complications occurred in the femoral access route. However, this review was based on patients in an intensive care unit.

Occasionally the SVC can be accessed through a dilated azygous vein. Other types of access have been described, including a translumbar [452], transhepatic approach [453] and, as a last resort, direct right atrial placement via thoracotomy.

These data are primarily retrospective, therefore considered weak. While other studies were randomized, the numbers were relatively small. The systemic review was based on data from ICUs: the different setting may weaken its impact for HPN application.

Table 13 shows the results of the RCT on the CVC-related complication risk associated with the type of the vein catheterisation. All the studies have been performed in hospitalized patients.

85. **We recommend that central venous catheter-related infections are diagnosed according to current guidelines on catheter-related infections.** (Grade of evidence: **very low**)

Central venous catheter-related infections (CRIs) in the setting of (home) PN should be defined in line with current GLs for intravascular device-related infections [13,454–456] as local, including infections of the catheter exit site, port pocket, or subcutaneous catheter tunnel, or systemic, in the form of CRBSI. Catheter-related bloodstream infections, according to the Centers for Disease Control and Prevention (CDC) criteria, are defined by a positive culture of the catheter (on removal) or paired blood cultures from a peripheral vein and the catheter (when left in place) with isolation of identical organisms (both species and antibiograms) from cultures of catheter segments and blood drawn from a peripheral vein in a patient with clinical symptoms of sepsis (see below) and the absence of another source of infection [454]. Defervescence of sepsis, defined as a fall in temperature of 1 °C in 24 h or 2 °C within 48 h and/or a fall in white blood count plus an associated resolution of clinical signs and symptoms of sepsis within one or two days following catheter removal, after removal of culture-positive CVCs has been advocated for diagnosis of CRBSI even without positive blood culture and was formally included in the CDC guidelines in 1996 [454].

For clinical purposes, strict definitions for colonization and infection, such as those presented by Pearson, are important tools [454]. Here, catheter colonization is defined as growth of >15 colony-forming units in semi-quantitative culture, or >103 colony-forming units in quantitative culture from a proximal or distal catheter segment, in the absence of clinical symptoms. Local CRIs are defined by similar criteria, with the presence of inflammation (redness, heat, swelling, pain) at the device site. Exit-site infections are defined by inflammation or purulence within 2 cm of the skin at the catheter exit, whereas tunnel infections are characterized by inflammation of tissue overlying the catheter with a distance of >2 cm from the exit site. In patients using implantable ports, pocket infections may occur, with inflammation and necrosis of the skin overlying the reservoir.

In a study in 1365 PN patients, 165 patients developed 192 CRBSI episodes over a period of 15 thousand CVC-days of which 152 met the standard criteria for CRBSI. The mean CRBSI incidence of 10.6 ± 5.8 per 1000 CVC-days was increased by 27% (40 episodes) when defervescence criteria were included, suggesting that the blood culture positivity rate for CRBSI is only 79% (152/192) [457]. It is assumed that CRIs develop after colonization of the device from the luminal or the outer catheter surface. Infections can be bacterial or fungal in origin, but most problems are caused by skin-derived flora. When investigating differences in bacteriology between colonized catheters and CRBSIs in 354 HPN patients, the authors found that culturing of fungi invariably indicated catheter infection, whereas Gram-positive culture results indicated colonization [458]. These findings corroborate clinical experience that fungal CRBSIs require removal of the catheter, whereas in cases of bacterial CRBSI, the line can be salvaged in 30–80% of cases [93,459,460]. The catheter hub is regarded as a common cause of endo-luminal CRIs, whereas infections originating from the exit site or tunnel tract are considered extraluminal in nature.

Table 13
Randomized controlled stidies on the risk of major central venous catheter-related complications associated with the type of vein catheterization.

Author (ref)	Study design	Intervention		Setting	Patients				Results	Comments
		Vein access approach	Duration		n	Age (yr)	Diagnoses	Characteristics		
Verso et al., 2008 [442]	Retrospective review of prior RCT comparing LMWH vs. no prophylaxis		6 weeks	Multi-center study in 6 Italian hospitals	385	NR	Cancer	NR	RR for thrombus: 0.26 catheter tip in lower half of SVC vs. upper SVC, 0.39 for right-sided approach vs left-sided approach	1. All diagnoses were cancer 2. Moderate sized study group 3. Analysis was not part of original protocol 4. Catheter tip and side of approach were not randomized. 5. Therapy was most likely chemo not parenteral nutrition
Cowl et al., 2000 [447]	RCT	PICC vs. SCV	1–36 days	Two acute care hospitals: one teaching hospital, one Veterans hospital	102	21–88	GI diseases (no cancer)		Complication rate, higher with PICCs ($p < 0.05$); Infection rate (n.s.); Thrombophlebitis rate, higher with PICC ($p < 0.01$); Malposition at placement rate, higher with PICC ($p < 0.05$)	1. Patients were hospitalized/short-term study 2. SCV's not tunneled 3. All patients received PN 4. SCV placed mainly by surgery residents, most PICCs by nurses
Merrer et al., 2001 [448]	RCT	FV vs. SCV	NR	Multi-center study in French hospitals	289	Mean 60.1 vs 61.9	NR	Catheters use for antibiotics, blood products and PN	Infection rate, higher with FV ($p < 0.001$); Thrombosis risk, higher with FV ($p < 0.001$) Mechanical complications (n.s.)	1. In-patient ICU study 2. Short term study 3. First CVC in each patient 4. Number of lumens equal between FV and SCV 5. Intention to treat principle used
Parienti et al., 2008 [449]	RCT	FV vs. IJV	6–7 days	Multicenter: 9 tertiary care university centers and 3 general hospitals in France	736	Mean: FV 64.5; JV NR	NR	Hemodialysis	Overall infection rates (n.s.); in pt subgroup with BMI >28.4: colonization rate higher in FV ($p \leq 0.017$)	1. Short term study 2. Catheters used for short term dialysis only 3. Critically ill patients
Biffi et al., 2009 [450]	RCT	SCV, IJV or CV	Mean 356 days (range 0–1087)	Single center study	401	18–75	Cancer	Catheters used for chemotherapy	No significant difference in complications Fewer placement failures with subclavian vein ($P < 0.001$)	1. Cancer 2. CVC used only for chemotherapy 3. 75–84% were right sided approach
Ge et al., 2012 [451]	Cochrane Review	IJV, SCV, vs. FV		Total studies identified, 5854; potentially relevant studies, 28; included studies, 8	1513				Evidence moderate for & applicable for long-term catheterization in cancer; SCV & IJV similar risks for infection & thrombosis; short term SCV preferable to FV - colonization RR 6.43 and thrombotic complications RR 11.53; Evidence moderate for ICU dialysis use: FV (vs. IJV) fewer risks for mechanical complications RR 0.51	1. No studies compared all three access approaches 2. No reports of venous stenosis 3. Applicable for cancer patients 4. Not applicable for other diagnoses or out-patients

RCT = randomized controlled trial; CVC = Central venous catheter; IJV - internal jugular vein; PICC = Peripherally inserted central catheter; SVC = superior vena cava; LMWH = low molecular weight heparin; CV = cephalic vein; ICU = intensive care unit; RR = relative risk; NR = not reported; n.s. = not significant.

Local signs of CRI include limited redness of the skin, pain, and discharge of pus from the exit site or tunnel, which may also appear elevated due the inflammation. The signs of systemic infection cover a broad range of symptoms; typically patients will complain of fever and chills immediately or hours after the start of PN infusion. Nonspecific signs include cardiopulmonary symptoms (shortness of breath, arrhythmias) or gastrointestinal complaints. In any HPN patient, symptoms of infection without another confirmed source should raise the concern for a CRI. That the signs of even CRBSIs may be very subtle was shown in a retrospective study from the UK [459]. When looking at consecutive HPN patients presenting with proven CRBSI, the authors found that this diagnosis should be suspected in any patient with a newly raised C-reactive protein and/or serum bilirubin, decreased serum albumin and in non-specifically unwell patients, despite the presence of normal white cell counts and apyrexia in one-third of all patients. Of note, CRIs may also cause thrombo-embolic complications and catheter obstruction [461].

Central venous catheter-related sepsis rates can be regarded as a surrogate measure of overall quality of catheter care [81]. A recent European survey among 29 experts from 9 countries using a Delphi approach, and based on information in existing HPN GLs, found that the incidence of CRI was the main outcome quality indicator to guide HPN care, followed by number of readmissions, QoL, and dehydration [22].

Complications in patients on long-term HPN can be devastating, as was shown in an older French study where sepsis-related mortality was 30%, half of which originated from CRIs [384]. A survey of 527 patients in the US identified CRIs, mainly CRBSI (80%), exit site (17%), and tunnel (2%) infections, as the most common problems associated with HPN support [462]. An Italian survey of 296 HPN patients found that 76% of CRBSIs were caused by Gram positive *Staphylococcus epidermidis* (51%) or *S. aureus* (7%), whereas Gram-negative microbes comprised 16%, fungi 3%, and polymicrobial cultures 6% of infections [463].

A large survey (12 centres, 447 HPN patients) by the ESPEN HAN&CIF group one decade ago reported on experience in >100,000 catheter days and found that 25% of patients developed catheter problems over six years which were caused by infections in 50% of patients and resulted in catheter removal in 50% of these cases [464]. Implantable ports and daily PN were identified as risk factors, whereas use of catheters for non-nutritional purposes reduced the infection risk [464]. A study of 827 patients receiving home infusion therapy identified the administration of PN, regardless of whether lipids were included, and the use of multilumen catheters and previous CRBSIs as independent risk factors for infection [465].

Recent investigations that reported CRBSI rates in experienced referral centers showed a range from 0.14 to 1.09 episodes per catheter year and these accounted for about 70% of hospital admissions in HPN patients [44,73,93,126,383,388,459,462–469].

Not all types of venous access devices have an equal risk for CRI, as was concluded from a prospective study in 254 adult cancer patients who were candidates for CVC insertion [470]. The authors studied 289 devices for over 50,000 catheter-days and found that the incidence of CRBSI was low (0.35/1000 catheter-days), particularly for PICCs (0/1000) and for ports (0.19/1000). In contrast, a retrospective study in 101 HPN patients from the US found that CRBSI rates were particularly high during the first 4 months after hospital discharge, with a very high incidence of 11.5/1000 catheter-days, and with a significant increase in those patients with higher blood glucose levels and for those with a PICC, when compared with tunneled CVCs [471]. Jeppesen [93] identified the presence of a stoma and advanced age as risk factors for CRBSI, while others found a reduced infection risk in HPN patients who were under the care of a dedicated nutrition support team [93,472].

86. **We recommend that central venous catheter-related infections be managed according to current guidelines on long-term intravascular catheters and as described in the comments section. A conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections. Catheter removal should be the first choice in case of tunnel infections or blood cultures positive for virulent bacteria; catheter removal is mandatory for port abscesses, complicated infections, persistent hemodynamic instability, or blood cultures that are positive for fungi.** (Grade of evidence: **moderate**)

Available data on the diagnosis of mainly come from observational studies in oncology and ICU patients looking at tunneled and non-tunneled catheters. Once a CRBSI is suspected, two sets of blood cultures should be taken, one percutaneously and one from the catheter, to evaluate the possibility of bacteraemia. A diagnosis of CRBSI should be achieved by (a) quantitative or semiquantitative culture of the catheter (when the CVC is removed or exchanged over a guide wire), or (b) paired quantitative blood cultures or paired qualitative blood cultures from a peripheral vein and from the catheter, with continuous monitoring of the differential time to positivity (if the catheter is left in place) [13,455,473,474]. A probable CRBSI is characterized by a colonized catheter in association with clinical signs suggesting septicaemia, despite the lack of a positive peripheral blood culture. Blood cultures should not be taken on a routine basis in the absence of suspicion of a CRI [460,475].

Clinical assessment is recommended to evaluate whether the access device is the source of the CRBSI [476]. If this is the case, and concerning CRBSI treatment in general, in HPN patients a conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections due to *S. aureus*, coagulase-negative staphylococci, and Gram-negative bacilli, before removing the catheter [4,13,460]. Catheter removal is inevitable in case of tunnel infections, port abscesses, in patients with septic shock, or in case of complicated infections, including endocarditis, metastatic infections, septic thrombosis, and when paired blood cultures are positive for fungi or virulent bacteria [13]. For salvage of devices in patients with uncomplicated infections, antibiotic lock therapy should be used for 2 weeks with standard systemic therapy for treatment of CRBSI based on culture results for suspected intraluminal infection, in the absence of tunnel or pocket infection [13,384]. Reinsertion of long-term devices should be postponed until after appropriate systemic antimicrobial therapy is begun, based on susceptibilities of the bloodstream isolate, and after repeat cultures of blood samples yield negative results; if time permits, insertion of a new device in a stable patient ideally should be done after a systemic antibiotic course of therapy is completed, and repeat blood samples drawn 5–10 days later yield negative results [13]. Successful salvage of infected implanted ports by antibiotic treatment is rare and most of these devices have to be removed [440]. Antibiotic locks may have limited efficacy due to the presence of fibrin deposits that harbor bacteria inside the port reservoir [477]. Failure of antibiotic-lock therapy once infections have developed appears to be more frequent in patients with subcutaneous port infection, and in cases of bloodstream infection [455,477].

While thrombolysis with urokinase, streptokinase, or tissue plasminogen activator has been successfully used to unblock clogged catheters, these agents are also used in some centers as

part of a CRBSI treatment protocol to remove any (possibly infected) thrombus from the catheter tip [8,445].

87. **We recommend, for prevention of central venous catheter-related infections** (Grade of evidence: **high**):
    - **education of staff and patients/caregivers**
    - **implementation of an adequate policy of handwashing and disinfection by patients and staff**
    - **handwashing and disinfection by patient and caregivers before touching central venous catheter as well as after catheter care**
    - **disinfection of the hub connector every time it is accessed**
    - **use of tunneled single-lumen catheters, whenever possible**
    - **use of chlorhexidine 2% for antisepsis of hands, catheter exit site, stopcocks, catheter hubs, and other sampling ports**
    - **regular change of i.v. administration sets**
88. **We do not recommend, for prevention of central venous catheter-related infections** (Grade of evidence: **low**):
    - **use of in-line filters**
    - **routine replacement of catheters**
    - **antibiotic prophylaxis**
    - **use of heparin lock**
89. **We suggest, for prevention of central venous catheter-related infections** (Grade of evidence: **very low**):
    - **performing site care, including catheter hub cleaning on at least a weekly basis**
    - **changing catheter dressings at least once weekly**
    - **avoiding catheter care immediately after changing or emptying ostomy appliances**
    - **disinfecting hands after ostomy care**
90. **We suggest that catheter locking with taurolidine may be used to prevent central venous catheter-related infections.** (Grade of evidence: **low)**
91. **We suggest the creation of arterio-venous fistulae to prevent central venous catheter-related infections in carefully selected patients.** (Grade of evidence: **very low)**
92. **We do not recommend catheter locking with 70% ethanol to prevent central venous catheter-related infections, because its use is associated with systemic toxicity, catheter occlusion and catheter damage.** (Grade of evidence: **high)**
93. **We recommend in patients who repeatedly present with central venous catheter-related infections, re-education of the patient and/or caregiver and/or use of an antimicrobial catheter lock.** (Grade of evidence: **low**)

Central venous access device-related complications remain the Achilles' heel of HPN care and are associated with significant psychosocial stress in these patients, generating the need for preventive measures, whenever possible [478]. Implementation of an adequate written policy and education of healthcare personnel and patients is necessary for the prevention of complications [13,460].

Hand hygiene for healthcare professionals, caregivers, and those on HPN who perform their own care is critical to preventing healthcare-acquired infection [479]. CDC guidelines emphasize the importance of decontaminating the hands before and after caring for CVCs [460]. They recommend the use of soap and water or waterless alcohol-based gels or foams. A recent comparison of soap and water to alcohol-based hand rub against live H1N1 influenza virus on the hands of volunteers indicated that soap and water was statistically superior, although both products were highly effective [480]. A subsequent university hospital study compared two different standardized protocols using alcohol-based rubs and one protocol for a chlorhexidine wash on the hands of 120 nursing and medical personnel [481]. Hand samples obtained before and after cleaning hands determined that all three products effectively reduced bacteria.

In the home care setting, handwashing by HPN consumers and caregivers with appropriate disinfectants is essential before and after touching the CVC. The length of time for optimal hand washing is not defined in the literature. For patients with ostomies or fistulae, it is important that care of ostomy and fistula appliances should be temporally separated from catheter care.

Site care, including cleaning the catheter hub, should be done on a regularly prescribed schedule, at least once weekly, as well as every time the dressing becomes wet or contaminated [460]. This should be done with an appropriate disinfectant. A prospective single hospital center study of 668 CVCs and arterial lines randomized site care to use 10% povidone iodine, 70% alcohol, or 2% chlorhexidine. It identified bacteremias in 2.6%, 2.5%, and 0.5% of patients, respectively. Catheter hubs were contaminated with >10 CFU's in 5.3%, 2.6%, and 1.9%, respectively. Chlorhexidine was significantly superior for CVC site care [482]. A meta-analysis reviewed 8 randomized controlled studies using chlorhexidine or povidone-iodine in site care of 4143 catheters of hospitalized patients and found an overall relative risk of 0.51 (49% less risk of infection with chlorhexidine) [483]. The use of chlorhexidine 2% for skin antisepsis of the hands, catheter exit site, and of the skin before catheter insertion is recommended [13,460]. Stopcocks, catheter hubs, and other sampling ports should always be disinfected, preferably using chlorhexidine 2% in 70% isopropyl alcohol. Intravenous administration sets should be changed every 24 h. There is no definitive proof that the use of needle-free connectors reduces CRBSI risk in HPN patients.

Exit-site compression dressings are typically placed when catheters are inserted. These are changed the following day. The type of dressing used for site care has varied over time. A meta-analysis of 23 studies (6 RCT) judged to be sufficient for comparison, indicated no significant difference between gauze with tape versus transparent dressings with respect to infections [484]. However, a more recent Cochrane review by many of the same authors replaced two of the prior studies with two newer studies and found that patients using gauze and tape had fewer CRIs (4.19 fold less than transparent dressings), although the evidence was considered to be of low quality [485]. It was felt that the dressings may have varied in durability, ease of use, ability to prevent infections and skin reactions, and larger studies were urged [460].

Compared with non-tunneled devices, tunneled catheters are associated with lower infection rates due to decreased extraluminal contamination [13]. A single-lumen CVC is preferred, unless multiple ports are essential for the management of the patient. If a multi-lumen CVC is used, one lumen should be reserved exclusively for PN [13]. A randomized trial has provided evidence that interactive video-based education of both staff and patients reduces CRIs in HPN patients and improves problem-solving capacities and QoL [486]. Such training of all individuals who are involved in HPN care is currently considered a key strategy for decreasing CRIs. The same applies to the implementation of an adequate policy of hand washing by patients and staff, and the use of chlorhexidine 2% for skin antisepsis of the hands, catheter exit site, and of the skin before catheter insertion [13,460]. Stopcocks, catheter hubs and other sampling ports should always be disinfected, preferably using chlorhexidine 2% in 70% isopropyl alcohol.

Strategies that have been proven to be ineffective for prevention of CRIs include the use of in-line filters, routine replacement of catheters, antibiotic prophylaxis, and the use of heparin [4,13,460]. Antimicrobial-coated access devices should only be considered in

short-term PN care in patients in whom other infection prevention strategies fail [13].

Concerns that CRBSIs may arise from dental treatment in HPN patients frequently result in the use of antibiotics. Clear prophylaxis guidance specific to this patient group is lacking but is needed, as was shown by a survey in the UK [487]. Here, over 50% of HPN care providers recommended parenteral prophylactic antibiotics even though associations between patient-reported CVC infection, dental status, and the interval since dental treatment or prophylaxis received in the previous year were not significant.

Strict adherence to insertion policies also seems to reduce catheter-related complications as was shown in cancer patients in whom HPN ultrasound-guided venipuncture and catheter securement using sutureless devices was associated with a decreased risk of CRBSI [470].

Catheter locking

Numerous techniques have been tested and implemented to prevent CRBSIs, including the use of several types of catheter lock and flush solutions. Catheter locking is a technique by which an antimicrobial solution is used to fill the catheter lumen and then left for a period of time while the catheter is not in use: antibiotics, either alone or in combination, have been used to this end as well as antiseptics such as ethanol, taurolidine, and trisodium citrate. These agents are frequently combined with an anticoagulant such as heparin or EDTA. However, several meta-analyses have concluded that CVC patency is not prolonged in catheters that are not used for blood processing by intermittent flushing with heparin when compared with normal saline [488–490]. Although antimicrobial effects of heparin have been claimed, preservative-free heparin at concentrations <6000 U/ml lacks antimicrobial properties and might even promote catheter colonization and bio-film growth [491,492]. A Belgian RCT in >750 cancer patients with a newly inserted port compared low-dose heparin (300 U/3 mL) versus 0.9% saline locking. There were no significant differences between groups in primary outcomes (ease of injection, possible aspiration), but the CRBSI rate was 0.03/1000 catheter days in the saline group versus 0.10/1000 catheter days in the heparin group [493].

Antibiotics: evidence is lacking that prophylactic use of antibiotic locks (or systemic antibiotics for that matter) reduce the incidence of CRBSIs in HPN patients, while this strategy carries an inherent risk for the development of microbial resistance, especially in patients requiring long-term HPN [13].

Ethanol: 70% ethanol has not only been used to dissolve debris and unclog PN catheters, but ethanol locking therapy (ELT) has also been shown to be a promising therapy for the prevention of CRBSI in small studies in adult and pediatric HPN patients [494–496]. Benefits over antibiotics include the lack of development of microbial resistance, potent bactericidal and fungicidal properties, and low cost. For instance, Opilla et al. [496] studied 9 HPN patients with a crossover design using ELT. Patients developed 81 CRBSIs before ELT and 9 CRBSIs thereafter (8.3 vs 2.7 per 1000 catheter-days). A larger group of 31 HPN patients in the US who were studied pre- and post-ELT developed 273 CRBSI-related admissions prior to ELT in comparison to 47 CRBSI-related admissions post-ELT, with an adjusted CRBSI-related admission rate drop from 10.1 to 2.9 per 1000 catheter days, without any reported side effects or complications in any patient undergoing ELT [497]. A study from the US that evaluated hospital readmissions for CRBSI in home patients found that there was no LOS difference for CRBSI between home patients with or without ELT, but those not receiving ELT were more likely to have a CRBSI from *Staphylococcus* sp (48% vs 27%) [498]. However, a recent systematic review on the adverse effects associated with ELT showed that ethanol locks are associated with structural changes in catheters, as well as the elution of molecules from the catheter polymers, precipitation of plasma proteins, and increased risk of venous thrombosis [499]. These data do not allow us to recommend ethanol lock for the prevention of CRBSI in patients on long-term HPN.

Taurolidine: taurolidine, a derivative of the amino acid taurine, prevents microbial adhesion to catheter surfaces and biofilm formation by an irreversible reaction of its metabolites with bacterial cell walls. Taurolidine has a very broad spectrum of activity against bacterial and fungal pathogens and also neutralizes bacterial endo- and exotoxins [500,501]. The earliest experience with taurolidine as a catheter lock in the setting of HPN came from Jurewitsch and Jeejeeboy [502] who used taurolidine in a non-controlled study in 7 HPN patients, resulting in a decreased infection rate from 10.8 infections per 1000 catheter days pre-treatment to 0.8 thereafter. Bisseling et al. [503] conducted the first prospective controlled trial by randomizing HPN patients after treatment for CRBSI to receive either 2% taurolidine ($n = 16$) or heparin (150 U/ml, $n = 14$). This study was terminated due to its open label character when an interim analysis demonstrated that taurolidine locking decreased re-infections by more than 90% when compared with heparin, with a mean infection-free period of 641 catheter days in the taurolidine group versus 176 in the heparin group ($P < 0.0001$). There were no reported adverse effects or catheter occlusions. These authors also showed that there was no evidence for the development of microbial resistance to taurolidine in cultures of patients who developed CRBSIs while being treated with taurolidine locks [504]. In 2013, Liu and co-workers [505] published a meta-analysis of available trials on the effects of taurolidine locks for preventing CRBSIs. Six RCTs conducted from 2004 through 2013 involving 431 patients and 86,078 catheter-days were included and showed that the use of taurolidine locks was significantly associated with a lower incidence of CRBSIs when compared to heparin locks (RR 0.34; 95% CI 0.21–0.55), decreased the incidence of CRBSIs from Gram-negative bacteria (P = 0.004; RR, 0.27; CI, 0.11–0.65), and was associated with a non-significant decrease in Gram-positive infections (P = 0.07; RR, 0.41; CI, 0.15–1.09). No association was observed with taurolidine locks and catheter-associated thrombosis. Overall, the use of taurolidine reduced CRBSIs without obvious adverse effects or bacterial resistance. However, the limited sample sizes and methodological deficiencies of several studies necessitate additional well-designed and adequately powered RCTs to confirm these findings.

The largest survey in this field retrospectively analyzed catheter-related complications from 212 patients on HPN between 2000 and 2011, comprising 545 and 200 catheters during lock therapy with low-dose (150 U/ml) heparin and taurolidine, respectively [506]. CRBSI rates were 1.1/year for heparin and 0.2/year for taurolidine-locked catheters, while occlusion incidence rates were 0.2/year for heparin and 0.1/year for taurolidine. Adjusted incidence ratios of heparin compared to taurolidine were 5.9 (95% CI 3.9–8.7) for bloodstream infections and 1.9 (95% CI 1.1–3.1) for occlusions. These data also suggest that taurolidine decreases CRBSI and occlusions in HPN patients compared with heparin. A retrospective study compared CRBSI rates 12 months before and 12 months after implementation of locking with taurolidine-citrate in 15 HPN patients with a high risk of catheter infection. CRBSI decreased from 6.58/1000 catheter-days in the first period to 1.09/1000 catheter-days in the second period, and did so both in patients who used the lock daily or only once a week [507]. Important issues that remain to be solved in future studies are whether the addition of anticoagulants such as citrate to taurolidine affects its efficacy, whether the use of 0.9% sodium chloride (saline) as catheter lock is as effective as taurolidine, whether taurolidine should be considered in all or only in high-

risk patients, and whether locks should be withdrawn or flushed into the patient upon the next catheter use. Potential problems related to all of these locks include the development of side effects, toxicity, allergic reactions, or the emergence of microbial resistance.

Overall, at this point, general recommendations for the use of any catheter lock therefore cannot be given due to the fact that the only studies that are available are underpowered, used a wide variety of compounds, and studied heterogeneous patient populations [460].

Arteriovenous fistulae: that an almost forgotten technique, i.e. the use of arteriovenous fistulae (AVFs) constructed in the forearm, is a feasible alternative to catheters in the setting of HPN was reported in a Dutch study [445]. In 127 consecutive patients receiving HPN between 2000 and 2006, comprising 344 access years of tunneled catheters/ports and 194 access years of AVFs, the rate of bloodstream infections per year was 0.03/yr for AVFs and 1.37/yr for ports and tunneled catheters, with occlusion rates of 0.60 and 0.35 per year, respectively, showing that although occlusions were somewhat more frequent for AVFs than for tunneled catheters, the incidence of bloodstream infections was much lower. Of note, these authors consider the use of PICC lines contraindicated in patients in whom creation of an AVF is considered due to the PICC-associated risk for loss of vessels due to thrombosis.

Table 14 shows the results of the studies on the types of catheter locks available for the primary prevention of central venous catheter-related infections and thrombosis.

4.9. CVC-related occlusion/thrombosis

94. **We recommend** (Grade of evidence: **low**):
    - **treating HPN patients with central venous catheter-related venous thrombosis with anticoagulation**
    - **the duration of this treatment be chosen on an individual basis**
    - **the decision to maintain the catheter be dependent on individual factors (e.g. necessity of a central line, lack of infection, clinical outcome)**

Development of thrombotic complications of the catheter is a dynamic process with varying severity from the appearance of the fibrin sheath at the tip of the catheter, intraluminal blood clot, mural thrombosis to venous thrombosis [508]. Mural thrombosis is a blood clot that adheres to the vessel wall and can occlude the tip of the catheter but does not completely occlude the vein. A catheter-related vein thrombosis (CRVT) occludes the vein and is the most significant thrombotic complication.

CRVT is a severe complication that is responsible for the loss of central venous accesses in patients on HPN and may be an indication for ITx if it affects two or more of the central venous vessels [6,430,431,509]. CRVT may be clinically manifest or subclinical and can develop soon after catheter insertion or be delayed in patients with long-term catheterization.

Most of the data on the incidence of CRVT in HPN comes from retrospective series with large patient cohorts that reported on only clinically manifest thrombosis. In these studies, the incidence of CRVT is around 0.02–0.09 cases/catheter/yr or 0.12/1000 catheter-days [6,44,126,510–512].

The incidence of subclinical CRVT associated with routine diagnostic imaging in patients on HPN with benign disease is much less well known. In a cross-sectional study in 42 adult patients on HPN with a mean dwelling time of 37 weeks, the authors reported rates of 26% for clinical obstruction of the upper venous system, 51% for radiologic thrombotic changes of the vessels wall and/or catheter tip, and 66% for catheter dislocation from the original site, although this study is quite old and probably does not reflect current practice [513].

In a prospective study including 30 consecutive patients receiving intravenous feeding (16 of whom had cancer), venography was performed in the 24-h period prior to catheter removal. The percentage of thrombosis found was 33%, but only one patient had symptoms [514].

In a recent prospective study of the HAN&CIF group in 62 patients on HPN, the incidence of CRVT with serial Color Doppler Duplex Sonography (CDDS) evaluations for 12 months after catheter insertion was 0.045/catheter/yr, quite similar to that found in retrospective studies [515]. In this study, all the catheters were inserted with ultrasound guidance or radiologic control and the catheter tip was located in the atrio-caval junction or in the lower third of the superior cava vein in all the subjects.

Symptomatic venous thrombosis may present clinically with pain, tenderness to palpation, oedema, warmth, erythema, and the development of regional collateral vessels, usually along with catheter malfunction, although these symptoms and signs are non-specific. The gold standard method for CRVT diagnosis is venography, but it is invasive and requires exposure to intravenous constrast and radiation. The preferred method for CRVT screening is ultrasonography, which may be employed in both symptomatic and asymptomatic thrombosis as it is a non-invasive method [516]. Duplex ultrasound can accurately detect CRVT involving the jugular, axillary, distal subclavian, and arm veins. Contrast venographic imaging is required for indeterminate duplex findings and to evaluate the deep central veins and pulmonary arteries.

In a systematic review, compression ultrasonography had good sensitivity (97%) and specificity (96%) compared to venography for the diagnosis of clinically-suspected upper extremity deep vein thrombosis [516]. In this review, only one study evaluated the value of the clinical findings, D-dimer, magnetic resonance imaging, rheography, and plethysmography and found a wide range of sensitivity and specificity [516]. Reliable data on the accuracy of ultrasound in CRVT are limited [517]. In lower extremity CRVT no studies are available. In upper extremity CRVT specifically, Color Doppler Flow Imaging had the best performance (sensitivity 94%, specificity 96%). In patients with normal ultrasound, additional venography could be performed. Alternative strategies such as serially-performed ultrasound, spiral CT, or MRI may be useful and of potential interest, but are not yet validated [517]. According to the results of a recently published prospective study, CDDS is not recommended for routine screening of CRVT in asymptomatic patients with benign diseases on HPN [515].

The optimum management of CRVT is controversial as there are few prospective studies on this topic [517,518]. CRVT is usually treated with anticoagulation, usually low molecular weight heparin (LMWH) or oral anticoagulants. Initial anticoagulation treatment usually involves LMWH, followed by vitamin K antagonists, except in patients with cancer and patients with poor oral absorption, for whom LMWH is preferred. Compared with warfarin, the LMWHs exhibit a superior safety profile and a more predictable effect without the need for monitoring. The role of new oral anticoagulants (oral direct factor Xa inhibitors or direct thrombin inhibitors) in the treatment of CRVT in patients with IF may be promising as they need little monitoring [519]. The length of time a patient should be anticoagulated will depend on individual case characteristics (risk factors, extent and characteristics of the thrombus, catheter removal) but generally is 3–6 months and in some cases forever [520].

The decision to remove or maintain the catheter will be based on each individual situation as it does not appear to influence the outcome of the thrombosis [13]. Moreover, there is a risk of

Table 14
Studies on type of catheter lock for the primary prevention of central venous catheter-related infections and thrombosis.

Author (ref)	Study design	Intervention				Patients		Results			
		Drug/tool	Amount/ day	Duration	Diagnostic tool	n. (studies n.)	Characteristics	CRBSI rate/ 1000 days		CRBSI RR (95% CI)	CVC replacement RR (95% CI)
Bisseling et al., 2010 [503]	RCT	TL 2% vs HL 150 U/mL	5 mL	Follow up (mean) TL 336 HL 353 CVC-days	Time until re-CRBSI	30	Adult HPN patients with CRBSI	TL 0.19 (0.03 −1.3) vs HL 2.02 (1.1−3.8)	reinfections: HL 10/14 vs TL 1/ 16		
Olthof et al., 2014 [506]	Retros. cohort	TL 2% vs HL 150 U/mL	5 mL	TL 71.112 HL 147.842 CVC-days	CRBSI/ occlusion	212	Adult HPN patients	TL 0.2 (0.1−0.2) vs HL 1.1 (0.9 −1.3)/access yr	Catheter occlusion TL 0.1 (0.1−0.2) vs HL 0.2 (0.2−0.3)	Adjusted incidence rate ratio HL/TL: 5.9 (3.9−8.7)	CVC occlusion adjusted incidence rate ratio 1.9 (1.1 −3.1)
Versleijen et al., 2009 [445]	Retros. cohort	AVF vs tunneled CVC (Hickman or port)		Access years: AVF 194 CVC 344	CRBSI/ occlusion	127	Adult HPN patients	AVF 0.03/yr vs 1.37/yr for tunneled CVC	Occlusion rate: AVF 0.60/yr vs tunneled CVCs 0.35	Adjusted incidence rate ratio CVC/AVF: 47 (19−117)	Occlusion adjusted incidence rate ratio 0.53 (0.31 −0.89)
Oliveira et al., 2012 [404]	MA and SR	EL 70% versus HL 10 U/mL	NR	Dwell time from ≥2 h per day to 4 h for 3 day per wk	CRBSI	53 (4 retros.; 3 used for CRBSI; 2 for replacement analysis)	Pediatric PN patients	EL 81% ↓ vs HL per 1000 days	72% replacement reduction by EL vs HL per 1000 catheter days	EL vs HL: 0.19 (0.12−0.32)	EL vs HL: 0.28 (0.06−1.23)
Liu et al., 2013 [505]	MA and SR	TL 2% vs HL 150 U/mL	NR	NR	CRBSI	431 (6 RCT)	HPN, hemodialysis, pediatric oncology	TCL ↓ CRBSI: RR 0.34 (0.21 −0.55)	no effect on catheter occlusion due to thrombosis: RR 1.99 (0.75 −5.28)		
Smith et al., 2003 [486]	RCT	Videotaped Educational Intervention vs placebo		18 months		73	Adult HPN patients	CRBSIs at 6 months: 14% (exp) vs 37% (control) (p = 0.03)	CRBSIs at 18 months: 31% (exp) vs 58% (controls); p = 0.035		
Liu et al. 2014[a]	MA and SR	TCL vs HL (5.000 U/mL)	NR	NR	CRBSI	236 (3 RCT)	Hemodialysis (2 RCT), Pediatric cancer patients (1 RCT)	TCL ↓ CRBSI: RR 0.47 (0.25 −0.89)	TCL ↑ need for thrombolytic therapy: RR 2.10 (1.16 −3.78)		
Goosens et al. 2013[b]	RCT	Saline 0.9% lock vs HL 100 U/mL	NR	180 days postop		802	Cancer patients with new totally implantable CVC	Saline 0.03 vs HL 0.10 (p = 0.18)	Central venous trombosis: Saline 2.8% vs HL 3.3%		

EL = ethanol lock; HL = heparin lock; TL = taurolidine lock; TCL = taurolidine citrate lock (1.35% taurolidine. 4% citrate); HPN = home parenteral nutrition; CRBSI = catheter related bloodstream infection; AVF = arteriovenous fistulae; RCT = randomized controlled trial; Retros = retrospective; MA = meta-analysis; SR = systematic review; RR = relative risk; NR = not reported.

[a] Liu H. Liu H. Deng J. Chen L. Yuan L. Wu Y. Preventing catheter-related bacteremia with taurolidine-citrate catheter locks: a systematic review and meta-analysis. Blood Purif 2014; 37:179−87.

[b] Goossens GA. Jerome M. Janssens C. Peetermans WE. Fieuws S. Moons P. et al. Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomized. non-inferiority. open trial. Ann Oncol 2013; 24:1892−9.

embolization of the thrombus attached to the catheter during the removal. Removal is generally warranted when HPN is no longer necessary, if it is infected or occluded, if there is contraindication to anticoagulation treatment, or if there are persistent symptoms and signs despite anticoagulation [520].

Thrombolytic agents are not usually employed in upper limb thrombosis, except in cases of massive thrombosis with severe symptoms and signs, if the bleeding risk is low and the thrombus is recent (less than 10 days long). In some cases it may be necessary to place an SVC filter if there is contraindication to anticoagulant treatment, if the thrombus progresses despite anticoagulation, or if there is a symptomatic pulmonary thromboembolism despite anticoagulation. Catheter mechanical interventions (aspiration, fragmentation, thrombectomy, balloon angioplasty, or stenting) or surgical procedures (thrombectomy, venoplasty, venous bypass, or decompression at the venous thoracic outlet) are indicated only in those patients with persistent symptoms and signs and failure of anticoagulation or thrombolysis [520].

95. **We recommend, for the primary prevention of central venous catheter-related venous thrombosis, insertion of the catheter using ultrasound guidance and placement of the tip at the superior vena cava-right atrium junction.** (Grade of evidence: **low**)
96. **We do not recommend routine thromboprophylaxis with drugs (heparin, warfarin) as primary prevention of central venous catheter-related venous thrombosis for all adults on HPN based on the risk/benefit balance.** (Grade of evidence: **low**)

Prevention of CRVT in patients on HPN for benign disease is an important issue as one of the causes of HPN failure in these patients is the loss of central venous access. To prevent venous thrombosis, it is very important to minimize the damage to the vein wall during catheter insertion. We recommend using ultrasound-guided catheterization, choosing a catheter with the smallest caliber compatible with the infusion therapy, and placing the tip of the catheter at or near to the atrio-caval junction [13]. Central venous catheters composed of silicon or polyurethane are less often associated with local thrombosis than those made of polyethylene [517]. The role of the puncture site of CVC insertion is still much debated, right jugular vein is the preferred one due to its direct route to the right atrium [521]. Left-sided catheters also have been associated with higher thrombosis risk [517]. In a systematic review, PICCs and insertion of CVCs at femoral sites increases CRVT when compared with other catheter types or insertion sites, respectively [522]. These general recommendations are included in some clinical guidelines on prevention of CRVT [11,13,521].

An association between CRI and CRVT has been reported [517]. In recent studies, an increased risk has been described for vein thrombosis associated with ethanol lock therapy in the paediatric HPN population [523].

In the prevention of catheter-related thrombosis, several drugs have been used including heparin (in the catheter lock, inside the HPN bag, or administered subcutaneously) and oral anticoagulation (vitamin K antagonists). These studies have evaluated primary and/or secondary prevention techniques for CRVT and have been summarized in several meta-analyses and systematic reviews. However, the results are difficult to analyze as they often include a mixed population (cancer and benign disease), hospitalized and at home, different types of catheters, and there are differences in the diagnosis of thrombotic complications (with routine diagnostic imaging or with clinical endpoints) [488,524–532]. Based on the current evidence, previous published guidelines have not recommended the use of routine prophylactic anticoagulation in patients with CVC [521,532].

At least 5 older randomized studies in patients on PN (none in HPN) used unfractionated heparin in various doses added to the bag or intravenously and found a trend toward fewer thrombotic events in the venogram [533–537]. However, the risks associated with heparin prophylaxis due to risks of bleeding, thrombocytopenia, and bone disease, for example, presumably outweigh the risk of thrombosis in many cases.

Regarding HPN adult patients, there are only retrospective and prospective studies that evaluated the role of thromboprophylaxis. Studies on the effectiveness of warfarin in preventing thrombosis in HPN patients are limited and most have used low-dose warfarin (1 or 2 mg/day) which does not increase the INR. One of the factors that may influence the effectiveness of warfarin prophylaxis is vitamin K intake in these patients [538]. Three studies evaluated warfarin prophylaxis in HPN adults. In a prospective non-randomized trial of 2 mg of warfarin given to 23 HPN patients, the incidence of venous thrombosis was 1 in 1617 catheter days compared with 1 in 251 days prior to the study [539]. In a retrospective review of 47 HPN patients with HIV/AIDS, the thrombosis rate was 0.016 per patient per month in 9 patients receiving 1 mg/day warfarin compared with a rate of 0.09 thromboses per patient per month in 38 patients on no prophylaxis [540]. Finally, in a retrospective review of HPN patients who already had 1 thrombotic event, the use of therapeutic warfarin resulted in a significantly decreased thrombosis rate (1 in 18 patient months *vs* 1 in 184 patient months) [541]. In general, therapeutic warfarin has been associated with a 0.4–2% annual risk of non-intracranial hemorrhage and an annual intracranial hemorrhage risk of 0.1–0.9%, depending on the INR target range [542].

Based on this evidence, the decision to use anticoagulation therapy to prevent venous thrombosis requires an assessment of the risk of thrombosis, bleeding risk with anticoagulation therapy, and patient compliance. It seems necessary to perform prospective studies in selected patients (secondary prevention) to balance the risks and benefits of thromboprophylaxis. In the mean time, the decision to start thromboprophylaxis should be decided on an individual basis.

Table 15 shows the results of the studies on the primary prevention of catheter-related central venous thrombosis with anticoagulant drugs.

97. **We suggest flushing catheters with saline to prevent central venous catheter occlusion.** (Grade of evidence: **low**)

Catheter occlusion during catheter dwell is a common complication, causing difficulty with infusion therapy. The incidence of catheter occlusion in HPN patients is about 0.07 episodes/catheter/year (0.059–0.083) [543]. It is usually unpredictable and may occur at any time, but can be associated with the life span of the catheter, the type of catheter used, handling procedures, and repeated events of blood flushing back and possibly also the type of intravenous nutrition used.

The most common cause of catheter occlusion is catheter thrombosis, but it can be also due to HPN formula components, such as lipids and calcium-phosphate precipitates [544].

Adequate flushing with saline when the infusion of PN is completed can prevent catheter occlusion. The minimum flush volume should be twice the catheter volume. Flushing with heparin is a routine part of CVC maintenance in many guidelines, based largely on manufacturers' recommendations and expert opinion rather than clinical trial evidence. It is not advised to use the catheter for blood sampling and the use of infusion pumps for HPN may reduce the risk of this complication [13].

Table 15
Studies on the primary prevention of catheter-related central venous thrombosis with anticoagulant drugs.

Author (ref)	Study design	Intervention				Patients			Results			
		Drug	Amount/day	Duration	Diagnostic tool	n	Nº studies	Characteristics	% thrombosis	% thrombosis (controls)	Thrombosis RR (95% CI)	Others outcomes RR (95% CI)
Brismar et al., 1982 [533]	RCT	UFH	5000 IU q 6 h, IV	7–94 days (mean 25 days)	Venogram	49		Hospitalized patients	21.7	53.8		
Macoviak et al., 1984 [534]	RCT	UFH	1 IU mL^{-1}, with PN	At least 4 weeks	Venogram	37		Hospitalized patients	17.6	15.6		
Ruggiero et al., 1983 [535]	RCT	UFH	1000 IU L^{-1}, with PN	7–43 days (mean 18 days)	Venogram	34		Hospitalized patients	53	65		
Fabri et al., 1982 [536]	RCT	UFH	3000 IU L^{-1}, with PN	Not clear	Venogram	46		Hospitalized patients	8.3	31.8		
Fabri et al., 1984 [537]	RCT	UFH	3000 IU L^{-1}, with PN	22.1 ± 3.2 days	Venogram	40		Hospitalized patients	0	0		
Randolph et al., 1998 [488]	Meta-analysis	prophylactic does of heparin (UFH, LMWH) or heparin bonding	Variable doses		Line-o-grams and ultrasounds		14 RCT	Adults and children, medical and surgical, oncology			Prophylactic heparin: 0.43 (0.23–0.78); heparin bonding: 0.08 (0.02–0.37)	Bacterial colonization: 0.18 (0.06–0.60), CRB 0.26 (0.07–1.03)
Klerk et al., 2003 [524]	Systematic Review	UFH, low-dose warfarin, LMWH	Variable doses	Variable	Venography, ultrasound	2632	7 RCT, 14 prospective studies	PN (5 RCT, 1 prospective). Cancer patients (2 RCT, 9 prospective studies). Intensive Care (4 prospective studies)			Heparin added to PN: 0.77 (0.11–5.48). Cancer patients: warfarine 0.25 (0.09 −0.7), LMWH 0.10 (0.01 −0.71)	No apparent increase in bleeding events
Cunnigham et al., 2006 [525]	Systematic review	Minidose warfarin or LMWH, UFH	Variable doses	Variable	Venography, ultrasound	1932	9 studies (2 placebo RCT, 4 open RT, 3 cohort studies)	Cancer patients			There is no proved role for using thromboprophylaxis. However asymptomatic VT remains common. More highly powered studies needed.	
Kirkpatrick A et al., 2007 [526]	Meta-analysis	UFH infusion, oral low-dose VKAs or LMWH			Venogram/ ultrasound/ Echo-Doppler in all pts (13 studies) or only in symptomatic pts [2]	1714	15 RCT	10 RCT cancer patients, 5 RCT patients on PN	13.5	27.4	0.55 (0.45–0.66), $p < 0.0001$	Major Bleeding: 0.54 (0.2–1.42)
Rawson et al., 2007 [527]	Meta-analysis	Low-dose warfarin	1 mg warfarin and/or a variable dose to maintain an INR < 2.0	90 days–8 months	Doppler ultrasound or venography in all	1236	4 RCT	Cancer pts	6.4	7.5	RD 2% (−9%–5%), $p = 0.56$	
Akl et al., 2008 [529]	Systematic Review and Meta-analysis	UFH, LMWH, VKAs	Variable doses	3 weeks–6 months	Venography, ultrasound	2083	9 RCT	Cancer patients (adults and children)			Heparin therapy (UFH or LMWH): symptomatic VT 0.43 (0.18–1.06),	Mortality: 0.74 (0.40–1.36), infection 0.91 (0.36 −2.28), major

Chaukiyal et al., 2008 [528]	Systematic Review and Meta-analysis	Low-dose warfarin, UFH, LMWH	Warfarin 1 md/day	6–16 weeks	Venography, ultrasound	1428	8 RCT (Heparin vs placebo 4, warfarin vs placebo 3, heparin vs warfarin 1)	Cancer patients	asymptomatic VT 0.82 (0.51–1.32). VKA symptomatic VT 0.62 (0.30–1.27). Post-hoc analysis (LMWH, UFH, warfarin) symptomatic VT 0.56 (0.34–0.92) warfarin: 0.75 (0.24–2.35), heparin: 0.46 (0.18–1.20), warfarin, UFH or LMWH: 0.59 (0.31–1.13), LMWH vs warfarin: 1.71 (0.56–5.26)
Akl et al., 2011 [531]	Meta-analysis	Low dose VKAs, LMWH, UFH	Variable doses	Variable	Venography, ultrasound, CT scan	3611	12 RCT	Cancer patients (adults and children)	Heparin: Symptomatic VT (0.54, 0.28–1.05), asymptomatic VT 0.81 (0.64–1.02). Warfarin: Symptomatic VT (0.63, 0.35–1.11), asymptomatic VT (0.42, 0.28–0.61)

	bleeding 0.68 (0.10–4.78), thrombocytopenia 0.85 (0.49–1.46)	
	No differences in bleeding (RR 1.24, 0.84–1.82) and risk of thrombocytopenia (RR 0.85, 0.49–1.46)	
	Mortality: heparin (0.85, 0.53–1.37), VKAs (0.97, 0.82–1.15). Bleeding: heparin (0.68, 0.10–4.78), VKAs (6.93, 0.86–56.08). Thrombocytopenia: heparin (0.85, 0.49–1.46). Infection: heparin (0.91, 0.49–1.68)	

RCT = randomized controlled trial; UFH = unfractioned heparin; LMWH = low molecular weight heparin; VKAs = Vitamin K Antagonists; PN = parenteral nutrition; VT = vein thrombosis; INR = International normalized ratio; RR = relative risk; RD = risk difference.

A systematic review in adults with CVCs (excluding ports) comparing the effectiveness of different means of maintaining catheter patency (heparin flush, saline flush, urokinase flush, continuous heparin, heparin-bonded catheters, and pressure caps) concluded that there is weak evidence that heparin flushing reduces occlusion of catheters, but no evidence that it reduces CRBSI rate [545]. Results from clinical trials of pressure caps are inconsistent regarding their ability to maintain catheter patency, but provide moderate evidence that at least some varieties of caps are associated with increased bloodstream infections. The authors conclude that the evidence base on heparin flushing and other interventions to prevent catheter occlusion is small, and published studies are of low quality. There is insufficient evidence on which to conclude that flushing catheters with heparin is more effective than flushing with saline solution [545]. However many of the studies included in this systematic review included short-term catheters and hospitalized patients, so the results cannot be fully applied to patients on HPN.

In conclusion, the literature suggests that the current practice of frequent heparin locks for CVCs might not be necessary, and that randomized studies are needed to identify the ideal flush solution, its concentration, and delivery schedule for each type of long-term CVC.

98. **We suggest irrigation of the catheter with saline as the first attempt to restore catheter patency in intra-lumen catheter occlusion.** (Grade of evidence: **low**)
99. **We suggest using fibrinolytic drugs for the treatment of acute catheter occlusion likely caused by blood clotting.** (Grade of evidence: **low**)

A proper initial assessment of catheter occlusion is the key to successful management. The assessment screens are for both thrombotic and non-thrombotic causes (including mechanical occlusion) [544]. If mechanical occlusion is excluded, the first attempt to restore catheter patency should be forceful irrigation of the catheter with saline, which will be enough to unclog the catheter in many cases [546]. If this fails, we should try with other solutions. Non-thrombotic occlusions are treated according to their primary etiology: lipid occlusion is treated with 70% ethanol or sodium hydroxide, mineral precipitates are treated with 0.1N hydrochloric acid (HCl), drug precipitates are treated according to their pH, acidic drugs can be cleared with 0.1N HCl, basic medications can be cleared with sodium bicarbonate or 0.1N sodium hydroxide (NaOH) [546]. No large studies of these approaches have been done, and there is concern about damage to the wall of the catheter, and other side effects with these solutions [508].

Thrombotic occlusion is treated with fibrinolytics. Urokinase and alteplase are the two mainly used agents. Current recommendations include delivery of a thrombolytic agent into the catheter lumen with a dwell time of at least 30 min and a repeated dose if needed. If catheter patency is not restored, a low dose of fibrinolytic can be infused over 6–8 h. New thrombolytic drugs with potentially higher efficacy and shorter dwell times than alteplase are being investigated: reteplase, recombinant urokinase, alfimeprase [508].

If the treatment with a thrombolytic drug does not clear the catheter, a guide wire can be inserted through the catheter lumen to dislodge a thrombus at the tip of the CVC, or fibrin sheath stripping can be used, but these procedures are more invasive and are only used when necessary.

In a Cochrane review on different interventions (chemical, surgical, or drug) used to restore patency of occluded CVC lumens in adults and children, no randomized trials were found that investigated the efficacy and safety of either chemical (HCl, sodium

bicarbonate, NaOH, 70% ethanol solution) or surgical interventions (brush, snare, guidewire exchange). Seven studies with a total of 632 participants investigated different comparisons of the strengths of thrombolytic or anticoagulant drug interventions for treating CVC lumen occlusion thought to be caused by a thrombus. The authors concluded that there is inadequate evidence to draw strong conclusions on the efficacy or safety of the drug interventions included in this review. There is some low quality evidence from a meta-analysis of two studies investigating urokinase (various strengths) and some very weak evidence from two single studies investigating alteplase 2 mg/2 mL that suggest that these two drug interventions may be effective in treating withdrawal or total occlusion of CVC lumens caused by thrombosis. Further high quality, sufficiently powered research is still required to look at the efficacy and safety of urokinase, alteplase, and other chemical, surgical, and drug interventions for treating CVC lumen occlusion [547].

Another chemical agent used for catheter clearing is sodium hydroxide. In a retrospective study that included data from 6 years of 45 adults on HPN, treatment with 0.1N NaOH restored patency in 77% of partially-occluded catheters. In this study, the incidence of occlusion was significantly higher in fat-containing HPN. The authors concluded that NaOH solution is safe and effective [548].

Recently, the first report of the safe and effective use of endoluminal brushing to manage occluded CVCs in patients requiring long-term HPN has been published [549]. In this study, those patients admitted with a CVC occlusion to one of the two national IF centres in the UK, were entered into a prospectively-managed database and the data were then analyzed retrospectively. The study used data from patients who had CVC occlusions from December 2003 to March 2006 (Cohort 1, managed using endoluminal brush) and from April 2006 to September 2010 (Cohort 2, standard technique of urokinase with or without adjuncts such as ethanol, hydrochloric acid, or sodium hydroxide). The number of CVCs where patency was achieved was 86% in Cohort 1 (endoluminal brush) compared to 50% in Cohort 2 (standard care) ($p < 0.0001$) with no complications associated with endoluminal brushing or standard therapy.

4.10. Prevention/treatment of intestinal failure-associated liver disease

100. **We recommend for prevention of intestinal failure-associated liver disease that** (Grade of evidence: **low**):
   - **sepsis is prevented and/or managed, if present**
   - **attempts are made to preserve small intestinal length and retain the colon in continuity with small bowel**
   - **oral/enteral intake is maintained**
   - **PN is cycled**
   - **PN overfeeding is avoided**
   - **the dose of soybean-oil based lipid is limited to less than 1 g/kg/day**

There is no standardized definition of IFALD. The term IFALD refers to liver injury as a result of several factors relating to CIF, including, but not limited to, PN [44]. Diagnosis and monitoring of IFALD requires the synthesis of clinical, biochemical, radiological and, where appropriate, histological information. It is important that other causes of deranged liver function are excluded such as choledocholithiasis, hepatitis (e.g. viral or autoimmune), and sepsis. Hepatotoxic medication should be reviewed and insults removed. The decision to perform a liver biopsy should be made on a case-by-case basis. Most study definitions of IFALD vary and usually rely on biochemical abnormalities rather than histological characteristics, as few liver biopsies have been performed within studies [130,131,383,550–553]. As a result, study definitions are heterogenous, including terms such as 'abnormal liver function tests', 'chronic cholestasis' and 'advanced' or 'severe liver disease' [130,131,383,550–553]. However, reliance on biochemistry alone for definition can lead to inconsistent reports of the true incidence and prevalence of IFALD. This must be balanced against the risks inherent to an invasive procedure such as a liver biopsy. A consensus definition, that sets parameters of biochemical and histological abnormality, is therefore required to truly standardise the use of the term IFALD, both in clinical and research spheres.

Histological abnormalities associated with IFALD include steatosis, portal inflammation, portal oedema, ductal reaction, ductopenia, and portal and perivenular fibrosis [554]. Unlike infants, adults are more likely to demonstrate steatosis and are less susceptible to hepatocellular injury or cholestasis, probably as a result of a mature ability to transport and metabolize bile more effectively [554]. Furthermore, the rate of progression of liver dysfunction in adults varies and does not always correlate with biochemical markers of hepatic dysfunction; serial biopsies have therefore been suggested as a means to monitor those at perceived risk [554]. However, liver biopsy carries risks including haemorrhage and, in rare cases, death. Advances in imaging techniques, as alternatives to liver biopsy, include transient elastography, although a recent study demonstrated correlation with cholestasis rather than hepatic fibrosis or cirrhosis [555]. Further research into these imaging techniques, as well as other serological markers of hepatic fibrosis, is required before guidance can be set regarding the role of such markers in diagnosing and monitoring the progression of IFALD.

There is no formally agreed categorization of adult IFALD. At the Xth International Small Bowel Transplant Symposium, Santa Monica, California 2007, an international panel of experts, categorized IFALD in children into early/mild, established/moderate, and late/severe, on the basis of the serum levels of biochemical markers of cholestasis, abdominal ultrasound, and liver histology features, as well as clinical features [75]. A consensus categorization appropriate to adults is now required that ideally incorporates defined histological and/or radiological parameters.

The incidence or prevalance of IFALD cannot be accurately gauged against a standardized consensus definition. The incidence of liver disease in adults with CIF receiving long-term HPN has, however, been reported in a small number of observational studies that have varied in the biochemical and/or histological parameters used to define liver dysfunction. As a result, studies report the prevalence of abnormal liver tests and/or cholestasis with rates ranging from 19% to 95% [130,131,383,551–553].

Moreover, the incidence of clinically-advanced liver disease also varies in published studies from 0% to 50% [130,131,383,551–553]. Two cohort studies exemplify this variation: Cavicchi and colleagues evaluated 90 patients requiring HPN for a median of 49 (range 6–108) months and found that 50% of these patients developed 'complicated liver disease' (defined by a serum bilirubin of greater than 60 μmol/L, decompensated liver disease and/or fibrosis or cirrhosis on liver biopsy) at 6 years [130]. By contrast, Luman and colleagues evaluated 107 patients receiving HPN for a median of 40 (range 4–252) months, but reported that no patients suffered from a conjugated bilirubin of greater than 60 μmol/L (3.5 mg/dL) and/or decompensated liver disease [553]. Furthermore, mortality in patients with IFALD has been reported to range from 0 to 22% in various studies [130,131,383,551–553]. Thus, a more accurate estimate of IFALD incidence, prevalance, morbidity, and mortality can only be ascertained once a consensus regarding definition is reached.

IFALD is a multifactorial condition. Aetiological influences can be categorized as sepsis, intestinal anatomy, oral/enteral nutrition, PN infusion modality, nutrient deficiency or eccess.

Sepsis

Evidence for sepsis as a risk factor for IFALD derives from two retrospective studies of PN in paediatric patients [556,557]. A more recent observational study in adults demonstrated an elevation in serum bilirubin in patients with CRBSI but showed no evidence that recurrent septic episodes predispose to chronic liver complications [459]. Furthermore, it has been postulated that antibiotic therapy inhibits bacterial translocation and reduces hepatocellular injury in patients with small bowel bacterial overgrowth, thereby decreasing the incidence of hepatic dysfunction; indeed, two small studies demonstrated that metronidazole stabilized or improved liver biochemistry in adults receiving short-term PN [558,559]. However, there are no large prospective, randomized controlled data supporting the prophylactic use of antibiotics to prevent IFALD in CIF.

Intestinal anatomy

Cavicchi et al. [130] and Luman et al. [553] demonstrated that a small bowel remnant of ≤50 cm or ≤100 cm, respectively, was independently associated with chronic cholestasis in adults receiving long-term PN. However, although Lloyd and colleagues' retrospective study [560] also found an association between shorter small bowel length and chronic cholestasis on univariate analysis, this was not significant on multivariate analysis, which incorporated an adjustment for parenteral energy provision. The latter study also demonstrated that the presence of colon in continuity reduced IFALD risk [560].

Oral/enteral nutrition

Data demonstrating the benefit of enteral nutrition are limited to studies in infants and neonates receiving short-term PN [561,562]. Nonetheless, lack of enteral stimulation likely plays a role in the development of IFALD in adults, although it is difficult to disentangle whether the benefit relates to enhanced enteral use or reduced PN. Both factors likely play a role.

PN infusion modality

A two-week prospective study of adults receiving PN demonstrated that cycling improved bilirubin levels [563]. Clearly, cyclic PN yields greater freedom and improved QoL for patients requiring long-term PN.

Nutrient deficiency

Protein and/or EFA deficiency is associated with steatosis in animal studies [564]. Deficiencies in methionine metabolites (choline, carnitine, and taurine) can result in hepatic steatosis and chronic cholestasis in premature infants [565]. Taurine supplementation has been shown to be effective in decreasing cholestasis in neonates and infants [566], but there are no comparable studies in adults. Carnitine deficiency did not influence IFALD in an intervention study in adults [567]. Small studies have shown that choline replacement can improve liver transaminases in adults [568,569]; however, sufficient quantities are unstable in PN solutions, complicating delivery [569].

Nutrient excess

Glucose overfeeding can result in greater insulin surges, hepatic lipogenesis, and the build-up of triglycerides within hepatocytes, increasing the risk of hepatic dysfunction [570,571]. Excessive lipid can also have a deleterious effect on hepatic function; soybean-based lipid emulsions in excess of 1 g/kg/day have been shown to be detrimental to liver function, with associated morbidity and mortality [130]. A recent 4-week randomized controlled, double-blind study in adults demonstrated that a combination lipid emulsion (soybean/MCT/olive/fish oil) yielded lower levels of transaminases and bilirubin within the normal reference range compared to soybean-based lipid [572]; however, longer term studies are required before the routine use of this or other novel (e.g. MCT/LCT mixtures and monounsaturated fatty acids) combination lipids can be recommended to reduce the risk of IFALD in adults with CIF.

101. **We suggest for treatment of intestinal failure-associated liver disease** (Grade of evidence: **low**):
    - **to re-consider all the measures to prevent intestinal failure-associated liver disease**
    - **to revise the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω6/ω3 PUFA ratio**
    - **to revise any potential inflammatory/infective foci**

Nutritional approaches

Since overfeeding can be deleterious [130,570], energy requirements should be tailored to the individual, with optimization of oral/enteral nutrition, wherever possible (see relevant section in CIF Guidelines). A prospective, non-randomized study evaluating adults with hyperbilirubinaemia receiving PN demonstrated an improvement in liver function following cycling of the infusion [563]. There are minimal data delineating the risks vs. benefits of restoring intestinal continuity in order to improve liver function in patients with IFALD.

While there are no randomized, controlled studies published that demonstrate the long-term benefit of limiting soybean-based lipid, observational data in adults support the rationale that this type of lipid should be limited to less than 1 g/kg/day [130]. A small retrospective study of ten children on long-term HPN demonstrated that a temporary decrease, a switch from LCT to LCT-MCT emulsions or cessation in soybean-based lipid administration, led to normalisation of bilirubin levels [573]. There are currently no data to support the role of lipid-free regimens to treat IFALD. Equally, while there are case reports [129,574], case series [575], and reviews [576,577], to support the role of pure fish oil emulsion or newer combination lipid emulsions (e.g. MCT/LCT mixtures, olive oil, and fish oils) in improving liver function in children and adults with IFALD, more data are required before their routine use can be recommended to treat IFALD.

Pharmacological approaches

Ursodeoxycholic acid (UDCA), when taken orally in other cholestatic conditions, displaces hepatotoxic bile salts and protects against hepatocellular injury. However, the evidence base for the use of UDCA to treat IFALD is limited. A retrospective study demonstrated that UDCA use was associated with a shorter duration of cholestasis in infants receiving PN [578], while a small, non-randomized study in adults also demonstrated that a two-month course of UDCA was associated with an improvement in liver function in patients receiving PN [579]. Based on the evidence outlined earlier, the use of choline, taurine, or carnitine cannot currently be recommended to treat IFALD in adults with CIF [566–569].

Transplantation

Impending or overt liver failure is an indication for small intestinal/multivisceral transplantation (see: relevant section in CIF Guidelines). A consensus categorization of IFALD is required to

facilitate future risk stratification of referral indications and timing for isolated small bowel or multivisceral transplantation for adults with CIF.

4.11. Prevention/treatment of gallbladder sludge and stones

102. **We suggest for the prevention/treatment of gallbladder sludge to maintain/resume oral feeding.** (Grade of evidence: **very low**)
103. **We recommend for the treatment of gallbladder sludge and stones to perform cholecystectomy and/or endoscopic procedures in case of biliary complications as for the general population.** (Grade of evidence: **low**)

Patients on PN have been recognized as at risk of developing biliary sludge or cholelithiasis [4,580]. In a prospective study that included 23 selected adult patients on total PN, serial ultrasonographic studies indicated that the percentage of sludge-positive patients during PN increased from 6% during the first 3 weeks–50% during the fourth and the sixth week and reached 100% after 6 weeks [581]. In a retrospective study that included 119 patients on long-term HPN, the same Paris team reported that the probability of developing cholelithiasis during HPN was estimated to be 6.2%, 21.2%, and 38.7% at 6, 12, and 24 months, respectively [582]. Roslyn et al. described an incidence of developing gallbladder cholelithiasis in 25 out of 128 patients (23%) in a mean time of 13.5 months on PN [583]. In 2 retrospective studies that included patients with a short bowel, the prevalence of cholelithiasis was 31% (n = 35) and 43% (n = 38), respectively [95,584]. In the Dray's study, biliary complications developed in 7% of the patients during follow-up [582].

Primary prevention is indirectly related to the factors that have been recognized to increase the risk of developing biliary sludge or stones. Several risk factors for developing sludge or stones have been identified including an intestinal remnant length less than 180 cm [95], an absent ileocaecal junction [585], the duration of PN, and Crohn's disease but risk is mostly attributable to nil or negligible ingesta [580,581,585,586]. This is probably due to bile stasis during fasting that is due to lack of cholecystokinin hormone that usually empties the gallbladder [581,587,588]. In the eighties, prophylactic cholecystectomy was advocated by some authors [589] but has never been confirmed in a prospective trial. It has been also suggested that bile composition may be altered by fasting [590] or lipid infusion [591], more likely by MCT/LCT [592], or the use of narcotics or anticholinergics [588].

There were a few randomized studies in humans (very limited number of patients) that showed that rapid intravenous administration of amino acids [593] or omega-3 fatty acids [594] could reduce the risk of developing biliary stones. Sinealide (cholecystokinin) that was used in 5 human studies, failed to show long-term effects in preventing and treating PN-associated gallbladder disease [595–597]. In animal studies it has been observed that intravenous chenodeoxycholate prevents calcium bilirubinate gallstones [598] and glutamine-enriched total PN prevents the lithogenic effect of PN [599]. In practice, the major recommendation for preventing biliary sludge or stone formation is to encourage oral and/or enteral feeding as fast as possible. The use of narcotics or anticholinergics should be limited as much as possible. Messing et al. showed that biliary sludge is reversible in the majority of the patients within 4 weeks after resuming oral feeding [581]. Besides the effect of resuming oral feeding on biliary sludge, treatment of biliary stones is similar to that in the general population [580,600].

4.12. Prevention/treatment of intestinal failure-associated renal failure and stones

104. **We recommend for the primary prevention of renal failure and of renal stones, regular monitoring of renal function and fluid balance as well as a timely adjustment of fluid supplementation in order to avoid episodes of dehydration in patients with CIF.** (Grade of evidence: **low**)
105. **We recommend for the primary prevention of renal failure, that acute and chronic infections as well as acute and chronic dehydration are addressed by the relevant clinical intervention.** (Grade of evidence: **low**)
106. **We suggest for the primary prevention of renal stones a low oxalate and low fat diet, in addition to an increase of oral calcium, to reduce the risk of oxalate stone formation in patients with SBS with a colon in continuity.** (Grade of evidence: **low**)
107. **We suggest avoiding metabolic acidosis and giving citrate supplementation, to reduce the risk of uric acid stones.** (Grade of evidence: **very low**)
108. **We recommend treating renal failure and renal stones in patients with CIF according to the standards for these conditions.** (Grade of evidence: **very low**)

The first-line treatment for CIF is HPN. As outcomes improve, much of the focus is shifting towards discovery and prevention of collateral damage. Renal complications, reduced kidney function, and renal stones are among the metabolic complications that patients on long-term HPN are up against. Also, for the clinician, this is a challenge since the possible end-stage scenario with chronic renal failure makes HPN management much more complicated and further impairs the QoL of the patient.

The knowledge about possible mechanisms that result in severe renal complications with progression to end-stage renal failure is scarce and very little medical evidence on renal failure and renal stones related to CIF is at hand. We learned from an early retrospective study testing the change in glomerular filtration rate, measured as creatinine clearance (CrCl) in 33 long-term HPN patients [601], that renal clearance decreased by 3.5% ± 6.3% per year, and the authors concluded that this is more than you would expect from increasing age alone. Renal function was examined in another study by more parameters in 16 patients with SBS [602], 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. In another study, Lauverjat et al. found an association with patient hydration status [603]. 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 significantly higher in the transplanted group compared to the HPN group [604]. Chronic renal failure was defined as estimated glomerular filtration rate below 60 mL/min. This study reports an annual decline in renal function of 2.8% and a 5-year probability of 84% of retaining normal renal function. In the transplanted group, the study reported a significantly higher yearly decline in renal function of 14.5% and the 5-year probability of retaining normal renal function was only 44% [604].

Still, we do not know the causes of decreased renal function that are reported in other studies in transplanted patients [605]. Expert opinions in reviews state that CIF is associated with renal failure due to chronic dehydration caused by stomal losses [431,603]. Also, a suggested mechanism for renal damage is repeated CRBSI but this has not definitely been demonstrated by the data. The use of nephrotoxic medications (as may be the case particularly in transplanted patients) and existing renal disease may also play a

role. Speculations have been put forward that PN might induce renal damage, but this is not supported by evidence.

Renal stones and nephrocalcinosis are linked to increased absorption of oxalate and hypovolemia and dehydration [606]. Hypomagnesemia and metabolic acidosis may also increase the risk of renal precipitations including uric acid stones. 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 [95], 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 [95]. The prevalence and incidence of renal damage caused by this mechanism is unknown [607]. In prevention, one should focus on sufficient parenteral supply with good hydration and high urinary flow. Preventive measures with reduced intake of oxalate and the use of cholestyramine have been reported, but are not always successful [608]. A low fat diet or replacing with MCT and oral calcium supplementation at meal time have also to be considered [15].

Correction of metabolic acidosis and supplementation with citrate and magnesium supplementation may prevent stone formation, citrate particularly prevents one of the first steps of stone formation, nucleation, and low citrate excretion is common in short bowel patients. Altogether these data do not allow us to more precisely estimate the incidence and prevalence of neither renal failure or renal stones in the population of patients with CIF.

4.13. Prevention/treatment of intestinal failure-associated metabolic bone disease

109 **We recommend that for routine purposes, diagnosis of metabolic bone disease is based on a combination of bone densitometry scanning and biochemistry**. (Grade of evidence: **low**)

110 **We recommend that the HPN population is routinely monitored for metabolic bone disease by bone densitometry scanning and biochemistry**. (Grade of evidence: **low**)

111 **We recommend to promptly address general risk factors for developing osteoporosis, as well as factors with a possible negative impact on bone health, i.e. chronic inflammation, infections, drugs and other relevant factors related to the underlying disease, in all patients on long-term HPN**. (Grade of evidence: **very low**)

112 **We recommend as the primary step to treat metabolic bone disease to optimize the program for parenteral nutrition with the required supplements of vitamin D, calcium and phosphate. Further, medical treatment may be useful to increase bone mineral density and lower the fracture risk**. (Grade of evidence: **low**)

The gold standard for diagnosing metabolic bone disease (MBD) currently is dual-energy X-ray absorptiometry (DEXA). Measurement of bone density cannot distinguish between osteomalacia and osteoporosis. For a more specific diagnosis, bone histology may be needed, but the invasive character of this diagnostic approach is a barrier. In order to diagnose MBD as HPN-associated or related you need to rule out other causes including life-style factors and the impact of the underlying disease causing CIF. Studies of bone turnover in patients on HPN by biochemistry indicate that HPN patients at first present with hyperkinetic bone turnover and later show features of low rates of bone formation; a histomorphometric study approach shows osteomalacia as well as osteoporosis [609–612]. The pathogenesis of MBD is most likely related to the underlying disease, malabsorption, chronic inflammation, or the use of medications, in particular corticosteroids. Also, treatment with PN may affect bone health. Possible PN-related factors include toxicity from aluminum contamination of the nutrition formula, increased sensitivity to vitamin D suppressing PTH secretion, and hypercalciuria induced by the intravenous infusion of nutrients. Home parenteral nutrition-related MBD might also be caused by deficiencies or toxic effects of other micronutrients known to interfere with bone metabolism. This is potentially the case for vitamin K, vitamin C, copper, fluoride, boron, and silicon deficiency, and for vitamin A, cadmium, strontium, and vanadium toxicity. However, no data have yet convincingly linked abnormal micronutrient levels to MBD in patients on HPN [609–612].

Metabolic bone disease is common in patients on HPN as reported in several studies. An ESPEN multicentre cross-sectional survey [613] of 165 patients evaluated the prevalence of MBD by DEXA. In 84% of the patients, the bone mineral density (BMD) T-score of the femoral neck or spine was lower than 1 (the number of standard deviations below the mean BMD of young healthy individuals). By the WHO criteria, 41% of the patients presented with osteoporosis, with a T-score below 2.5. This underlines the importance of monitoring as well as prevention. The incidence of MBD in the HPN population remains unknown, but follow-up studies on relatively large patient groups [614–616] 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.

Taking into account general factors and disease-specific causes as well as the possible impact of PN is important. Aluminum contamination of PN fluids must be reduced to a minimum and be less than 25 μg/L [617]. Hypercalciuria and a negative calcium balance may influence bone health and may be induced by providing more sodium or amino acids than needed to reach nutritional goals. Also, reducing infusion rates may decrease hypercalciuria [609–611].

The calcium, magnesium, and phosphate content of the PN must aim at maintaining 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 [609–611]. In adults, it has been shown that increasing the inorganic phosphorus content of the PN formula up to 90 mmol, with a calcium content of 6 mmol, decreases urinary calcium excretion by increasing renal tubular calcium resorption [618]. However, solubility of calcium in PN solutions is limited by formation of calcium, phosphate, carbonate and magnesium salts. It is suggested that calcium and phosphate be given starting from a ratio of 1:2 and adjusting it as needed (i.e. 15 mEq of calcium and 30 mmol of phosphorus to the PN solution each day) [610].

The recommended intravenous dose of vitamin D is 200 IU/day. Consider withdrawing vitamin D temporarily in patients with low BMD, low serum parathyroid hormone, and low 1,25-dihydroxyvitamin D concentrations associated with normal 25-hydroxyvitamin D [619]. In the case of elevated PTH and low 25-hydroxyvitamin D, additional parenteral supplementation with vitamin D is indicated [620]. Preventive measures that apply to the general population should also be recognized for patients on HPN. It is important to address underlying disease-related factors, including infections and chronic inflammation.

For monitoring purposes, we recommend repeated DEXA measurements at yearly intervals, although the benefit of this routine is not well supported by studies [612–614]. We recommend scanning the spine and femoral neck or arm. The biochemical assessment of MBD includes the measurement of serum

concentrations and optionally 24-h urinary excretion of minerals, serum concentrations (and/or urinary excretion) of biochemical markers of bone turnover and plasma concentrations of PTH, 25-hydroxyvitamin D and possibly 1,25-dihydroxyvitamin D. Also, consider measurement of serum aluminum concentrations in patients with low BMD T-scores.

Bisphosphonates provided intravenously at regular intervals (Clodronate, Pamidronate, or Zolindronic acid), may support bone mineral health in patients with osteopenia. This medical therapy may be useful for the prevention and treatment of MBD in HPN patients, but to date only a single randomized controlled study of bisphosphonate treatment has been carried out in patients on HPN [621]. Intravenous clodronate decreased the urinary excretion of markers of bone resorption, and BMD of the lumbar spine was maintained in patients on HPN after 12 months, but a significant increase in BMD was not observed. Anecdotal reports suggest that IV pamidronate is also useful [622,623].

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