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ESPEN Guideline

ESPEN guideline on chronic intestinal failure in adults – Update 2023

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ABSTRACT

Background & aims: In 2016, ESPEN published the guideline for Chronic Intestinal Failure (CIF) in adults. An updated version of ESPEN guidelines on CIF due to benign disease in adults was devised in order to incorporate new evidence since the publication of the previous ESPEN guidelines.
Methods: The grading system of the Scottish Intercollegiate Guidelines Network (SIGN) was used to grade the literature. Recommendations were graded according to the levels of evidence available as A (strong), B (conditional), 0 (weak) and Good practice points (GPP). The recommendations of the 2016 guideline (graded using the GRADE system) which were still valid, because no studies supporting an update were retrieved, were reworded and re-graded accordingly.
Results: The recommendations of the 2016 guideline were reviewed, particularly focusing on definitions, and new chapters were included to devise recommendations on IF centers, chronic enterocutaneous fistulas, costs of IF, caring for CIF patients during pregnancy, transition of patients from pediatric to adult centers. The new guideline consist of 149 recommendations and 16 statements which were voted for consensus by ESPEN members, online in July 2022 and at conference during the annual Congress in September 2022. The Grade of recommendation is GPP for 96 (64.4%) of the recommendations, 0 for 29 (19.5%), B for 19 (12.7%), and A for only five (3.4%). The grade of consensus is "strong consensus" for 148 (99.3%) and "consensus" for one (0.7%) recommendation. The grade of consensus for the statements is "strong consensus" for 14 (87.5%) and "consensus" for two (12.5%).
Conclusions: It is confirmed that CIF management requires complex technologies, multidisciplinary and multiprofessional activity, and expertise to care for the underlying gastrointestinal disease and to provide HPN support. Most of the recommendations were graded as GPP, but almost all received a strong consensus.

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Abbreviations

BMD	bone mineral density
BMI	body mass index
CIF	chronic intestinal failure
CIPO	chronic intestinal pseudo-obstruction
CLABSI	central line-related bloodstream infection
CRBSI	catheter-related bloodstream infection
CRP	C-reactive protein
CRVT	central venous access device-related vein thrombosis
CTE	controlled tissue expansion
CVAD	central venous access device
CVC	central venous catheter
DEXA	dual-energy X-ray absorptiometry
EAF	enteroatmospheric fistulas
ECF	enterocutaneous fistula
ED	enteric dysmotility
EDTA	tetrasodium ethylenediaminetetraacetic acid
EFA	essential fatty acids
EFAD	essential fatty acid deficiency
ELT	ethanol locking therapy
EMA	European Medicines Agency
EN	enteral nutrition
FGF	fibroblast growth factor
GFR	glomerular filtration rate
GIP	Glucose-dependent insulinotropic polypeptide
GLP-2	glucagon-like peptide-2
GL	guideline
hGH	human growth hormone
HPN	home parenteral nutrition
ICU	intensive care unit
IF	intestinal failure
IFALD	intestinal failure-associated liver disease
INR	international normalized ratio
ITx	intestinal transplantation
IVS	intravenous supplementation
LCT	long-chain triglyceride
LILT	longitudinal intestinal lengthening and tailoring
LITx	liver-small bowel transplants
LMWH	low molecular weight heparin
MBD	metabolic bone disease
MCT	medium-chain triglyceride
MMC	migrating motor complex
MRI	magnetic resonance imaging
NST	nutritional support team
PICC	peripherally inserted central catheter
PN	parenteral nutrition
PN-DR	parenteral nutrition daily recommended doses
PPI	proton-pump inhibitors
PTH	parathyroid hormone
PUFA	polyunsaturated fatty acids
QALY	quality adjusted life year
QoL	quality of life
RCT	randomized controlled trial
RDA	Recommended Daily Allowance
REE	resting energy expenditure
SBS	short bowel syndrome
SCFA	short chain fatty acids
SRSB	segmental reversal of the small bowel
STEP	serial transverse enteroplasty
T:T	triene:tetraene
TPN	total parenteral nutrition
UDCA	ursodeoxycholic acid

Societies, organizations and working groups mentioned in the guideline

AMA	American Medical Association
ASPEN	American Society for Parenteral and Enteral Nutrition
BAPEN	British Association for Parenteral and Enteral Nutrition
BIFA	British Intestinal Failure Alliance
ESPEN	European Society for Clinical Nutrition and Metabolism
FDA	U.S. Food and Drug Administration
FELANPE	Federación Latinoamericana de Terapia Nutricional Nutrición Clínica y Metabolismo
HAN&CIF	Home Artificial Nutrition and Chronic Intestinal Failure
NAG-AMA	Nutrition Advisory Group of the American Medical Association
ORS	Oral Rehydration Solution
PACIFHAN	International Alliance of Patient Organizations for Chronic Intestinal Failure and Home Artificial Nutrition
PINNT	Advocacy and Support for People on Home Artificial Nutrition
SIGENP	Italian Society of Pediatric Gastroenterology Hepatology and Nutrition
SIGN	Scottish Intercollegiate Guidelines Network
SINPE	Italian Society of Artificial Nutrition and Metabolism
WHO	World Health Organization

1. Introduction

Intestinal failure (IF) is “the reduction of the 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” [1]. Chronic intestinal failure (CIF) occurs when IF persists for months or years in a metabolically stable patient, who can be cared for outside the acute hospital setting [1]. The primary goal of CIF therapy is to support health via IVS provided through home parenteral nutrition (HPN) [1,2]. CIF may occur as result of severe gastrointestinal or systemic benign diseases, or because of end stage intra-abdominal or pelvic cancer. In Europe, HPN administration to patients with cancer differs significantly between countries, varying from 8% to 60% of the total population on HPN [1,2]. This wide range may be due to different medical and social attitudes toward palliative care [3]. Overall, scientific society guidelines do not recommend HPN for patients with a short life expectancy due to malignancy (generally considered inappropriate if this is less than one to three months) [2,4].

CIF is the rarest organ failure. In Europe, the prevalence of HPN for CIF due to benign disease (where the term benign means the absence of active malignant disease) has been estimated to range from five to 80 cases per million of the national population [5,6]. CIF due to benign disease has been included in the European Orphanet list of rare diseases [7]. Notably, the rarity of the condition has hindered its awareness both within and outside the medical arena. Indeed, the concept of CIF was initially developed in 1981 [8], even

though the first patients treated with long-term IVS were described in 1970 [9].

The European Society for Clinical Nutrition and Metabolism (ESPEN) has recently helped to develop the topic of IF in adults by devising recommendations on IF definition and classification [5], publishing a position paper on acute IF [10] alongside guideline for CIF [1]; holding a workshop to highlight major areas requiring further investigation [11]; and supporting international surveys on CIF carried out through a dedicated structured database [12,13].

The guideline on CIF were based on papers published up to 2015 and aimed to generate comprehensive recommendations for the safe and effective management of adult patients with CIF due to benign disease [1]. In light of the aforementioned varying approaches to managing CIF in patients with cancer, the guideline was limited to "CIF due to benign disease". In 2020, ESPEN released a new version of the guideline on HPN, the primary treatment for CIF [2]. In 2021, the ESPEN definition of IF has also been included in the 11th Revision of the International Classification of Diseases (ICD-11) of the World Health Organization (WHO) [14]. A PubMed search in January 2022, using "intestinal failure" as a general term, retrieved 3617 papers published between 2016 and 2021. Thus, an updated version of ESPEN guideline on CIF due to benign disease in adults was commissioned in order to incorporate new evidence since the publication of the previous ESPEN guidelines. The recommendations of the 2016 guideline were reviewed, particularly focusing on definitions, and new chapters were included to devise recommendations on IF centers, chronic enterocutaneous fistulas (ECF), costs of IF, caring for CIF patients during pregnancy, transition of patients from pediatric to adult centers, and quality of care. Furthermore, inclusion of members of CIF/HPN patient associations into the guideline-working group represents a novel initiative for this updated guideline.

2. Methodology of guideline updating

The working group included gastroenterologists, surgeons, endocrinologists, anesthesiologists, dietitians and patient association representatives, with long-term expertise in IF and HPN. Nine members of the panel were coauthors of the 2016 guideline on CIF (LP, CC, PBJ, FJ, SL, KS, AVG, GW, SMS).

The first step was to define the chapters of the guideline. Nineteen chapters were identified: definition, diagnosis, classification and treatment pathway of CIF, HPN management, including central venous access device choice, CIF centers, parenteral nutrition formulation, short bowel syndrome, chronic small intestinal dysmotility, radiation enteritis, chronic ECF, intestinal transplantation, central venous access device-related complications, intestinal failure-associated liver disease, gallbladder sludge and stones, intestinal failure-associated renal failure and stones, intestinal failure-associated metabolic bone disease, pregnancy and breast feeding, quality of life assessment, cost analysis, transition from pediatric to adult centers, patient associations.

The updating process started from the previous CIF guideline, published in 2016 [1] and the recent HPN guideline [2], published in 2020. A systematic literature search comprising the period between one year before the publication of the previous guidelines (2015 for CIF and 2019 for HPN) until December 2021 was carried out to check whether the recommendations from those guidelines were still relevant and whether there was the need to add new recommendations or to delete/modify the existing ones. According to standard operating procedures for ESPEN guidelines and consensus papers, the chapters not included in the previous guidelines were investigated through the PICO question methods: **p**roblem, **i**ntervention, **c**omparison, **o**utcome [15].

The grading system of the Scottish Intercollegiate Guidelines Network (SIGN) was used to grade the literature [16]. Allocation of studies to the different levels of evidence is shown in Table 1. The working group added commentaries to the recommendations detailing the basis of the recommendations made.

Recommendations were graded according to the levels of evidence available [17] (Table 2). In some cases, a downgrading was necessary, for example, due to the lack of quality of primary studies included in a meta-analysis.

The wording of the recommendations reflects the grades of recommendations; level A is indicated by "shall", level B by "should" and level 0 by "can/may". A good practice point (GPP) is based on experts' opinions due to the lack of studies; in this situation, the choice of wording was not restricted.

The recommendations of the 2016 guideline which were still valid, because no studies supporting an update were retrieved, were reworded accordingly.

Between 7th July 2022 and 9th August 2022, online voting on the recommendations was undertaken using the "guideline-services.com" platform. All ESPEN members were invited to agree or disagree with, and to comment upon, each of the original 149 recommendations and 16 statements generated by the guideline committee: 144 recommendations and 14 statements reached an agreement of >90%, five recommendations and two statements reached an agreement of >75–90%.

Table 1
Levels of evidence.

1++	High quality meta-analyzes, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyzes, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyzes, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system. Source: SIGN 50: A guideline developer's handbook. Quick reference guide October 2014 [16]. Abbreviation: RCT, randomized controlled trial.

Table 2
Grades of recommendation [15].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

Abbreviation: GPP, Good practice point; RCT, randomized controlled trial.

Table 3
Classification of the strength of consensus.

Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of >50–75% of the participants
No consensus	Agreement of <50% of the participants

According to the methodology of the Association of the Scientific Medical Society [17].

Those recommendations/statements with an agreement >90% (indicating a strong consensus, Table 3) were directly passed, while all others were revised according to the comments made and then voted on again during a consensus conference which took place during the 2022 ESPEN congress in Vienna on 4th September 2022. During the consensus conference, also five recommendations and two statements that received >90% in the online voting were voted on due to major changes originating from commentaries of online voting participants. Thus, ten recommendations and four statements were discussed and voted on during the consensus conference. Seven recommendations and two statements received an agreement of >90%, all others received an agreement of >75–90% (Table 4). To support the recommendations, the ESPEN guideline office created evidence tables of relevant meta-analyzes, systematic reviews and (randomized) controlled trials, all of which are available online as supplemental material to this guideline.

2.1. Recommendations and statements

Table 5 lists the 146 recommendations and the 16 statements of the present guideline on CIF, along with their Grade of recommendation and of consensus. The Grade of recommendation is GPP for 96 (64.4%) of the recommendations, 0 for 29 (19.5%), B for 19 (12.7%), and A for only five (3.4%). The grade of consensus is "strong consensus" for 148 (99.3%) and "consensus" for one (0.7%) of the recommendation. The grade of consensus for the statements is "strong consensus" for 14 (87.5%) and "consensus" for two (12.5%).

3. Chapter 1 – Definition, diagnosis and classification of chronic intestinal failure

3.1. What is the definition of chronic intestinal failure?

3.1.1. Statement 1

CIF is defined as "persistent reduction of the gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that IVS is required to maintain health and/or growth, in a patient who is metabolically stable". Conditions where the reduction of gut absorptive function does not require IVS to maintain health and/or growth are defined as "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning).

Strong consensus 100% agreement.

3.2. What are the criteria for the diagnosis of intestinal failure?

3.2.1. Statement 2

Two criteria have to be simultaneously present for the diagnosis of IF: "decreased absorption of macronutrients and/or water and electrolytes due to loss of gut function" and "need for IVS to maintain health and/or growth".

Consensus 81% agreement.

3.2.1.1. Commentary. In 2015, ESPEN devised recommendations regarding the "definition and classification of intestinal failure in adults", endorsing a common language to facilitate communication and cooperation among professionals in clinical practice, organization, management and research [5]. The recommendations comprise the definition of IF, as well as functional and pathophysiological classifications for IF, based on an analysis of the published literature (Table 6). After reviewing the original definition from Fleming and Remington [8] and proposed adaptations 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 IVS is required to maintain health and/or growth" [5]. This definition of IF has been used to code the condition in the current 11th Revision of the International Classification of Diseases (ICD-11) of the WHO, code DA.96.05, parent of code 96.0 intestinal malabsorption [14]. 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 does not require IVS to maintain health and/or growth [5]. According to the definition, two criteria must be simultaneously present to diagnose IF: "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 provision 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, those who refuse otherwise effective enteral nutrition (EN), or those receiving fluids for another reason (e.g. to manage postural orthostatic hypotension).

The "functional classification of IF" [5] was based on onset, metabolic and expected outcome criteria, as originally proposed by Shaffer [18].

- Type I – acute IF: 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 – prolonged acute IF: a prolonged critical condition, often in metabolically unstable patients, requiring complex multidisciplinary 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

Table 4
Classification of the strength of consensus and results of the online and consensus conference voting.

		Online Voting	Consensus Conference
Strong consensus	Agreement of >90% of participants	157	9
Consensus	Agreement of >75–90% of participants	7	5
Majority agreement	Agreement of >50–75% of participants	0	0
No consensus	Agreement of <50% of participants	0	0
Deleted		0	0

Table 5
List of recommendations and statements on chronic intestinal failure due to benign disease (absence of active cancer disease).

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
Definition, diagnosis and classification of chronic intestinal failure			
S1	CIF is defined as "persistent reduction of the gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that IVS is required to maintain health and/or growth, in a patient who is metabolically stable". Conditions where the reduction of gut absorptive function does not require IVS to maintain health and/or growth are defined as "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning).	–	Strong
S2	Two criteria have to be simultaneously present for the diagnosis of IF: "decreased absorption of macronutrients and/or water and electrolytes due to loss of gut function" and "need for IVS to maintain health and/or growth".	–	Consensus
S3	The clinical classification and reporting of CIF shall be based on the pathophysiologic mechanism of IF and the underlying disease from which IF originates.	–	Strong
S4	The pathophysiologic mechanisms of IF shall be classified as short bowel syndrome (SBS), intestinal dysmotility, intestinal ECF, intestinal mechanical occlusion, or extensive small bowel mucosal disease.	–	Strong
S5	The underlying disease from which IF originates shall be categorized according to the ICD codes and should also be clearly distinguishable from the pathophysiological mechanism.	–	Strong
R1	The severity of CIF should be based on the eight categories of type and volume of the IVS required by patients, as outlined in Table 8. CIF requiring IVS of fluids and electrolytes alone is less severe than CIF requiring IVS of parenteral nutrition admixtures that also contain macronutrients. The severity of CIF requiring IVS of PN progressively increases in parallel with the volume of the PN admixture, calculated on weekly basis.	B	Strong
R2	HPN should be prescribed as the primary and life-saving therapy for patients with transient-reversible or permanent-irreversible CIF.	B	Strong
R3	Patients with CIF should have an early referral to IF/rehabilitation centers with expertise in both medical and surgical treatment for CIF, to maximize the opportunity of weaning off HPN, preventing HPN failure, and ensuring timely assessment of candidacy for intestinal transplantation (ITx).	GPP	Strong
HPN management (including CVAD choice)			
R4	The aims of an HPN program shall include provision of evidence-based therapy, prevention of HPN −related complications such as CVAD-related infections and metabolic complications and ensure QoL is maximized.	GPP	Strong
S6	For a safe HPN program, the patient and/or the patient's legal representative shall give fully informed consent to the treatment proposed.	–	Strong
S7	For a safe HPN program, the patient shall be sufficiently metabolically stable and emotionally cope with HPN therapy outside the acute hospital setting.	–	Strong
S8	For a safe HPN program, the patient's home environment shall be adequate to safely deliver the therapy proposed; the suitability of the home care environment should be assessed and approved by the nurse of the NST or of a qualified HPN provider.	–	Strong
R5	For a safe HPN program, the choice of the central venous access device (CVAD), the infusion control device, and the infusion line and CVAD care shall be in keeping with recommendations #9–38 of the ESPEN guideline on HPN.	A	Strong
S9	For a safe HPN program, the patient and/or the caregiver has to be able to understand and perform the required procedures for the safe administration of therapy.	–	Strong
R6	The patient and/or the caregiver should be trained by an NST to safely infuse the PN with appropriate monitoring and prompt recognition of any complications.	GPP	Strong
R7	A formal individualized HPN training program for the patient and/or caregiver and/or home care nurses shall be performed, including catheter care, pump use and preventing, recognizing and managing complications; training can be done in an in-patient setting or at the patient's home.	GPP	Strong
R8	The prescribed nutritional admixture and ancillaries required for safe and effective therapy should be delivered by an experienced/certified health care provider.	GPP	Strong
R9	The NST should provide appropriate monitoring and treatment for routine and/or emergency care, with appropriate contact details provided to the patient 24 h per day, seven days per week.	GPP	Strong
R10	Incidence of CVAD-related infection, incidence of hospital readmission and patient's and family and/or caregiver feed-back should be used as criteria to assess and improve the quality of care of HPN program.	GPP	Strong
R11	For a patient to travel safely, he/she shall receive a sufficient supply of PN and relevant ancillaries during the journey and at the destination and the NST responsible for the patient's care shall endeavor to establish contact with a skilled NST at the patient's destination in case medical support is required.	GPP	Strong
R12	Monitoring of patients with CIF shall include the underlying disease from which the IF originated, the intestinal function, the effectiveness and safety of the HPN program, and the patient's clinical condition, nutritional status, and QoL.	GPP	Strong
R13	Patients receiving HPN shall be monitored at regular intervals, to review the indications, the efficacy and the risks of the treatment.	GPP	Strong
R14	The time between reviews should be adapted to the patient, the care setting and duration and stabilization of nutrition support; the severity of the IF and the underlying disease; intervals can increase as the patient is stabilized on nutrition support.	GPP	Strong
R15	In clinically stable patients on long-term HPN, body weight, body composition and hydration status, energy and fluid balance and biochemistry (hemoglobin, ferritin, albumin, C-reactive protein (CRP), electrolytes, venous blood gas analysis or serum bicarbonates, kidney function, liver function and glucose) can be measured at all the scheduled visits.	GPP	Strong
R16	In patients on long-term HPN, clinical signs and symptoms as well as biochemical indexes of vitamin and trace element deficiency or toxicity should be evaluated at least once per year.	GPP	Strong

Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
R17	In patients on long-term HPN, bone metabolism and BMD should be evaluated annually or in accordance with accepted standards.	GPP	Strong
R18	HPN monitoring should be carried out by the hospital NST with skills and experience in IF and HPN management, in collaboration with experienced home care specialists, home care agencies and/or general practitioners.	GPP	Strong
R19	Patients and/or caregivers can be trained to monitor nutritional status, fluid balance and the infusion catheter.	0	Strong
Chronic intestinal failure centers			
R20	Patients with CIF should be cared for by specialized, dedicated and a clearly identifiable hospital unit, normally termed "HPN center or IF center or intestinal rehabilitation center".	GPP	Strong
R21	The CIF unit should have offices for outpatient visits and dedicated beds for patients who need hospitalization.	GPP	Strong
R22	All CIF patients should be cared for by a NST with experience in HPN management.	GPP	Strong
R23	The NST consists of experts in CIF and HPN provision. This includes physicians, specialist nurses (including in catheter, wound and stoma care), dietitians, pharmacists, social workers, psychologists, as well as an appropriate practitioner with expertise in central venous catheter (CVC) placement. Surgeons with expertise in IF should also be available for structured consultation.	GPP	Strong
R24	The NST for HPN/CIF shall have clear written pathways and protocols in place for the management of patients with complications relating to HPN.	GPP	Strong
R25	The NST for HPN/CIF shall provide patients and caregivers with written information relating to the recognition and subsequent management of HPN-related complications, including details (e.g. telephone number) of an appropriate NST member to contact in the case of an emergency, available 24 h per day.	GPP	Strong
Parenteral nutrition formulation			
R26	The protein and energy requirements for CIF patients shall 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-energy malnutrition), and that the adequacy of the regimen is regularly evaluated through clinical, anthropometric, and biochemical parameters.	GPP	Strong
R27	Optimal blood glucose control, based on blood glucose below 180 mg/dL (10.0 mmol/L) during HPN infusion and normal HbA1c levels <7% in patients with diabetes can be targeted, through regular monitoring.	0	Strong
R28	No recommendation at this time can be made regarding optimal approach to achieving glycemic control in HPN patients; addition of insulin to HPN admixtures has been noted to be safe in multiple case series.	0	Strong
R29	In patients totally dependent on HPN, a minimum of 1 g/kg/wk of intravenous lipid emulsion containing essential fatty acids (EFA) may be supplied to prevent EFA deficiency; changing a soybean oil-based lipid emulsion to either a fish oil containing lipid emulsion or an olive oil based lipid emulsion may be safe regarding the provision of enough EFA.	0	Strong
R30	No type of lipid emulsion alone should be uniformly applied; the choice of lipid emulsion should be made on patient individual basis.	B	Strong
R31	When a soybean-based lipid emulsion is supplied, no more than 1 g/kg/d of lipid emulsion should be provided.	B	Strong
R32	When more than 1 g/kg/d of lipid emulsion is required, alternative lipid emulsions (olive oil, MCT, and fish oil) should be used to reduce the soybean-oil content of intravenous lipid emulsions, which tends to be high in ω-6 polyunsaturated fatty acids (PUFA) and phytosterols.	GPP	Strong
R33	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 shall be made regularly.	GPP	Strong
R34	The PN formula shall be adjusted with the aim of normalizing laboratory tests related to electrolytes and mineral balance in patients on HPN.	GPP	Strong
R35	Timely adjustment of sodium supplementation can allow anabolism in patients on HPN.	0	Strong
R36	Regular monitoring of acid-base status in patients on long-term HPN (serum concentration of chloride and bicarbonate), shall be made because either metabolic acidosis or metabolic alkalosis can occur.	GPP	Strong
R37	In patients on HPN, clinical signs and symptoms as well as biochemical indexes of vitamin deficiency or toxicity should be regularly evaluated.	GPP	Strong
R38	Baseline serum vitamin concentrations should be measured, according to laboratory availability, at the onset of HPN and then at least once per year.	GPP	Strong
R39	Vitamin doses in HPN can be adjusted as needed.	GPP	Strong
R40	The route of vitamin supplementation can be selected according to the characteristics of the individual patient	GPP	Strong
R41	In patients on HPN, clinical signs and symptoms as well as biochemical indexes of trace element deficiency or toxicity should be regularly evaluated.	GPP	Strong
R42	Baseline serum trace element concentrations should be measured, according to laboratory availability, at the onset of HPN and then at least once per year.	GPP	Strong
R43	Trace element doses in HPN can be adjusted as needed.	GPP	Strong
R44	The route of trace element supplementation can be selected according to the characteristics of the individual patient.	GPP	Strong
R45	In case of intravenous micronutrient shortage, the intravenous supplementation with multivitamin and multi-trace element vials should be prioritized for patients on exclusive/total HPN	GPP	Strong
R46	In patients on exclusive/total HPN, when the micronutrient shortage doesn't allow the daily IVS with multivitamin and multi-trace element vials, the micronutrients requirements should be met by single micronutrient supplementation through any other available route in the individual patient.	GPP	Strong

(*continued on next page*)

Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
R47	In patients on supplemental/partial PN, the micronutrient supplementation through sublingual, oral, enteral, intramuscular and subcutaneous route should be maximized.	GPP	Strong
R48	During period of intravenous micronutrient vial shortage, a more frequent monitoring of serum micronutrient concentrations may be required to prevent micronutrient deficiency.	GPP	Strong
R49	During period of intravenous micronutrient vial shortage, pediatric multivitamin and multi-trace element vials shall not be used for adult patients on HPN, if there is a risk of shortage of pediatric vials as well.	GPP	Strong
R50	The routine addition of individual amino acids (glutamine, cysteine, taurine) in the parenteral formula to decrease complications in adults on HPN cannot be recommended.	0	Strong
Short bowel syndrome			
S10	In adults, SBS is defined as the clinical feature associated with a residual small bowel in continuity shorter than 200 cm.	–	Strong
S11	The presence of clinical feature of SBS notwithstanding a residual small-bowel length >200 cm is defined “functional SBS”.	–	Strong
S12	On the basis of the anatomy of the residual intestine in continuity, SBS is classified as SBS with end small bowel ostomy (or SBS type 1), SBS with jejuno-colic anastomosis (or SBS type 2) and SBS with jejunoileal anastomosis with intact colon and the presence of the ileocecal valve (or SBS type 3).	–	Strong
R51	SBS patients should have dietary counselling 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.	GPP	Strong
R52	The diet of SBS patients with a preserved colon in continuity can be high in complex carbohydrates, low in mono- and disaccharides and low in fat.	0	Strong
R53	The diet of SBS patients with a preserved colon in continuity should have a high content of MCT, that confers a marginal benefit on overall energy absorption compared to a diet containing regular LCT.	B	Strong
R54	The diet of SBS patients without a preserved colon in continuity can have any fat:carbohydrate ratio, with a low mono- and disaccharides content.	0	Strong
R55	SBS patients consuming a low-fat diet or where the LCT have been replaced by MCT should be monitored for the potential deficiency in EFA and fat-soluble vitamins.	GPP	Strong
R56	In patients with SBS, soluble fiber (e.g. pectin) may not be added to the diet to enhance overall intestinal absorption.	0	Strong
R57	Lactose may 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.	0	Strong
R58	Isotonic oral nutritional supplements can be added to the diet of SBS patients at risk of malnutrition.	GPP	Strong
R59	The EN in combination with oral feeding can be prescribed in patients with CIF in whom the expected gain with EN could allow to wean off HPN.	GPP	Strong
R60	In patients with CIF treated with EN, the use of polymeric isotonic enteral diets may be the first choice.	0	Strong
R61	The addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process cannot be recommended.	0	Strong
R62	Patients with type 1 SBS (end jejunostomy) can use salt liberally and restrict the administration of oral fluids in relation to meals.	GPP	Strong
R63	SBS patients who have borderline dehydration or sodium depletion can use an isotonic high sodium oral rehydration solution to replace stoma sodium losses.	0	Strong
R64	SBS patients with net-secretion and a high output jejunostomy shall limit 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 the stoma output.	GPP	Strong
R65	H_2-receptor antagonists or PPI may be used to reduce fecal wet weight and sodium excretion, especially during the first six months after surgery, mainly in those SBS patients with a fecal output exceeding 2 L/d.	0	Strong
R66	In the individual patient, H_2-receptor antagonists or PPI can also be used to reduce fecal wet weight and sodium excretion in the long-term.	GPP	Strong
R67	Especially in the short-term after intestinal resection, octreotide can be used for patients with high-output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments.	GPP	Strong
R68	Patients treated with octreotide should be carefully monitored to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects, fluid retention and potential negative interference with the process of intestinal adaptation during long-term use.	GPP	Strong
R69	Oral loperamide shall be used to reduce wet weight and sodium fecal excretion in SBS patients with an ostomy.	A	Strong
R70	Loperamide shall be preferred to opiate drugs, such as codeine phosphate or opium, because it is not addictive or sedative.	A	Strong
R71	In SBS patients with a high ostomy output, the use of loperamide may be guided by objective measurements of its effect.	0	Strong
R72	SBS patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who are suspected with bacterial overgrowth, can benefit from occasional antibiotic treatment.	GPP	Strong
R73	The routine use of antibiotics in SBS patients with a preserved colon cannot be recommended, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to SCFA, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation.	GPP	Strong
R74	In SBS-IF patients, intestinal growth factors should be considered in an SBS patient requiring PN continuation, if that patient is stable after a period of post-surgery intestinal adaptation, which is	B	Strong

Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
	usually the case twelve 24 months after the last intestinal resection and in the absence of contraindications.		
R75	In case of intestinal growth factors consideration, colonoscopy (if remnant colon and/or rectum), abdominal ultrasound, and gastroscopy shall be performed on all patients before initiation of treatment, to assess for the presence of polyps and to exclude neoplastic disease, as well as to clarify unclear anatomic situations (e.g. suspected strictures, blind loops, and unclear anastomotic sites) or disease activity in the gastrointestinal remnant (e.g. Crohn's disease).	GPP	Strong
R76	Patients with CIF due to SBS should be carefully informed of the potential benefits and risks associated with intestinal growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of QoL 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.	GPP	Strong
R77	For carefully selected SBS patients who are candidates for intestinal growth factor treatment, the GLP-2-analogue which is the only one approved by FDA and EMA so far, teduglutide, shall be the first choice.	A	Consensus
R78	The efficacy of growth factor treatment shall be done according to standardized protocols measuring fluids, electrolytes and energy balance.	GPP	Strong
R79	Intestinal growth factors shall be 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.	GPP	Strong
R80	To patients with SBS, oral drugs should be prescribed on an individual basis, 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.	GPP	Strong
R81	In patients with SBS, during intestinal resection, bowel length should be conserved to the fullest extent possible to avoid dependence on HPN.	B	Strong
R82	In patients with SBS, restoration of intestinal continuity should be realized whenever possible, to decrease HPN dependency.	B	Strong
R83	Regarding non-transplant surgery in patients with SBS, bowel lengthening procedures may be considered in selected patients.	0	Strong
R84	In patients with SBS, management should be performed through a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome.	GPP	Strong
Chronic small intestinal dysmotility			
S13	Chronic small intestinal dysmotility is defined as “impaired gastrointestinal propulsion of the gut content in the absence of fixed occluding lesions causing chronic/recurrent obstructive type symptoms and intolerance to oral or enteral nutrition”.	–	Strong
S14	Chronic small intestinal dysmotility is diagnosed by the clinical features of recurrent/chronic episodes of intestinal occlusion with abdominal pain, nausea and/or vomiting and intolerance to oral or enteral nutrition, with or without radiological features of dilated intestine with air/fluid levels and/or, where feasible, manometric evidence of gastro-intestinal dysmotility.	–	Consensus
S15	Chronic small intestinal dysmotility is classified as CIPO, when there are radiological features of dilated intestine with air/fluid levels, or ED when no radiological features of a dilated intestine are present. Both CIPO and ED are categorized as primary/idiopathic, when no underlying disorder can be demonstrated, or secondary, when related to underlying gastrointestinal or systemic diseases, either sporadic or familial, or other known factors such as side effects of medications.	–	Strong
R85	Dietary counselling can be used as the first-line management in patients with chronic small intestinal dysmotility; patients can be encouraged to eat according to individual tolerance and may benefit from frequent small meals of low-fiber and low-fat content alongside texture modified food and liquid supplements as well as minerals and micronutrients to prevent specific deficiencies.	0	Strong
R86	Any decision to escalate from oral nutrition to EN or PN should involve careful multidisciplinary team consideration of the potential risks and benefits with the patient.	GPP	Strong
R87	EN should be considered as a first step in patients with chronic gastrointestinal dysmotility who are not able to meet their energy needs with oral nutrition alone and who continue to lose weight, before using HPN.	GPP	Strong
R88	HPN shall not be delayed in malnourished patients with chronic gastrointestinal dysmotility when oral/enteral nutrition is obviously inadequate.	GPP	Strong
R89	Trials with prokinetics can be attempted in patients with chronic small intestinal dysmotility.	0	Strong
R90	Antibiotic therapy can be used to treat intestinal bacterial overgrowth and to reduce malabsorption in patients with chronic small intestinal dysmotility.	0	Strong
R91	Periodic antibiotic therapy can be used to prevent intestinal bacterial overgrowth in patients with chronic intestinal dysmotility who have frequent relapsing episodes.	GPP	Strong
R92	Surgery should be avoided in chronic small intestinal dysmotility patients, whenever possible, due to the risk of postoperative worsening of intestinal function and need for subsequent reoperation.	GPP	Strong
R93	In patients with chronic small intestinal dysmotility, venting ostomy (either endoscopically or surgically), can be performed to diminish symptoms in case-by-case selected patients.	GPP	Strong
Radiation enteritis			
R94	In patients with chronic radiation enteritis EN may be used if oral nutrition, including use of oral nutritional supplements, is inadequate.	0	Strong
R95	In malnourished radiation enteritis patients, HPN should not be delayed, if oral nutrition/EN is obviously inadequate.	GPP	Strong

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Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
R96	In patients with chronic radiation enteritis, the PN regime should follow the same criteria for the HPN of patients with other causes of CIF.	GPP	Strong
R97	No recommendation can be made for or against the use of glutamine to prevent or treat radiation enteritis.	0	Strong
Entero-cutaneous fistulas			
S16	The ECF is classified by anatomic location (proximal: jejunum and more proximal; distal: ileum or more distal), fasting output volume (low: <200 mL/d; medium: 200–500 mL/d; high: >500 mL/d), location in the open abdomen (deep vs superficial) and number of fistula openings (single opening, multiple in close proximity; multiple distant from each other).	–	Strong
R98	Withholding EN cannot be of benefit regarding fistula closure, whereas some oral/enteral nutrition may protect the integrity of the mucosal barrier as well as the immunologic and hormonal function of the gut.	GPP	Strong
R99	Optimizing nutrition and wound care may stabilize ECF and potentially allow spontaneous closure.	0	Strong
R100	Refeeding enteroclysis (chyme reinfusion) may be recommended in double enterostomies high output fistulas.	0	Strong
R101	Drug therapy for ECF can be the same used for SBS.	0	Strong
R102	Surgical intervention with regard to the restoration of continuity may be individualized and only performed by experienced surgeons in specialized interdisciplinary units.	0	Strong
Intestinal Transplantation			
R103	Patients with CIF should be assessed for candidacy for ITx, when they have been evaluated by a multidisciplinary team, rehabilitation options have been explored, and a state of permanent/ irreversible or life-limiting CIF and one of the following exist: • Evidence of advanced or progressive IFALD, as described below: – Hyperbilirubinemia >75 μmol/L (4.5 mg/dL) despite intravenous lipid modification strategies that persists for >2 months - Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio(INR)), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 month in the absence of a confounding infectious event(s) • Thrombosis of three out of four discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) • Invasive intra-abdominal desmoids • Acute diffuse intestinal infarction with hepatic failure • Failure of first intestinal transplant • Any other potential life-threatening morbidity.	B	Strong
R104	Patients with advanced or progressive IFALD and those with an invasive intra-abdominal desmoid tumor should be listed for a life-saving ITx (with or without liver transplantation).	B	Strong
R105	Patients with CVC related thrombosis of two or more central veins (internal jugular, subclavian or femoral) may be listed for a life-saving ITx on a case-by-case basis.	GPP	Strong
R106	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 should not be listed for a life-saving ITx.	B	Strong
R107	Patients with CIF with high morbidity or low acceptance of HPN may be listed for a rehabilitative ITx on a careful case-by-case basis.	GPP	Strong
R108	Whenever possible, patients listed for ITx should undergo the procedure while they are in a stable clinical condition, as represented by being able to stay at home and not requiring hospitalization while waiting for transplant.	GPP	Strong
R109	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 awaiting and after transplantation.	GPP	Strong
Prevention/treatment of CVAD-related complications			
R110	For the prevention of CVAD-related infections, the infusion line and CVAD care shall be in keeping with recommendations #19–38 of the ESPEN guideline on HPN (Table 10).	A	Strong
R111	The creation of arterio-venous fistulas to prevent CVAD-related infections may be considered in carefully selected patients.	0	Strong
R112	Catheter locking with 70% ethanol should not be used to prevent CVAD-related infections, because its use is associated with systemic toxicity, catheter occlusion and catheter damage.	B	Strong
R113	Re-education of the patient and/or caregiver shall be made in patients who repeatedly present with CVAD-related infections.	GPP	Strong
R114	CVAD-related infections should be managed according to current guidelines on long-term CVAD and as described in the comment section: a conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections; CVAD removal should be the first choice in case of tunnel infections or blood cultures positive for virulent bacteria; CVAD removal is mandatory for port abscesses, complicated infections, persistent hemodynamic instability, or blood cultures that are positive for fungi.	B	Strong
R115	Treatment of CVAD-related venous thrombosis should be made with anticoagulation, the duration of which to be chosen on an individual basis.	B	Strong
R116	In CRVT, the decision to maintain the CVAD should depend on individual factors (e.g. necessity of a central line, lack of infection, clinical outcome).	GPP	Strong
R117	For the primary prevention of CVAD-related venous thrombosis, insertion of the CVAD should be made using ultrasound guidance with placement of the tip at the superior vena cava-right atrium junction.	B	Strong

Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
R118	Routine thromboprophylaxis with drugs (heparin, warfarin) should not be made for the primary prevention of CVAD-related venous thrombosis for all adults on HPN based on the risk/benefit balance.	B	Strong
R119	Pulsatile flushing of catheters with saline can be made instead of flushing with heparin solution to prevent CVAD occlusion.	0	Strong
R120	Irrigation of the CVAD with saline can be made as the first attempt to restore catheter patency in intra-lumen CVAD occlusion.	GPP	Strong
R121	Fibrinolytic drugs can be used for the treatment of acute CVAD occlusion likely caused by blood clotting.	GPP	Strong
Prevention/treatment of intestinal failure-associated liver disease			
R122	The following intervention should be made to prevent the development of IFALD: • prevention of sepsis or managing it, if present • preservation of small intestinal length and retainment/restoration of the colon in continuity with small bowel; • maintenance of oral/enteral intake and, where feasible, considering distal EN/chyme reinfusion in patients with non in continuity small intestine; • cycling PN infusion; • avoiding PN overfeeding; • limiting the dose of soybean-oil based lipid to less than 1 g/kg/d • avoiding any hepatoxic insults wherever possible (e.g. alcohol)	B	Strong
R123	Treatment of IFALD should rely on: • re-consideration of all the measures to prevent IFALD • revising the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω-6/ω-3 PUFA ratio • revising any potential inflammatory/infective foci • excluding/managing any other causative factors of abnormal liver function	B	Strong
Prevention/treatment of gallbladder sludge and stones			
R124	Maintenance/resumption of oral feeding can be made be considered to prevent/treat of gallbladder sludge.	0	Strong
R125	Cholecystectomy and/or endoscopic procedures should be performed in the case of biliary complications as for the general population.	B	Strong
R126	Cholecystectomy during abdominal surgery for other indications can be considered in patients with CIF known to have gallstones at the time of surgery, providing this additional procedure is felt to have a low risk of morbidity and the risk vs. benefit of cholecystectomy is carefully considered with the patient.	GPP	Strong
Prevention/treatment of intestinal failure-associated renal failure and stones			
R127	For the primary prevention of renal failure and of renal stones in patients with CIF, regular monitoring shall be performed of renal function and fluid balance as well as a timely adjustment of fluid supplementation in order to avoid episodes of dehydration.	GPP	Strong
R128	For the primary prevention of renal failure, acute and chronic infections as well as acute and chronic dehydration shall be timely addressed by the relevant clinical intervention.	GPP	Strong
R129	For the primary prevention of oxalate renal stones, a low oxalate and low fat diet, in addition to an increase of oral calcium, should be prescribed to reduce the risk of oxalate stone formation in patients with SBS with a colon in continuity.	GPP	Strong
R130	Avoiding metabolic acidosis and giving citrate supplementation can be recommended, to reduce the risk of uric acid stones.	GPP	Strong
R131	In patients with CIF, renal failure and renal stones shall be treated according to the standards for these conditions.	GPP	Strong
Prevention/treatment of intestinal failure-associated metabolic bone disease			
R132	Patients with CIF should be routinely monitored for MBD by bone densitometry scanning, biochemistry, and clinical history.	GPP	Strong
R133	General risk factors for developing MBD 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, should be addressed promptly in all patients with CIF.	GPP	Strong
R134	Optimization of PN admixture with the required supplements of vitamin D, calcium and phosphate can be the initial step in management of MBD in patients with CIF. Further, medical treatment can be used to stabilize/increase BMD and lower fracture risk.	0	Strong
Pregnancy and breast feeding			
R135	Attempts shall be made to optimize the nutritional status of those considering pregnancy, ensuring adequate vitamin and trace element supplementation with particular emphasis on ensuring adequate oral or parenteral folate.	GPP	Strong
R136	Close monitoring of pregnant patients with CIF, at least on a four-weekly basis, shall be made by the IF multidisciplinary team, maintaining close dialogue with, and close overview from, a 'high-risk' obstetric service throughout all trimesters.	GPP	Strong
R137	Strategies to optimize maternal underlying disease and minimize HPN-related complications, with a pre-emptive approach to tailored macronutrient and adequate micronutrient support shall be implemented.	GPP	Strong
R138	Individualized birth plans shall be devised for patients with CIF, as per the general population and dependent on the underlying disease, with caesarean section reserved for obstetric indications or in the presence of active perianal Crohn's disease.	GPP	Strong
R139	Breast feeding should be considered wherever possible, with mindful consideration of any concomitant medications that may be secreted into breast milk as per other diseases.	GPP	Strong
R140	The patient shall be monitored closely by the CIF NST team during lactation to ensure adequate nutritional status.	GPP	Strong

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Table 5 (*continued*)

#	Recommendation (R) and Statement (S)	Grade of recommendation	Grade of consensus
Quality of life assessment			
R141	The QoL of CIF patients should be regularly measured using validated tools as part of standard clinical care.	GPP	Strong
R142	Validated tools to measure QoL of CIF patients should be able to distinguish factors depending on the HPN program from those depending on the underlying disease.	GPP	Strong
Cost analysis			
R143	Studies on CIF costs and the cost associated with its treatment (HPN, ITx, teduglutide, etc) should include at least the direct healthcare and non-health care costs.	GPP	Strong
R144	Full economic evaluations, including cost-utility analyzes can help inform resource allocation decisions across different health care settings.	GPP	Strong
Transition from pediatric to adult centers			
R145	The transition from pediatric to adult care in patients with CIF should be carefully prepared and should cover medical care and logistics concerning the treatment of the underlying disease and the HPN.	GPP	Strong
R146	In the transition process from pediatric to adult centers, the care should be transferred from the adult caregiver to the patient.	GPP	Strong
R147	The transition process should start at least one year before the patient adult birthday and can last a couple of years during which the referring pediatric center and the referral adult CIF center should cooperate.	GPP	Strong
R148	Patients with CIF should be informed about the possibility to join non-profit groups that provide HPN education, support and networking among members.	GPP	Strong
R149	Patient support groups should play a complimentary role to healthcare professionals, on the recognition of CIF as a medical condition and practical aspects of living with HPN.	GPP	Strong

seen in the setting of an intra-abdominal catastrophe. It is usually an acute event, occurring in a previously healthy subject (e.g. mesenteric ischemia, volvulus or abdominal trauma) or complicating intestinal surgery and necessitating massive enterectomy and/or resulting in one or more ECF. Less frequently, it may occur following a complication of type III chronic IF (see below), representing "acute on chronic" IF. These patients often initially 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 – CIF: a chronic condition, in metabolically stable patients, who require IVS over months or years. It may be reversible or irreversible; CIF may evolve following prolonged acute (type II) IF or may result from progressive and devastating gastrointestinal or systemic, acquired or congenital, benign or malignant diseases. IVS 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 typically trained, wherever possible, to become independent in managing IVS at home.

3.3. What are the criteria for the clinical classification and reporting of chronic intestinal failure?

3.3.1. Statement 3

The clinical classification and reporting of CIF shall be based on the pathophysiologic mechanism of IF and the underlying disease from which IF originates.

Strong consensus 100% agreement.

3.3.2. Statement 4

The pathophysiologic mechanisms of IF shall be classified as short bowel syndrome (SBS), intestinal dysmotility, intestinal ECF, intestinal mechanical occlusion, or extensive small bowel mucosal disease.

Strong consensus 95% agreement.

3.3.3. Statement 5

The underlying disease from which IF originates shall be categorized according to the ICD codes and should also be clearly distinguishable from the pathophysiological mechanism.

Strong consensus 100% agreement.

Table 6
ESPEN recommendation: 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 does not require any intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency".
Functional classification
On the basis of onset, metabolic, and expected outcome criteria, IF is classified as:
• Type I – acute IF; acute short-term and often self-limiting condition
• Type II – prolonged acute IF: prolonged acute condition, typically in metabolically unstable patients, requiring complex multidisciplinary care and intravenous supplementation over periods of weeks or months
• Type III – chronic IF: a 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 syndrome
• intestinal fistula
• intestinal dysmotility
• mechanical obstruction
• extensive small bowel mucosal disease

Abbreviation: IF, intestinal failure.

3.3.3.1. Commentary. The "pathophysiological classification" of IF has identified five major conditions that may complicate various gastrointestinal or systemic diseases: SBS, intestinal fistula, intestinal dysmotility, mechanical obstruction and extensive small bowel mucosal disease [5]. In the case of SBS, ECF or extensive small bowel disease, the primary mechanism of IF is the malabsorption of ingested food, due to a reduction in, or bypass of, the absorptive mucosal surface. In the case of intestinal dysmotility or intestinal mechanical obstruction, the primary mechanism is the restriction or avoidance of oral/enteral nutrition due to feed-related exacerbation of digestive symptoms and/or of episodes of mechanical or non-mechanical intestinal obstruction; in addition, these conditions can be complicated by bacterial overgrowth leading to malabsorption [5].

In adults, SBS is the clinical condition associated with a small bowel remnant in continuity less than 200 cm, because of extensive surgical resection required for acute or chronic acquired diseases or for congenital gastrointestinal malformations. SBS is the main pathophysiological mechanism of CIF, accounting for around two-thirds of cases in adults [12].

Intestinal fistulas are abnormal communications between two parts of the gastrointestinal tract, between the gut and the other organs (e.g. the bladder), or between the gastrointestinal tract and the skin (ECF) or between the gastrointestinal tract and a laparostomy wound (enteroatmospheric fistulas, EAF). Most ECF or EAF 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. ECF or EAF are among the most common causes of type II IF [10] and a minor cause of CIF [12].

The term intestinal dysmotility is used to indicate the presence of disorders of the propulsion of gut content in the absence of fixed occluding lesions, either with or without a radiological feature of dilated intestine [5,19-21]. 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 and/or intra-abdominal inflammation [5,10]. The term chronic intestinal pseudo-obstruction (CIPO) describes chronic intestinal dysmotility with dilated small intestine, where the modifier "pseudo" is used to underscore the absence of occluding lesions. CIPO may be congenital or acquired, due to a variety of diseases [5]. Chronic enteric dysmotility (ED) is another cause of CIF, not associated with a dilated intestine. Intestinal dysmotility accounts for about 20% of adult patients with CIF [12].

Mechanical obstruction of the intestinal lumen results from a physical abnormality affecting the intestine that may be intraluminal, intrinsic or extrinsic, of benign or malignant origin. It may be an acute event as 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 [5]. Intestinal mechanical obstruction is the mechanism of a small percentage of cases of CIF due to benign disease [12].

Extensive small bowel mucosal disease describes a condition characterized by an intact, or almost intact - albeit inefficient - mucosal surface, that may be of congenital or acquired origin [5]. Mucosal disease too represents a minor cause of CIF in adults [12] but, together with intestinal dysmotility, represents around 50% of children (dysmotility 28% and mucosal disease 22%) transitioning from pediatric to adult CIF centers [22].

Table 7 shows the frequency of the pathophysiological mechanism of CIF and the underlying diseases from which they may originate.

Table 7
Pathophysiology and underlying diseases of patients on long-term home parenteral nutrition for chronic intestinal failure due to benign disease [previously unpublished data from the ESPEN database for CIF, referring to the patients' cohorts included in references 12 and 22].

	Adults (n. 2919)	Children (n. 524)
Short bowel syndrome (No. (%)	**1880 (64.4%)**	**265 (50.6%)**
• Mesenteric ischemia	28.2%	5.5%
• Crohn's disease	28.1%	
• Surgical complications	17.9%	
• Radiation enteritis	6.7%	
• Volvulus	3.8%	24.0%
• Adhesions	2.4%	
• Intestinal malformation		27.7%
• Necrotizing enterocolitis		16.6%
• Others	10.9%	26.2%
Motility disorder	**510 (17.5%)**	**145 (27.7%)**
• CIPO primary[a]	51.7%	60.4%
• Collagenous disease	13.3%	
• Surgical complications	11.7%	
• CIPO secondary[b]	9.1%	18.7%
• Neurologic disease	3.6%	5.2%
• Others	10.6%	15.7%
Extensive mucosal disease	**199 (6.8%)**	**114 (21.8%)**
• Crohn's disease	32.5%	1.8%
• Radiation enteritis	18.4%	
• Autoimmune enteropathy	8.3%	6.3%
• Chemoterapy enteritis	5.3%	
• CVID	5.3%	1.8%
• Celiac disease	4.9%	
• Other congenital mucosal D.	3.4%	24.3%
• Lymphangectasia	2.9%	3.6%
• Microvillus inclusion disease	2.9%	19.8%
• Tufting enteropathy		18.0%
• Others	16.1%	24.4%
Intestinal fistulas	**203 (7.0%)**	
• Surgical complication	45.8%	
• Crohn's disease	33.2%	
• Radiation enteritis	5.8%	
• Adhesions	2.1%	
• Others	13.1%	
Mechanical Obstruction	**127 (4.3%)**	
• Radiation enteritis	38.3%	
• Adhesions	29.0%	
• Crohn's disease	13.1%	
• Surgical complications	7.5%	
• Others	12.1%	

[a] Primary CIPO, chronic intestinal pseudo-obstruction, idiopathic.
[b] Secondary CIPO, due to a known underlying disorder (including Hirschsprung's disease); CVID, common variable immunodeficiency.

3.4. What are the criteria for the severity classification of chronic intestinal failure?

3.4.1. Recommendation 1

The severity of CIF should be based on the eight categories of type and volume of the IVS required by patients, as outlined in Table 8. CIF requiring IVS of fluids and electrolytes alone is less severe than CIF requiring IVS of parenteral nutrition admixtures that also contain macronutrients. The severity of CIF requiring IVS of PN progressively increases in parallel with the volume of the PN admixture, calculated on weekly basis.

Grade of recommendation B - Strong consensus 96% agreement.

3.4.1.1. Commentary. ESPEN's recommendation on the definition and classification of IF also included a "clinical classification of CIF". Relying on the experience of a panel of experts, 16 categories were defined, based on the patient's requirements for energy as well as the volume of IVS infused [5]. An international cross-sectional survey was carried out to investigate the applicability of this classification and to evaluate factors associated with the IVS requirements of individual adult patients with CIF due to benign

Table 8
Severity classification of chronic intestinal failure in adults [13].

Odds of weaning off HPN:
- PN1> FE (any volume), PN2, PN3 and PN4; FE (any volume) = PN2=PN3=PN4 (no difference among PN volumes >1000 mL/d)

Odds of patients' death:
- FE (any volume) < any volume of PN; no difference among PN volumes

Odds of intestinal failure-associated liver disease (IFALD), cholestasis or liver failure:
- FE (any volume) = PN1; PN4>PN3>PN2>PN1

Odds of catheter related bloodstream infection (CRBSI):
- FE (any volume) = PN1; PN4>PN3>PN2>PN1

Type of the IVS	Volume of the IVS[a] mL/d			
	≤ 1000	1001–2000	2001–3000	> 3000
	1	2	3	4
Fluids and electrolytes (FE)	FE 1	FE 2	FE 3	FE 4
Parenteral nutrition (PN)	PN 1	PN 2	PN 3	PN 4

[a] calculated as daily mean of the total volume infused per week = volume per day of infusion x number of infusions per week/7. Abbreviations: FE, Fluids and electrolytes alone; PN, Parenteral Nutrition Admixture containing also macronutrients.

disease [12]. The loss of intestinal function appeared more comprehensively represented by IVS volume requirement than by energy requirement. These results enabled the derivation of a new simplified 8-category clinical classification of CIF, based on two types of IVS, either fluid and electrolyte alone (FE) or parenteral nutrition admixture containing energy (PN), and four categories of volume calculated as a daily mean of the total volume infused per week (mL/d), ≤1,000, 1001–2,000, 2001–3,000, >3000 (Table 7). To determine whether the clinical classification of CIF could be used to indicate the "severity of CIF", a one-year prospective follow up study involving patients enrolled in the cross-sectional analysis was carried out to investigate the relationship between those eight categories of IVS and the patients' outcomes, which included the development of major complications related to HPN/CIF [13]. The results showed that both IVS type and volume were independently associated with the odds of weaning off HPN (higher for PN ≤ 1000 mL/d than for FE and all PN > 1000 mL/d), patients' death (lower for any volume of FE), presence of intestinal failure-associated liver disease (IFALD), cholestasis or liver failure, and occurrence of catheter related bloodstream infection (CRBSI) (both progressively higher for all PN prescriptions with volumes >1000 mL/d in comparison with FE and PN ≤ 1 L/d). These results supported the previously devised clinical classification of CIF as a "severity classification of CIF in adults".

3.5. What is the treatment pathway of chronic intestinal failure?

3.5.1. Recommendation 2

HPN should be prescribed as the primary and life-saving therapy for patients with transient-reversible or permanent-irreversible CIF.

Grade of recommendation B - Strong consensus 100% agreement.

3.5.2. Recommendation 3

Patients with CIF should have an early referral to IF/rehabilitation centers with expertise in both medical and surgical treatment for CIF, to maximize the opportunity of weaning off HPN, preventing HPN failure, and ensuring timely assessment of candidacy for intestinal transplantation (ITx).

Grade of recommendation GPP - Strong consensus 96% agreement.

3.5.2.1. Commentary. The outcome of patients on HPN for CIF due to benign disease has been reported in many single and multicenter retrospective studies [6,23-30] and by an ESPEN prospective five year follow up [31-33]. 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 five years) [23]. Weaning from HPN after one to two years may occur in 20%–50% of patients, depending on underlying CIF characteristics [29]. In patients with SBS, CIF may be reversible because of intestinal adaptation and/or intestinal rehabilitation programs based on medical and surgical treatments [24]. Weaning off HPN has been reported to occur in about 50% of adults and in up to 73% of 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 two to three years have elapsed following the most recent intestinal resection [23]. In patients with CIPO, CIF reversibility is lower than that reported in SBS, occurring in 25–50% of adults and 25–38% or children [23,27]. Intestinal rehabilitation and weaning from HPN in CIF due to ECF primarily depends on the possibility of performing reconstructive surgery to recover bowel continuity and intestinal absorptive surface [30]. Reversibility of CIF due to extensive mucosal disease rarely occurs [23].

Overall, about two-thirds of patients may achieve partial or total social and working rehabilitation as well as a good family life [34]. 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) [34]. Treatment of CIF is based on complex technologies and requires multidisciplinary and multiprofessional input and expertise. The outcome of patients with benign CIF, in terms of reversibility, treatment-related morbidity and mortality, and survival probability is highly dependent on care and support from an expert specialist team [23,35,36]. Indeed, outcomes such as CRBSI are better in centers caring for larger numbers of patients, reflecting team experience [13].

Patients with irreversible CIF are destined to need life-long HPN or require an ITx [37-39]. On the basis of data on safety and efficacy, HPN is considered the primary treatment for CIF, whereas ITx is primarily reserved for those patients at risk of death because of life-threatening complications related to HPN or to the underlying gastrointestinal disease [23,39].

4. Chapter 2 - HPN management (including CVAD choice)

Most of the recommendation related to this topic have been addressed in the recent ESPEN guideline on HPN [2, https://doi.org/10.1016/j.clnu.2020.03.005]. No studies have been published since then, requiring changes in the recommendations. This also applies to some recommendations included in the previous guideline on CIF [1]. Therefore, to avoid redundant duplications of comments, only the text, the grade and the strength of those recommendations from previous guidelines that are still valid are reported in the present guideline.

4.1. What are the criteria for an effective HPN program for CIF?

4.1.1. Recommendation 4 (recommendation #1 of the 2016 CIF guideline (GL))

The aims of an HPN program shall include provision of evidence-based therapy, prevention of HPN–related complications such as CVAD-related infections and metabolic complications and ensure QoL is maximized.

Grade of recommendation GPP - Strong consensus 100% agreement.

4.1.1.1. Commentary. HPN is a complex, life-saving therapy that may result in serious harm if not properly prescribed, prepared and administered. The HPN program shall provide an individualized, safe, effective and appropriate nutrition support plan at discharge from hospital. The program should then be supervised and evaluated on a regular basis, by the nutritional support team (NST) of the hospital HPN/CIF center, as well as by general practitioner and expert healthcare professionals in the community. The rate of HPN-related major complication and the patient's QoL are quality indicators of the HPN program [1,2,40].

4.2. What are the criteria for a safe HPN program for CIF?

4.2.1. Statement 6 (statement #1 of the 2020 HPN GL)

For a safe HPN program, the patient and/or the patient's legal representative shall give fully informed consent to the treatment proposed.

Strong consensus 96% agreement.

4.2.2. Statement 7 (statement #2 of the 2020 HPN GL)

For a safe HPN program, the patient shall be sufficiently metabolically stable and emotionally cope with HPN therapy outside the acute hospital setting.

Strong consensus 100% agreement.

4.2.3. Statement 8 (statement #3 of the 2020 HPN GL)

For a safe HPN program, the patient's home environment shall be adequate to safely deliver the therapy proposed; the suitability of the home care environment should be assessed and approved by the nurse of the NST or of a qualified HPN provider.

Strong consensus 94% agreement.

4.2.4. Recommendation 5 (recommendations #9 to 38 of the 2020 HPN GL)

For a safe HPN program, the choice of the central venous access device (CVAD), the infusion control device, and the infusion line and CVAD care shall be in keeping with recommendations #9–38 of the ESPEN guideline on HPN.

Grade of recommendation A - Strong consensus 100% agreement.

4.2.5. Statement 9 (statement #4 of the 2020 HPN GL)

For a safe HPN program, the patient and/or the caregiver has to be able to understand and perform the required procedures for the safe administration of therapy.

Strong consensus 100% agreement.

4.2.6. Recommendation 6 (recommendation #6 of the 2020 HPN GL)

The patient and/or the caregiver should be trained by an NST to safely infuse the PN with appropriate monitoring and prompt recognition of any complications.

Grade of recommendation GPP - Strong consensus 100% agreement.

4.2.7. Recommendation 7 (recommendation #58 of the 2020 HPN GL)

A formal individualized HPN training program for the patient and/or caregiver and/or home care nurses shall be performed, including catheter care, pump use and preventing, recognizing and managing complications; training can be done in an in-patient setting or at the patient's home.

Grade of recommendation GPP - Strong consensus 100% agreement.

4.2.8. Recommendation 8 (recommendation #7 of the 2020 HPN GL)

The prescribed nutritional admixture and ancillaries required for safe and effective therapy should be delivered by an experienced/certified health care provider.

Grade of recommendation GPP - Strong consensus 93% agreement.

4.2.9. Recommendation 9 (recommendation #8 of the 2020 HPN GL)

The NST should provide appropriate monitoring and treatment for routine and/or emergency care, with appropriate contact details provided to the patient 24 h per day, seven days per week.

Grade of recommendation GPP - Strong consensus 100% agreement.

4.2.10. Recommendation 10 (recommendation #71 of the 2020 HPN GL)

Incidence of CVAD-related infection, incidence of hospital readmission and patient's and family and/or caregiver feedback should be used as criteria to assess and improve the quality of care of HPN program.

Grade of recommendation GPP - Strong consensus 96% agreement.

4.2.10.1. Commentary. At time of the indication for HPN, the NST shall inform the patient about the need, procedure, management, adverse events and reimbursement of HPN, in order to obtain the informed consent to the treatment. The ‘adequate’ metabolic and clinical stability of a patient can be assessed by vital parameters, energy, protein, fluid and electrolyte balances and glycemic control; the term adequate means no immediate risk of acute imbalance after hospital discharge. The home care environment (i.e. cleanliness, electricity, running water, refrigeration) should be assessed before discharge.

Prescription, implementation, and monitoring of an individualized HPN program shall be managed by an NST in centers with HPN management expertise. If the patient can achieve a stable HPN regimen and his/her overall clinical condition is acceptable, an education program for patients and/or caregivers should be initiated to teach correct and proper HPN care.

The management of PN in the home care setting differs from hospitalized patients because there is a shift in primary responsibility from health care professionals to patients and caregivers. The general goals in the education process are promoting independence with the infusion, (self-) monitoring of HPN, preventing complications and improving or maintaining QoL. The HPN center NST plays a key role in the individualized decision-making process and guides all the necessary measures or steps which must be taken. Training for HPN may be carried out in an inpatient setting or at patient's home and may take several days to weeks depending on patient skills, duration of HPN and underlying condition. Multiple education interventions are possible including one-on-one counselling, teach-back method, written handouts, computer-assisted learning and interactive presentations. All these

tools may not eliminate but reduce post discharge helpline contacts provided by telephone, videoconference or patient portals.

HPN is a complex therapy that requires coordination of many health care providers. Communication with the caregivers at home (especially the home care nurse) and in the hospital is a key-factor for a safe discharge on HPN.

An experienced and certified health care provider is also required for the appropriate delivery of nutritional admixture and ancillaries to patient's home. Table 9 lists the pre-discharge and post-hospital care assessments required for the coordination between heath-professionals and care providers within and outside the hospital [2].

Two surveys were carried out to identify the aims and the outcome indicators of the HPN therapy for benign CIF. An expert panel of health care clinicians identified incidence of CRBSI, incidence of rehospitalization and patient's QoL as the three major indicators of quality of care [41]. Survival rate was also considered important when patients were interviewed [42]. Table 10 reports the ESPEN Guideline for HPN recommendations for the choice of the CVAD, the infusion control device, and the infusion line and CVAD care [2].

4.2.11. Recommendation 11 (recommendation #70 of the 2020 HPN GL)

For a patient to travel safely, he/she shall receive a sufficient supply of PN and relevant ancillaries during the journey and at the destination and the NST responsible for the patient's care shall endeavor to establish contact with a skilled NST at the patient's destination in case medical support is required.

Grade of recommendation GPP - Strong consensus 96% agreement.

4.2.11.1. Commentary. Travelling with PN is an important factor for some patients' QoL and independency. The ESPEN guideline on HPN provides recommendations on appropriate and safe travelling based on statements of patients' representatives participating in the panel. Key points are: pre-travel planning discussion with the healthcare professionals/NST; doctor issuing of a letter/medical certificate for the patient/caregivers confirming that they are aware they are travelling, along with a brief overview of their condition and need for PN; organizing the provision of nutrition bags, nutrition pump and ancillaries for the infusion line care at destination; choosing an accommodation suitable for performing an HPN program; considering actions in case of emergency situation, including any required contact numbers; establishing local medical support or contact for the patient should it be required.

Table 9
Items to be included in the assessment at patient discharged on HPN [2].

- Medical, physical, psychological and emotional suitability/stability of the patient
- Stability of the PN regimen (dosage and admixture)
- Level of home care and support required
- Lifestyle/activities of daily living
- Rehabilitative potential
- Potential for QoL improvement
- Potential for learning self-management of HPN (patient/caregivers)
- Knowledge and experience of the home nursing team (if no self-management)
- Basic home safety, facilities and general cleanliness instruction
- Need for extra equipment (e. g. backpack, infusion pump, hospital bed, extra drip stand)
- Home care provider of nutritional admixture, equipment and ancillaries
- Reimbursement for bags, services and supplies
- Around the clock (on-call) availability of an experienced home care provider
- Post-discharge monitoring necessities/possibilities (including scheduled laboratory tests)
- Medication prescription with administration details

Abbreviations: HPN, home parenteral nutrition; PN, parenteral nutrition; QoL, quality of life.

4.3. How should patients with CIF be monitored?

4.3.1. Recommendation 12

Monitoring of patients with CIF shall include the underlying disease from which the IF originated, the intestinal function, the effectiveness and safety of the HPN program, and the patient's clinical condition, nutritional status, and QoL.

Grade of recommendation GPP - Strong consensus 92% agreement.

4.3.2. Recommendation 13 (adapted from recommendation #53 of the 2020 HPN GL)

Patients receiving HPN shall be monitored at regular intervals, to review the indications, the efficacy and the risks of the treatment.

Grade of recommendation GPP - Strong consensus 92% agreement.

4.3.3. Recommendation 14 (recommendation #50 of the 2020 HPN GL)

The time between reviews should be adapted to the patient, the care setting and duration and stabilization of nutrition support; the severity of the IF and the underlying disease; intervals can increase as the patient is stabilized on nutrition support.

Grade of recommendation GPP - Strong consensus 97% agreement.

4.3.4. Recommendation 15 (recommendation #54 of the 2020 HPN GL)

In clinically stable patients on long-term HPN, body weight, body composition and hydration status, energy and fluid balance and biochemistry (hemoglobin, ferritin, albumin, C-reactive protein (CRP), electrolytes, venous blood gas analysis or serum bicarbonates, kidney function, liver function and glucose) can be measured at all the scheduled visits.

Grade of recommendation GPP - Consensus 80% agreement.

4.3.5. Recommendation 16 (recommendation #55 of the 2020 HPN GL)

In patients on long-term HPN, clinical signs and symptoms as well as biochemical indexes of vitamin and trace element deficiency or toxicity should be evaluated at least once per year.

Grade of recommendation GPP - Strong consensus 96% agreement.

4.3.6. Recommendation 17 (recommendation #56 of the 2020 HPN GL)

In patients on long-term HPN, bone metabolism and bone mineral density (BMD) should be evaluated annually or in accordance with accepted standards.

Grade of recommendation GPP - Strong consensus 96% agreement.

4.3.7. Recommendation 18 (adapted from recommendation #51 of the 2020 HPN GL)

HPN monitoring should be carried out by the hospital NST with skills and experience in IF and HPN management, in collaboration with experienced home care specialists, home care agencies and/or general practitioners.

Grade of recommendation GPP - Strong consensus 96% agreement.

Table 10
Recommendations #R9-R38 of the ESPEN guideline on HPN for the CVAD choice and the safe infusion line care [2]. For the underlying evidence, please consult the original guideline (https://doi.org/10.1016/j.clnu.2020.03.005).

- The choice of CVAD and the location of the exit site shall be made by an experienced HPN NST, as well as by the patient.
(R9, GPP, strong consensus 100%)
- The exit site of the CVAD should be easily visualized and accessible for self-caring patients.
(R10, GPP, strong consensus 100%)
- Tunneled CVAD or totally implanted CVADs shall be used for long-term HPN.
(R11, GPP, strong consensus 90.9%)
- Access to the upper vena cava should be the first choice for CVAD placement, via the internal jugular vein or subclavian vein.
(R12, B, strong consensus 100%)
- Right-sided access should be preferred to the left-sided approach to reduce the risk of thrombosis.
R13, B, strong consensus 95.2%)
- The tip of the CVAD should be placed at the level of the right atrial-superior vena cava junction.
(R14, B, strong consensus 100%)
- Peripherally inserted central venous catheters (PICCs) can be used if the duration of HPN is estimated to be less than six months.
(R15, 0, strong consensus 100%)
- HPN should be administered using an infusion pump for safety and efficacy reasons.
(R16, GPP, strong consensus 91.3%)
- In exceptional circumstances a flow regulator can be temporarily used for HPN; administration sets with only a roller clamp should not be used.
(R17, GPP, strong consensus 100%)
- A portable pump can improve the patient's QoL when compared to stationary pumps.
(R18, 0, strong consensus 95.7%)
- Either a sterile gauze or sterile, transparent, semipermeable dressing should be used to cover the CVAD exit site.
(R19, B, strong consensus 90.9%)
- When transparent dressings are used on tunneled or implanted CVAD exit sites, they can be replaced no more than once per week (unless the dressing is soiled or loose).
(R20, 0, strong consensus 95.5%)
- A tunneled and cuffed CVAD with a well healed exit site might not require dressing to prevent dislodgement.
(R21, GPP, strong consensus 100%)
- Tubing to administer HPN should be replaced within 24 h of initiating the infusion.
(R22, B, strong consensus 100%)
- Strict aseptic technique for the care of home CVAD shall be maintained.
(R23, A, strong consensus 100%)
- Hand antisepsis and aseptic non-touch technique should be used when changing the dressing on CVADs.
(R24, GPP, strong consensus 100%)
- A 0.5–2% alcoholic chlorhexidine solution shall be used during dressing changes and skin antisepsis; if there is a contraindication to chlorhexidine, tincture of iodine, an iodophor, or 70% alcohol shall be used as an alternative.
(R25, A, strong consensus 95.2%)
- Hand decontamination, either by washing hands with soap and water but preferably with alcohol-based hand rubs, should be performed immediately before and after accessing or dressing a CVAD.
(R26, B, strong consensus 95.2%)
- A needle-free connector should be used to access intravenous tubing.
(R27, B, strong consensus 100%)
- Needle-free systems with a split septum valve may be preferred over some mechanical valves due to increased risk of infection with mechanical valves.
(R28, 0, strong consensus 100%)
- Contamination risk shall be minimized by scrubbing the hub connectors (needleless connectors) with an appropriate antiseptic (alcoholic chlorhexidine preparation or alcohol 70%) and access it only with sterile devices.
(R29, A, strong consensus 100%)
- For passive disinfection of hub connectors (needleless devices) antiseptic barrier caps should be used.
(R30, B, strong consensus 90.9%)
- If HPN is delivered via an intravenous port, needles to access ports should be replaced at least once per week.
(R31, GPP, strong consensus 100%)
- The CVAD or CVAD site should not be submerged unprotected in water.
(R32, B, strong consensus 95.2%)
- Sodium chloride 0.9% instead of heparin should be used to lock long-term CVAD.
(R33, B, strong consensus 95.5%)
- As an additional strategy to prevent CRBSIs, taurolidine locking should be used because of its favorable safety and cost profile.
(R34, B, strong consensus 100%)
- If a PICC is used for HPN, a sutureless device should be used to reduce the risk of infection.
(R35, B, strong consensus 100%)
- For the securement of medium– to long-term PICCs (>1 month) a subcutaneously anchored stabilization device can be used to prevent migration and save time during dressing change.
(R36, 0, strong consensus 100%)
- In multilumen catheters, a dedicated lumen should be used for PN infusion.
(R37, GPP, strong consensus 95.5%)
- Routine drawing of blood samples from CVAD should be avoided if possible due to an increased risk of complications.
(R38, B, strong consensus 95.2%)

Abbreviations: CRBSI, catheter-related bloodstream infection; CVAD, central venous access device; GPP, good practice point; HPN home parenteral nutrition; NST, nutrition support team; PICC, peripherally inserted central catheter; PN, parenteral nutrition; R, recommendation.

4.3.8. Recommendation 19 (recommendation #52 of the 2020 HPN GL)

Patients and/or caregivers can be trained to monitor nutritional status, fluid balance and the infusion catheter.

Grade of recommendation 0 - Strong consensus 92% agreement.

4.3.8.1. Commentary. The purpose of monitoring is to assess the nutritional efficacy of the HPN program, preventing and timely diagnosing and treating HPN related complications and measuring QoL and quality of care. Monitoring of HPN patients should be carried out by an experienced hospital NST and by home care

specialists as well as by a home care agency with experience in HPN and should involve the general practitioner.

Recommendation #12 highlights that patients with CIF need to be also monitored for the outcome and complications of the underlying disease which generated the IF and the mechanism as well as the severity of the IF [5,12,13]. This requires the cooperation among doctors and healthcare professionals with expertise in medical and surgical treatment of the gastrointestinal and/or systemic diseases from which the IF originated as well as in the organs and systems, which may complicate as a consequence of CIF and HPN, such as liver and renal failure or metabolic bone disease (MBD) [43].

The recommendations #13–19 are the ESPEN HPN guideline recommendations #50–56 [2]. The indications, route, risks, benefits and goals of nutrition support should be reviewed at regular intervals. Patients and caregivers should be trained in self-monitoring of their nutritional status, fluid balance and infusion catheter, as well as in recognizing early signs and symptoms of complications and responding to adverse changes in both their well-being and management of their nutritional delivery system [42,44-46].

Parameters to be monitored, frequency and setting of monitoring are indicated in Table 11 [2].

Monitoring should be more frequent during the early months of HPN, or if there is a change in the patient's clinical condition. Intervals may increase as the patient is stabilized on nutrition support. Fluid balance requires the most frequent monitoring, especially in the first period after discharge and in patients with SBS with a high output stoma or with intestinal dysmotility with recurrent episodes of vomiting. On the other hand, vitamin and trace element deficiency may take more time to develop and to present clinical signs and symptoms, so that a six-to-twelve-month interval of assessment is appropriate. However, monitoring of micronutrients is as important as monitoring other parameters, especially in patients on long-term HPN and in those who are undergoing intestinal rehabilitation and weaning from HPN. In the latter case, while intestinal rehabilitation is associated with maintenance of energy, protein, fluid and electrolyte balance without PN support, this is not necessarily the case for micronutrient balance. Decreasing or totally stopping PN infusion decreases micronutrient supplementation, thus creating a risk for deficiency.

After hospital discharge, it is critical that the HPN NST has contact with patients and caregivers 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 HPN infusion, and general health.

5. Chapter 3 – Chronic intestinal failure centers

The recommendations related to this topic were addressed in the recent ESPEN guideline on HPN under the topics #13 “requirements for the hospital centers that care for HPN patients” and #14 “the requirements of the NST” [2, https://doi.org/10.1016/j.clnu.2020.03.005]. No studies have been published since then, requiring changes in the recommendations. Therefore, the texts of the HPN guideline recommendations concerning this topic have been adapted to CIF and proposed for voting. The detailed comments regarding this topic are described in the HPN guideline [2] and are summarized below.

Table 11
Parameters to be monitored, frequency and setting of monitoring in patient on HPN for CIF [2].

Parameter	Frequency	Setting
General condition	Daily if unstable, twice weekly to once a week if stable	Nurse at home
Body temperature		Patient and/or caregivers
Body weight	Daily if unstable, twice weekly to once a week if stable	In the hospital (outpatient visit)
		Nurse at home
		Patient and/or caregivers
Body mass index	Monthly	In the hospital (outpatient visit)
		Nurse at home
Fluid balance	The frequency and type of parameters will depend on	Nurse at home
- Urine output	etiology of CIF, and stability of patients	Patient and/or caregivers only in case of training program
- Stoma output	In case of high stool output (end jejunostomy), the	
- Number or consistency of stools	monitoring after the first discharge should be daily, then	
- Presence of edema	twice weekly to once a week when stable	
Catheter cutaneous exit site	Daily	Nurse at home
		Patient and/or caregivers only in case of training program
Full count blood	The frequency and type of parameters will depend on	At home
C-reactive protein	etiology of the underlying condition requiring HPN and the	Verify at each visit
Serum glucose	stability of patients	
Serum and urine electrolytes and minerals (Na, Cl, K, Mg, Ca and P)	Weekly or monthly, then every three to four months when stable	
Serum Urea and Creatinine		
Serum bicarbonates		
Urine analysis		
Serum albumin and prealbumin	Monthly, then every three to four months when stable	At home
		Verify at each visit
Serum liver function tests including INR	Monthly, then every three to four months when stable	At home
		Verify at each visit
Liver ultrasound	Yearly	In the hospital
Serum Folate, vitamins B12, A and E	Every six to twelve months	Dosage at home or in the hospital
Serum ferritin, Fe	Every three to six months	Dosage at home or in the hospital
Serum 25-OH Vitamin D	Every six to twelve months	Dosage at home or in the hospital
Serum Zn, Cu, Se	Every six to twelve months	Dosage in the hospital
Serum manganese	Yearly	Dosage in the hospital
DEXA	Every twelve to eighteen months	In the hospital

Abbreviations: CIF, chronic intestinal failure; DEXA, Dual-energy X-ray absorptiometry; HPN, home parenteral nutrition; INR, international normalized ratio.

5.1. Which are the requirements for the hospital centers that care for CIF patients?

5.1.1. Recommendation 20 (adapted from recommendation #59 of the 2020 HPN GL)

Patients with CIF should be cared for by specialized, dedicated and a clearly identifiable hospital unit, normally termed "HPN center or IF center or intestinal rehabilitation center".

Grade of recommendation GPP - Consensus 87% agreement.

5.1.2. Recommendation 21 (adapted from recommendation #60 of the 2020 HPN GL)

The CIF unit should have offices for outpatient visits and dedicated beds for patients who need hospitalization.

Grade of recommendation GPP – Strong consensus 96% agreement.

5.1.3. Recommendation 22 (adapted from recommendation #61 of the 2020 HPN GL)

All CIF patients should be cared for by a NST with experience in HPN management.

Grade of recommendation GPP – Strong consensus 100% agreement.

5.1.4. Recommendation 23 (adapted from recommendation #62 of the 2020 HPN GL)

The NST consists of experts in CIF and HPN provision. This includes physicians, specialist nurses (including in catheter, wound and stoma care), dietitians, pharmacists, social workers, psychologists, as well as an appropriate practitioner with expertise in CVAD placement. Surgeons with expertise in IF should also be available for structured consultation.

Grade of recommendation GPP – Strong consensus 96% agreement.

5.1.4.1. Commentary. CIF patients shall be cared for by an NST with skills and experience in both CIF and HPN management. For optimal care and visibility for patients, healthcare providers and public authorities, the hospital departments dedicated to the care of these patients shall be clearly recognized, with dedicated beds and resources. Key issues are the identification of the persons, structures, and procedures responsible for the CIF and HPN care process [47,48], such as:

- Professionals who coordinate and manage the different phases of CIF and HPN management
- Place of initial care (center of IF, gastroenterology, surgery, other)
- Place and methods of training programs (on hospital beds, in day hospital, at home)
- Pathways of care in case of complications (example: emergency room, direct access to hospital beds, link with local hospitals of the patient residency)
- Place and procedures for CVAD positioning and managing of complications

Because of its complex nature, only experienced NST should take care of CIF and provide HPN treatment [2]. A positive impact of expertise in this field on both patient survival and major HPN/IF related complications has been reported [13,23,35,36,49,50].

The team should be "multidisciplinary" in nature and include physician specialists with a background in gastroenterology, nutrition and surgery, specialized nurses, dietitians, and pharmacists [43,51,52]. In light of the profound impact on personal and family life, psychologists and social workers should also form part of the team [43,53,54].

The appropriate size of an NST depends on the number of patients under the team's care [55]. The center needs to estimate the time that each professional has to dedicate to the single patient, in order to define the number of human resources required for managing their total number of patients.

The caregivers closer to the patient's home, such as the general practitioner and homecare nurses, although not direct team members, should be kept informed of patients' clinical course after discharge from hospital [56-60].

5.1.5. Recommendation 24 (recommendation #63 of the 2020 HPN GL)

The NST for HPN/CIF shall have clear written pathways and protocols in place for the management of patients with complications relating to HPN.

Grade of recommendation GPP – Strong consensus 100% agreement.

5.1.6. Recommendation 25 (recommendation #64 of the 2020 HPN GL)

The NST for HPN/CIF shall provide patients and caregivers with written information relating to the recognition and subsequent management of HPN-related complications, including details (e.g. telephone number) of an appropriate NST member to contact in the case of an emergency, available 24 h per day.

Grade of recommendation GPP – Strong consensus 100% agreement.

5.1.6.1. Commentary. Complications relating to CIF are categorized into those of HPN, those of the patient's underlying disease leading to CIF and those of CIF. Complications due to any non-CIF related comorbidities (i.e. cardiac or respiratory disease etc.) could also occur [40,43,61]. The CIF team should ensure that patients, caregivers as well as their general practitioners are aware of the roles and responsibilities of the health care professionals involved in each component of their condition. On the other hand, the NST needs to be timely informed of any changes in these conditions, including any alterations in medication for non-IF related problems, as well as any admissions to hospital. The NST should be responsible for the management of patients with complications related to HPN, including the emergency management of any HPN-related issues, 24 h per day, seven days per week [47,62,63]. The NST should generate written protocols for the management of HPN-related complications and, importantly, should ensure that specialist advice from the NST is available at all times. Where patients cannot attend the CIF center with emergency issues, the NST should provide the local hospital with those protocols (i.e. for CRBSI management) and with any relevant details of the patient's clinical condition.

Patient-education programs should be developed to minimize hospital admissions for complications associated with HPN and CIF. Patients and caregivers must be provided with clear written information relating to the recognition and management of CIF and HPN-related complications, such as CVC-related emergency situations [64] and fluid balance alterations [46]. The NST shall provide patients/caregivers and their general practitioners with contact details in case of any emergency.

6. Chapter 4 - Parenteral nutrition formulation

6.1. Which are the criteria for the appropriate prescription of PN formulation for patients with CIF?

6.1.1. Recommendation 26 (recommendation #12 of the 2016 CIF GL)

The protein and energy requirements for CIF patients shall 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-energy malnutrition), and that the adequacy of the regimen is regularly evaluated through clinical, anthropometric, and biochemical parameters.

Grade of recommendation GPP – Strong consensus 100% agreement.

6.1.1.1. Commentary. No new data have been retrieved about this issue. A systematic review published in January 2022 aiming to evaluate evidence for the differential effects of HPN solutions and to understand features associated with differences in clinical endpoints, did not found any studies comparing amino acid formulations [65]. Therefore, recommendation #12 of the 2016 ESPEN CIF guideline has been confirmed.

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 [66].

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 losing 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 [67] and thus infusions over time rather than bolus protein infusions are the preferred delivery method.

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 [68]. Protein prescriptions must therefore take in consideration the lack of equivalence of amino acids to dietary protein.

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/d 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 [40,69,70]. 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/d [40,69,70]. Limited outcome data is available on the effects of adjusting amino acid doses for HPN patients.

Energy sources for HPN prescriptions are derived from glucose and fat emulsions [40]. 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. A study measured energy expenditure by doubly-labelled water in patients on HPN who did not receive any oral feeding. It showed that HPN patients' energy requirements could be met by supplying 1.4 times the resting energy expenditure (REE) or about 30 kcal/kg/d. No significant difference was noted between REE calculated with the Harris-Benedict equations and REE measured with indirect calorimetry [71]. HPN patients often have significant oral intake which may be at least partly absorbed and contribute to energy intake. Another 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 [72]. 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 in SBS patients on HPN showed that preservation of substantial colonic function resulted in a reduction in HPN energy requirements of over 1200 kcal/d in patients with less than 100 cm of small bowel compared to similar patients who had no colon [73]. The colon has been shown to be an energy salvaging organ [74–75] and its preservation in patients with SBS may make relative requirements for HPN less or sometimes unnecessary. 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 [40,70,71]. 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.

6.1.2. Recommendation 27 (recommendation #13 of the 2016 CIF GL)

Optimal blood glucose control, based on blood glucose below 180 mg/dL (10.0 mmol/L) during HPN infusion and normal HbA1c levels <7% in patients with diabetes can be targeted, through regular monitoring.

Grade of recommendation 0 - Strong consensus 96% agreement.

6.1.3. Recommendation 28 (recommendation #14 of the 2016 CIF GL)

No recommendation at this time can be made regarding optimal approach to achieving glycemic control in HPN patients; addition of insulin to HPN admixtures has been noted to be safe in multiple case series.

Grade of recommendation 0 - Strong consensus 92% agreement.

6.1.3.1. Commentary. Both these recommendations were confirmed from the 2016 guideline on CIF [1], as no new data were retrieved.

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 monosaccharides 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 preexisting diabetes mellitus or disease-related insulin resistance, mean that some patients on long-term PN have hyperglycemia [76].

Hyperglycemia is associated with adverse outcomes in patients with diabetes as well as non-diabetic patients when patients have hyperglycemia whilst receiving PN in the hospital setting. This effect may extend into the community [77–79]. 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 glycemic control in almost all patients who experience elevated blood glucose levels on HPN. A community recommendation for glycemic control is that patients should have an HbA1c target between 48 mmol/mol and 58 mmol/mol (6.5% and 7.5%) and ongoing review of treatment to prevent hypoglycemia [80,81]. Glycemic control can also be assessed by blood glucose measurements and may be used for checking hypoglycemia 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) [82,83].

There is limited data on strategies for managing hyperglycemia in patients receiving HPN but the deleterious effects of unchecked hyperglycemia are well documented [76,84]. Options for medically managing hyperglycemia range from decreasing the glucose load in the HPN prescription, prescribing oral hypoglycemic medication, giving a daily dose of injectable insulin, or adding insulin to the HPN admixture. Hyperglycemia, 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 hyperglycemia. 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) [83] but the metabolic consequences of this in HPN patients should be carefully considered.

Insulin protocols for management of hyperglycemia in patients receiving PN have been proposed [76]. When adding regular insulin in the PN bag, an initial ratio of one unit of insulin per 10 g of dextrose in patients with diabetes and one unit of regular insulin per 20 g of dextrose in nondiabetic patients having hyperglycemia, followed by titration of insulin dosage if blood glucose target is not achieved [84].

However, 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 hypoglycemic medications and separately-injected insulin rely on HPN subsequently being administered at full dose or hypoglycemia 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 [85]. However, a recent US study showed that insulin was a frequent non-nutrient inclusion in PN [86]. Even though it is still a matter of debate [87,88], the potential advantages of this practice include consolidating insulin dosage into the PN formula and minimizing the risk of hypoglycemia 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, as well as the PN admixture composition, thereby limiting availability to the patient [76,89,90]. A literature review reported a range of insulin availability from PN admixture from 44% to 95% [76]. Earlier reports from three to four decades ago suggested approximately 50% loss of insulin from PN solutions by nonspecific binding to infusion material [91]. 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) [89,92,93]. It has been shown that the presence of lipid emulsion [93] and of multivitamins/trace elements [92] increase the insulin availability. 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.

6.1.4. Recommendation 29 (recommendation #15 of the 2016 CIF GL, expanded)

In patients totally dependent on HPN, a minimum of 1 g/kg/wk of intravenous lipid emulsion containing essential fatty acids (EFA) may be supplied to prevent EFA deficiency; changing a soybean oil-based lipid emulsion to either a fish oil containing lipid emulsion or an olive oil based lipid emulsion may be safe regarding the provision of enough EFA.

Grade of recommendation 0 - Strong consensus 92% agreement.

6.1.4.1. Commentary. Patients on long-term PN on lipid-free or very limited lipid and high glucose admixtures may experience induction of hyperinsulinemia which suppresses mobilization of EFA from fat stores and induces EFA deficiency (EFAD) [94].

EFA (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 [95], other clinical manifestations of EFAD include neurological or hematological side effects, and may even lead to death [96-98]. Patients on long-term PN are in the group at high risk of development EFAD [99] if not given an external source of EFA. The clinical signs of EFAD may develop within two to six months of fat-free total PN (TPN) and oral fasting [98].

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 [100]. 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 [101], of olive oil lipid emulsion or composed lipid emulsion containing fish oil (Soy-MCT, olive oil, fish oil) [102,103].

Based on one observational study [104] and existing guidelines [40]), in long-term PN, the necessary minimum of lipid emulsion that should be administered to prevent EFAD is 1 g/kg/wk. If patients take some oral diet in the form of fat, EFAD is rarely a specific problem [40].

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 [105]. T:T ratio refers to the eicosatrienoic (mead) acid: arachidonic acid ratio. ω-3 and ω-6 are preferred substrates over ω-9 for elongase and desaturase enzymes that regulate fatty acid metabolism. In the absence of EFAs, ω-9 is metabolized to mead acid, thus increasing the T:T ratio.

6.1.5. Recommendation 30

No type of lipid emulsion alone should be uniformly applied; the choice of lipid emulsions should be made on patient individual basis.

Grade of recommendation B - Strong consensus 97% agreement.

6.1.5.1. Commentary. A systematic review [106] and a meta-analysis [107] assessed the effects of different lipid emulsions in adult patients requiring HPN. Even though lipid emulsions containing olive oil and/or fish oil appeared associated with some advantage with regards to liver function and blood cell fatty acid profiles, the evidence was insufficient to determine the superiority of one lipid emulsion over another. It was considered unlikely that one type of lipid emulsion alone could meet the needs of all

patients. Therefore, the suitable type of lipid emulsions for each patient should be assessed on an individual basis.

6.1.6. Recommendation 31 (recommendation #16 of the 2016 CIF GL expanded)

When a soybean-based lipid emulsion is supplied, no more than 1 g/kg/d of lipid emulsion should be provided.

Grade of recommendation B - Strong consensus 96% agreement.

6.1.6.1. Commentary. Lipids should be an essential component of PN 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 IFALD, which can be achieved by limiting the lipid dose [108].

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 [40].

The optimal amount of lipids for patients on HPN is not precisely established. At least 1 g/kg/wk 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 [101,109,110-114].

For long-term HPN treatment (>6 months), the amount of intravenous soybean oil-based lipid emulsion should not exceed 1 g/kg/d. Administration of soybean oil lipid emulsion in higher doses was associated with significantly increased risk of development of IFALD [115,116]. Infusion of 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/d (0.11 g/kg/h) because side effects have been reported for cases in which that threshold was exceeded [117]. Practitioners need to match the proper dose with the clinical situation and in accordance with established guidelines.

6.1.7. Recommendation 32

When more than 1 g/kg/d of lipid emulsionis required, alternative lipid emulsions (olive oil, MCT, and fish oil) should be used to reduce the soybean-oil content of intravenous lipid emulsions, which tends to be high in ω-6 polyunsaturated fatty acids (PUFA) and phytosterols.

Grade of recommendation GPP - Strong consensus 96% agreement.

6.1.7.1. Commentary. PN-related factors for the development of IFALD include CRBSIs, continuous PN infusion, excessive glucose intake, and the use of soybean oil lipid emulsions at doses higher than 1 g/kg/d [106–108]. When administration of lipid emulsions at doses higher than 1 g/kg/d is required, alternative lipid emulsions replacing soybean oil with olive oil, MCT and/or fish oil allows to reduce the amount of total soybean oil infused [106-108]. Furthermore, in comparison with soybean oil, alternative mixed lipid emulsions have the advantages to have reduced ω-6 PUFA and phytosterol content, increased ω-3 PUFA content, and increased amounts of α-tocopherol, the isoform of vitamin E with strong antioxidant effects [106-108,117]. Some evidence, needing to be confirmed by randomized controlled trials (RCT), suggest that lipid emulsion alternative to soybean oil-based lipid emulsion may reduce the risk of hepatic injury in adult home PN patients at risk for liver complications [118,119].

6.1.8. Recommendation 33 (recommendation #14 of the 2016 CIF GL)

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 shall be made regularly.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.1.9. Recommendation 34 (recommendation #15 of the 2016 CIF GL)

The PN formula shall be adjusted with the aim of normalizing laboratory tests related to electrolytes and mineral balance in patients on HPN.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.1.10. Recommendation 35

Timely adjustment of sodium supplementation can allow anabolism in patients on HPN.

Grade of recommendation 0 - Strong consensus 92% agreement.

6.1.11. Recommendation 36 (recommendation #16 of the 2016 CIF GL)

Regular monitoring of acid-base status in patients on long-term HPN (serum concentration of chloride and bicarbonate), shall be made because either metabolic acidosis or metabolic alkalosis can occur.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.1.11.1. Commentary. Patients on HPN (particularly those with SBS, high output ECF or gastro drainage tube) are at risk for fluid and electrolyte imbalance, which can lead to acute and chronic renal failure [120,121]. Persistent volume depletion, chronic hyponatremia, metabolic acidosis, as well as oxaluria and nephrolithiasis (particularly in SBS with colon in continuity) [52,122] 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 low salt intakes are major contributors to fluid loss into the intestine [123]. 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 [124,125].

The daily parenteral water requirement varies from 25 to 35 mL/kg (approximately 2.0–2.5 L) for the well-hydrated individual [125]. 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/d [126]. 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 PN 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 [127]. This is accompanied by laboratory parameters including increases in hematocrit, serum osmolality and sodium concentration, increased urine osmolality (>450 mOsm/kg) [127], random low urine sodium concentration, 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 [128]. 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 [129]. It is based on acceleration of co-transport of sodium with glucose [130,131]. 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 [132]. 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 who 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.

PN fluid and electrolyte dosing recommendations (Table 12) 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 [125].

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 [133], and hyponatremia occurs with excessive hydration using hypotonic fluids. 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 are followed by headache, obtundation, seizures, coma, and respiratory arrest [134]. The manifestations of hypernatremia are also neurological including lethargy, altered mental status, restlessness, irritability, hyperreflexia, nausea, vomiting, fever, intense thirst, and labored breathing. In both situations, correction must be done cautiously.

Table 12
Fluid and electrolyte recommendations for parenteral nutrition [from 40, 125,127].

	/kg/d[a]	/d (average adult)[a]
Water	25–35 mL[40]	1500–2500 mL
Sodium	1.0–1.5 mmol[40]	60–150 mmol[125,127]
Potassium	1.0–1.5 mmol[40]	40–100 mmol[127]
Chloride	1.0–1.5 mmol[40]	
Phosphate	0.3–0.5 mmol[40]	10–30[127]; 25 mmol[40]
Magnesium	0.1–0.15 mmol[40]	4–12[127]; 10 mmol[40]
Calcium	0.1–0.15 mmol[40]	2.5–7.5[127]; 10 mmol[40]

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

The role of sodium as anabolic factor was suggested by a retrospective study on a twelve month prospectively collected data of a cohort of 50 adult patients with CIF due to SBS was performed to analyze the dynamic changes in the composition of PN admixture, in order to characterize the specific effects of some of energy, volume, and sodium on body mass index (BMI) [135]. The results showed that increased sodium support was the strongest independent factor for the recovery of BMI. The time courses of phase angle, measured from body impedance analysis, and serum albumin indicated that the increased BMI was not a result of overhydration [135]. These results were in agreement with previous observations in children [136,137]. Potential physiological mechanisms for the anabolic action of increased sodium support could be the normalization of volume status in dehydrated patients counteracting hypovolemia as a potential catabolic factor or favoring the anabolic effect of euvolemia, through yet unknown mechanisms [138]. Indeed, evidence has been reported that sodium restriction impairs insulin secretion, which is an anabolic factor [139], and that cell swelling as a consequence of normalized volume status acts as an anabolic factor [140]. A Denmark study on a well-defined, total single-center IF cohort demonstrated the need of individualized tailor-made PN formulation due to the patients' various history, anatomy, complexity, and capability [141].

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 [126]. 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 amphotericin B cause hypokalemia). Furthermore, hypokalemia may result from hypomagnesemia in which case the magnesium must be corrected before the potassium level will improve [142]. Hyperkalemia can occur in patients on HPN with concurrent medications, such as potassium-sparing diuretics, octreotide, and heparin [143]. 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 for chronic hypokalemia 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, intravenous 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 [144]. In refeeding syndrome, circulating phosphorus shifts into cells, causing a precipitous drop in serum phosphorus [145]. 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 [146]. Most cases of hypophosphatemia occur in hospitalized patients. Hyperphosphatemia occurs most often in renal failure, but it is 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.

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 [147,148]. In patients with CIF, magnesium deficiency may occur through several mechanisms, including resection of the intestinal absorption sites, renal loss due to aldosteronism secondary to dehydration and chronic therapy with proton pump inhibitors (PPI) [149]. 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 [150]. A case control study compared serum magnesium versus 24-h urinary Mg in 16 patients 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 [151]. 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 [152]. 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 [40].

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 [153-158]. 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 [159]. 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 hyperchloremic 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 [158,160,161]. Metabolic hyperchloremic acidosis can also be observed in patients who have undergone urinary diversion using the ileum or the colon, due to increased intestinal absorption of chloride, and in patients on treatment with anti-PPI that reduce the excretion of chloride ions in the stomach thereby increasing net gut bicarbonate losses while decreasing gut chloride losses [153,158].

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 an 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 [156]. 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 [156]. 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 [158].

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 [153,158].

6.1.12. Recommendation 37 (recommendation #20 of the 2016 CIF GL)

In patients on HPN, clinical signs and symptoms as well as biochemical indexes of vitamin deficiency or toxicity should be regularly evaluated.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.1.13. Recommendation 38 (recommendation #21 of the 2016 CIF GL)

Baseline serum vitamin concentrations should be measured, according to laboratory availability, at the onset of HPN and then at least once per year.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.1.14. Recommendation 39 (recommendation #22 of the 2016 CIF GL)

Vitamin doses in HPN can be adjusted as needed.

Grade of recommendation GPP - Strong consensus 92% agreement.

6.1.15. Recommendation 40 (recommendation #23 of the 2016 CIF GL)

The route of vitamin supplementation can be selected according to the characteristics of the individual patient.

Grade of recommendation GPP - Strong consensus 96% agreement.

6.1.15.1. Commentary. The first recommendations for vitamins in PN were proposed by the Nutrition Advisory Group of the Department of Food and Nutrition and by the American Medical Association (AMA) in 1975. The values were extrapolated from the Recommended Daily Allowance (RDAs) based on knowledge about bioavailability. Most of the parenteral water-soluble vitamins were double the RDA dose to take into account greater utilization associated with illness, previous deficiencies, and increased rate of excretion due to systemic rather than portal delivery. The fat-soluble vitamins were rather reduced 30–50% from the RDA to take into account their absorption and potential toxicity [162].

These recommendations have been modified thereafter in the American Society for Parenteral and Enteral Nutrition (ASPEN) [163] and ESPEN [1] guidelines/documents and developed in response to deficiencies that were documented in the early years of PN.

Recently, ESPEN has published the micronutrient guideline that includes updated dose recommendations for both EN and PN, the latter being called PN-daily recommended doses (PN-DR) [164] (Table 13). Increased requirements may occur in patients with

Table 13
ESPEN Recommendations for daily vitamins intakes, also including clinical deficiency presentation and the recommended method of measurement [164].

Vitamin	HPN & long-term PN (all values per day)	Clinical deficiency	Measurement
Lipo-soluble			
A Retinol [a]	800–1100 μg	night blindness, Bitot spots, xerophthalmia, increased susceptibility to infections	serum retinol
D3 Cholecalciferol	200 IU/5 μg	rickets, osteomalacia, increased susceptibility to infections	serum 25-hydroxyvitamin D (25(OH)D)
E α-tocopherol	9–10 mg	neurological symptoms and muscle weakness	plasma α-tocopherol
K2	150 μg, usually provided by lipid emulsions	bleeding, poor bone development, osteoporosis, and increased cardiovascular disease	combination of biomarkers and dietary intake
Water-soluble			
Vitamin B family	**At least**[b]:		
B1 Thiamine	2.5 mg	neurological, psychiatric and cardiovascular symptoms, lactic acidosis.	Red blood cell or whole blood thiamine diphosphate
B2 Riboflavin	3.6 mg	oral-buccal lesions, seborrheic dermatitis, ocular manifestations, anemia and marrow aplasia	glutathione reductase activity in red blood cells.
B3 Niacin	40 mg	Pellagra manifested as diarrhea, dermatitis and dementia	Blood or tissue nicotinamide adenine dinucleotide
B5 Pantothenic acid	15 mg	neurological and gastrointestinal symptoms	Blood pantothenic acid
B6 Pyridoxine	4 mg	oral-buccal lesions, seborrheic dermatitis, microcytic anemia, neurological symptoms	direct plasma pyridoxal 5-phosphate levels
B7 Biotin	60 μg	dermatitis, alopecia, ataxia	direct measure of blood and urine biotin which should be completed by the determination of biotinidinase activity
B9 Folic acid	400 μg	megaloblastic anemia, and pancytopenia, oral-buccal lesions, neuropsychiatric manifestations	folate levels in serum/plasma or red blood cells
B12 Cyanocobalamin	5 μg	megaloblastic anemia, and pancytopenia, oral-buccal lesions, neuropsychiatric manifestations	Combination of at least two biomarkers (holotranscobalamin, methylmalonic acid) is optimal, with serum cobalamin as a replacement of when measurement of this latter is unavailable
C Ascorbic acid	100–200 mg	Scurvy manifested as petechiae and easy bruising, spongy and purplish gums, dry skin, anemia, poor wound healing, myalgia and bone pain	total plasma vitamin C (sum ascorbic acid and dehydroascorbic acid) or ascorbic acid

[a] retinol and retinyl ester.
[b] For water-soluble vitamins, amounts recommended are minimum amounts, and more can usually be safely delivered.

ongoing increased losses such as gastrointestinal losses, or who are depleted before commencing PN, and in pregnancy.

6.2. Studies on vitamin status in patients on HPN

An early report of laboratory analyzes consisting of 63 individuals on HPN (40 with 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. [165]. A study on 27 patients on HPN reported low serum vitamin E and Se concentrations and normal values of the other micronutrients [166].

Because of parenteral multivitamin shortages firstly in the United States, and recently in Europe during the COVID-19 pandemic, attention has turned to the length of time a patient on HPN could be maintained with only oral vitamins or less frequently intravenous administration in the face of restricted parenteral products. A study of eight patients during the time of an early multivitamin shortage reported the effects of decreasing intravenous vitamin doses from daily to three times weekly [167]. Blood testing for vitamins, which was not done prior to the shortages, was subsequently done every six months. The reduced administration of multivitamins resulted in diminished ascorbic acid levels in seven of eight patients receiving TPN. Less often, low levels of retinoids, niacin, pyridoxine, and riboflavin were seen. A study of ten Brazilian adults with SBS 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. In none of these studies, clinical signs or symptoms of deficiencies were described. Thus, these appear to be actually subclinical findings. Furthermore, the number of patients included in the few reported studies were relatively small.

6.3. Lipid-soluble vitamins and HPN

Vitamin A deficiency is frequent in patients with malabsorption and SBS. Subclinical deficiency is more prevalent in patients on HPN [165,169], especially during shortage periods [167-168]. However, marked visual complications may occur among patients who are not compliant with adding multivitamin products to their HPN. Serum retinol concentrations decrease with increasing inflammation, interpretation can be improved by also measuring CRP and retinol binding protein [164].

Low serum levels of vitamin D have been frequently reported in different series of patients on HPN, even receiving IVS [165]. 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 [170]. A retrospective study of 25-hydroxyvitamin D levels measured over a minimum of six 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 [171]. In a recent retrospective study in Canada including 62 patients with mean HPN duration of 56 (6–323) months, most of them with SBS, patients were categorized based on serum vitamin D status as follows: 15 (24.2%) sufficient (>30 ng/mL), 31 (50%) insufficient (20–30 ng/mL) and 16 (25.8%) deficient (<20 ng/mL). Despite an average of 1891 IU/d orally and 181 IU/

d intravenously vitamin D, the mean vitamin D level was 25.6 ng/mL (insufficiency) and 26.2 ± 11.9 ng/mL in patients with the highest ten-year fracture risk [172]. In a retrospective cross-sectional study including 167 clinically stable outpatients in Denmark with intestinal insufficiency or IF, mild vitamin D deficiency (25–50 nmol/L) was found in 28% of patients with IF and 31% with intestinal insufficiency (II). Moderate to severe deficiency (<25 nmol/L) was found in 14% of patients with IF and 17% of II. Vitamin-D deficiency was identified as an independent risk factor of osteoporosis [172]. In a cross-sectional study of 63 patients on HPN in Slovenia, severe vitamin D deficiency (<30 nmol/L) was diagnosed in 15 patients (24%) and insufficient vitamin D levels (30–50 nmol/L) were found in 30 patients (48%). All patients received 200 IU of vitamin D2 (ergocalciferol) daily through PN. Additionally, patients with initial vitamin D levels below 70 nmol/L receive 2000–4000 IU of cholecalciferol (D3) daily in the form of oral drops [174]. Conventional enteral replacement of Vitamin D may not be sufficient for patients with CIF, and a in a recently published study a buccal Vitamin D preparation delivered as micro droplets provides an alternative, useful and cost-effective method of replacement [175]. Blood levels of vitamin D are significantly reduced in the context of inflammation [164].

In adult patients receiving HPN, high breath pentane (indicator for lipid peroxidation) was associated with low vitamin E plasma levels [176]. In a study in Denmark [169], vitamin E deficiency was identified in about 20% of 44 individuals on HPN, compared to 7% of a non-PN control group who had various degrees of malabsorption. 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. There is a variable amount of the different isomers of vitamin E (α, β, γ, δ-tocopherol) in fat emulsions depending on the lipid base (Olive-, Fish-, Soybean-oil), but α-tocopherol should always be added to ensure an adequate intake [164].

Patients on HPN because of SBS or severe distal small bowel disease often have a deficiency of Vitamin K, this have been observed in different series [166,177] and during shortage [168]. Dietary intake of vitamin K is one of the primary determinants of vitamin K status. The natural source of vitamin K in PN is phylloquinone contained in the lipid emulsion. Depending on the lipid source, the vitamin K content may range from a minimum of 6 μg up to 300 μg/100 g. Weekly intravenous supply of 250–500 μg phylloquinone from lipids is sufficient to both restore and maintain plasma phylloquinone within the normal range. Nevertheless, adult multivitamin preparations with vitamin K provide additionally 150 μg which not only cover the requirements of all patients, but also is more effective in maintaining the carboxylation status of noncoagulation Gla proteins [164].

6.4. Water-soluble vitamins and HPN

There have been no reports of thiamine deficiency in patients receiving HPN with regular supply at doses of more than 2.5 mg/d. However, there are several cases of severe deficiencies with lactic acidosis and even deaths, during shortage periods in patients on HPN [178-180]. ESPEN recommend that PN should provide at least 2.5 mg/d, but the requirement may be higher in malnourished patients with IF commencing PN who are at risk of refeeding syndrome [164]. They should receive supplementary doses for replenishment.

Riboflavin, niacin, and pyridoxine PN at doses of 3.6–5 mg/d, 40 mg/d, and 4 mg/d, respectively, are safe to prevent deficiencies [164]. Only subclinical deficiencies have been reported in three patients on HPN receiving three times a week instead of daily doses due to shortage [167]. Patients with chronic renal failure receiving HPN with multivitamins may develop elevated pyridoxine levels, which might result in neurologic sequelae (167].

Since the deficiency cases of the 1980s, biotin has been included as a standard in PN vitamin solutions, at doses of 60 μg/d [181-183]. Folate deficiency is frequent in patients with inflammatory bowel disease, due to proximal intestinal alterations and the effect of medications used [184-186]. Historical cases of acute folate deficiency were described in the 1970s when B9 administration had not yet become routine during PN [187].

Vitamin B12 is often deficient in those who have undergone a distal small bowel resection [188]. It may also occur in cases of intestinal bacterial overgrowth and in inflammatory bowel disease of the ileum [164]. Regular assessment of these vitamins is of prime importance as long as the disease remains active while on HPN.

Low levels of vitamin C without clinical symptoms have been frequently described in patients on PN [165], and especially during shortage periods [167,168]. Vitamin C plasma levels decline rapidly with progressive inflammation, making interpretation difficult. In a retrospective study of 186 patients on HPN 29% had plasma vitamin C concentrations below the normal minimal range, i.e., 25 μmol/L (5–24 μmol/L). None of the patients had a plasma vitamin C level under 5 μmol/L, and only 8.1% of the patients had a plasma vitamin C concentration below 11 μmol/L (definition of biological scurvy). Patients with a normal range of vitamin C received a mean of 284.6 ± 230.1 mg (125–1400 mg) of vitamin C per parenteral infusion. In the multivariate analysis, only CRP ($p = 0.001$) and intake of 125 mg of vitamin C ($p < 0.0001$) were independently negatively associated with vitamin C levels [189]. Ascorbic acid in parenteral multivitamin formulations varies between countries from 100 to 200 mg. In the United States, the requirements were increased from 100 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 [190]. This was shown in a prospective study where 24-h urine collections were done in 13 patients on HPN before and one 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 [190].

6.5. 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.

It is important that baseline vitamin levels are 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.

6.5.1. Recommendation 41 (recommendation #24 of the 2016 CIF GL)

In patients on HPN, clinical signs and symptoms as well as biochemical indexes of trace element deficiency or toxicity should be regularly evaluated.

Grade of recommendation GPP - Strong consensus 100% agreement.

6.5.2. Recommendation 42 (recommendation #25 of the 2016 CIF GL)

Baseline serum trace element concentrations should be measured, according to laboratory availability, at the onset of HPN and then at least once per year.

Grade of recommendation GPP - Strong consensus 96% agreement.

6.5.3. Recommendation 43 (recommendation #26 of the 2016 CIF GL)

Trace element doses in HPN can be adjusted as needed.

Grade of recommendation GPP - Strong consensus 92% agreement.

6.5.4. Recommendation 44 (recommendation #27 of the 2016 CIF GL)

The route of trace element supplementation can be selected according to the characteristics of the individual patient.

Grade of recommendation GPP - Strong consensus 96% agreement.

6.5.4.1. Commentary. Requirements for trace elements during illness and in patients on long-term PN are still poorly defined. There is insufficient knowledge about how disease and inflammation affect the metabolism of micronutrients or on the impact of differences in mode of delivery, bioavailability, and absorption as a result of medical nutritional therapy [164]. 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 [164].

The known essential trace elements are Cr, Cu, I, Fe, Mn, Mo, Se, and Zn. Since the first guideline for essential trace element preparations for parenteral use were published by the Nutrition Advisory Group of the American Medical Association (NAG-AMA) in 1979 [191], the daily doses recommended for Zn, Cu, Mn, Cr and Se in adults have been modified as new research information became available [162]. Both trace element deficiencies and toxicities have been reported in patients on HPN, the latter probably related to contamination in various PN components [192]. A study on autopsy tissues of eight patients who lived on PN for two to 21 years receiving the NAG-AMA 1979 formula, confirmed very high concentrations of Cu, Mn, and Cr [193].

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 μg/d of iodine to a basic adult PN formula and 1 mg of Fe if stability and compatibility issues can be resolved for the latter. A case can also be made for the potential addition of Mo, B and Si, depending on the amounts present as contaminants [162]. Also, they recommended that all the products should be labeled with a maximum allowable trace element level.

In 2012, ASPEN developed a position statement to address evidence-based data for each micronutrient on its use in parenteral administration and to provide recommendations for changes in the products available in the market [163]. Some pharmaceutical companies changed the composition of the multitrace sources to meet these recommendations. The recent ESPEN micronutrient guideline includes the updated dose recommendations of trace elements for both EN and PN, the latter being called PN-DR [164] (Table 14). Increased requirements may occur in patients with ongoing increased losses such as gastrointestinal losses, malnourished or who are depleted before commencing PN, and in pregnancy.

6.6. Studies on trace elements status in patients on HPN

The gap for implementation of guidelines was shown in a survey in Canada, in which the mean daily supplementation of Zn, Mn, Cu, and Se exceed published recommendations [194]. A study with 26 adult and adolescent HPN patients, showed that the majority of patients had high levels of serum Mn and Cr, 22% of patients had high levels of Cu, and the levels of Se and Zn were low in 38% and 10%, respectively, which made necessary to review the recommendations of trace elements in long-term PN [195]. High levels of Mn and low levels of Se have been also reported in a series of 68 patients on HPN in Europe, using multi-trace element

Table 14
ESPEN Recommendations for daily trace element intakes, also including clinical deficiency presentation or toxicity and the recommended method of measurement (all values per day) [164].

Trace element	HPN & long-term PN (all values per day)	Clinical deficiency or toxicity[a]	Measurement
Chromium	10–15 μg	peripheral neuropathy, weight loss, elevated plasma free fatty acids, and hyperglycemia	response of glucose tolerance test to Cr supplementation
Copper	0.3–0.5 mg	microcytic anemia, neutropenia, osteoporosis, hair de-pigmentation, and myeloneuropathy	blood Cu simultaneously with CRP determination
Fluoride	0–1 mg	Tooth caries	Blood Fl
Iodine	130 μg	Goiter, hypothyroidism, growth and mental retardation (children)	urinary 24 h I excretion, combined with assessment of thyroid function and size
Iron	1.1 mg	Microcytic anemia, queilitis	blood Fe, transferrin, transferrin saturation, ferritin, CRP, hepcidin, and evaluation of red blood cell morphology
Manganese	55 μg	Mn toxicity is a greater concern than deficiency. Mn toxicity produces neurotoxicity and liver complications	Whole blood Mn, or red blood cells. Brain MRI can confirm the diagnosis, showing high intensity signals in globus pallidus being correlated with elevated Mn levels
Molybdenum	19–25 μg	nausea, rapid breathing and heart rate, vision problems, coma	Mo measurement is rarely required, and it should only be assessed in case of suspected Mo deficiency.
Selenium	60–100 μg	cardiac and skeletal muscle myopathy, and skin and nail effects	Blood Se determines status, but ideally the plasma Glutathione peroxidase 3 (GPX-3) shall be determined to reflect functional status
Zinc	3–5 mg	alopecia, skin rash of face, groins, hands, and feet, growth retardation, delayed sexual development and bone maturation, impaired wound healing and immune function, diarrhea, and blunting of taste and smell	Plasma Zn with simultaneous determination of CRP

Abbreviations: CRP, c-reactive protein; HPN, home parenteral nutrition; PN, parenteral nutrition.

[a] The ESPEN Micronutrient Guideline recommends against regular monitoring of chromium status; however, it can be required when there is clinical suspicion of deficiency or toxicity.

supplementation [196]. In a retrospective study that included 73 patients with CIF enrolled in a tertiary home PN center and receiving long-term PN with systematic multi-trace element supplementation, the prevalence of low serum trace element levels was 21.9%, 13.9% and 21.1% for serum Se, Cu and Zn, respectively. This suggests that frequent trace element dosage in this population as well as individually tailored supplementation may be beneficial [197]. These trace elements deficiencies may further increase during shortage periods [198].

6.7. Trace elements and HPN

Practical information on parenteral trace element use can be gleaned from case reports, some retrospective studies, and very few clinical trials [192].

From 1979, numerous case reports described Se deficiency in adults and children who used PN lacking in Se for periods ranging from months to years [192]. A nationwide shortage of intravenous Se occurred in April 2011 in the US and resulted in adults, children and infants receiving very low Se supply [199]. In a retrospective study that included 73 patients on HPN with systematic multi-trace element supplementations, Se deficiency exposed to a greater risk of serious infection (HR 2.65, 95% CI 1.01–6.97) [197]. In contrast, the literature contains no report of Se toxicity in patients using PN. Parenteral doses of 60–100 μg/d Se are sufficient for most adults yet do not maintain ideal levels in all patients. Simultaneous determination of CRP and albumin is required for interpretation of Se levels, as plasma Se levels fall proportionally to the level of inflammation [164].

Balance studies indicate that Cu requirements in TPN amount to 0.3–0.5 mg/d for adults [163,200]. 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 [192]. Cu contamination should be limited to less than 0.1 mg/d total in a typical adult PN formulation [163]. Blaszyk et al. performed liver biopsies on 28 long-term PN patients with cholestasis, and in eight of the 28 patients, hepatic Cu was >250 μg/g (in the range for Wilson's disease) [201]. 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. A rare cause of Cu deficiency in a patient on HPN using Zn in denture adhesive has been published [202]. Different from most micronutrients, Cu concentrations increase in the context of an inflammatory response since ceruloplasmin is a positive acute phase reactant [164,203].

Although current parenteral recommendation of Cr in adults is 10–15 μg [163], based on oral absorption in healthy individuals, the parenteral requirements may be as low as 0.14–0.87 μg/d [204]. However, the precise requirements during PN when there is a high intake of glucose provided over a prolonged period are not known. 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 [192,204]. In humans, three 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 [193]. Even in patients on short-term TPN, 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 [205]. Cr contaminants in PN solutions can increase the amount delivered by 10–100%. In autopsy tissues of patients on long-term PN, Cr levels were 10-100-fold higher than normal concentrations in heart, skeletal muscle, liver, and kidney [193]. However, in adults there are no reported cases of Cr toxicity in patients on long-term PN or in patients with hip protheses with very high levels of Cr, suggesting that these high Cr concentrations are not toxic. Cr toxicity may be more of a concern in pediatric patients, and an inverse correlation between serum Cr levels and glomerular filtration rates in PN-dependent children was found [206].

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 and also during shortage periods [207,208]. 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/d. Patients with ECF, diarrhea, and intestinal drainage may require up to 12–17 mg of Zn per liter of lost fluid [163]. The ESPEN Micronutrient Guideline recommends that PN should provide 3–5 mg Zn intravenously per day in patients without abnormal losses, and up to 12 mg per day in patients with gastrointestinal losses (fistulas, stomas, and diarrhea) [164].

Mn toxicity is a greater concern than deficiency. 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 [209]. 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 [192]. High levels of Mn in brain were detected in a deceased woman after long-term PN involving Mn supplementation [210] and in the autopsies of eight people on long-term HPN [193]. In a prospective study, patients on HPN were administered TPN solutions providing scaling doses from 0 to 20 μmol/d according to an on-off design. The optimal dose was 1 μmol/d for adults according to the levels of Mn in whole blood and magnetic resonance imaging (MRI) [211]. In a sample of 16 patients on long-term PN with a mean daily Mn supplementation of 400 ± 53 μg/d, 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) [212]. Also, a survey of 40 Australasian hospitals with data on 108 patients on HPN revealed that Mn doses were five to six times over current daily requirements [213]. In a longitudinal study including 15 patients on HPN, Mn levels in blood and brain (in MRI) significantly decreased after one year of Mn withdrawal in the PN [214]. In a recently published retrospective study including 100 patients on HPN incidence of elevated whole-blood Mn concentrations decreased from 60% to 30% upon discontinued use of a multi-trace element solution. Elevated levels remain a concern despite patients being prescribed “Mn-free” PN. Patients receive this trace element in amounts adequate to meet requirements through contamination and dietary intake alone, suggesting additional parenteral supplementation of Mn is not required [215].

The ESPEN Micronutrient Guideline recommends that PN shall provide 55 μg Mn per day [164]. 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 [163,216]. Mn contamination should be limited to less than 40 μg/d total in a typical adult PN formula [163].

For patients on PN, the estimated requirement for maintenance of Fe status is 1 mg/d for adult men and post-menopausal women, and about 2 mg/day for pre-menopausal women [217]. In Europe, the trace element products used in PN have been providing for many years elemental Fe without complications. However, the preparations available in the US do not contain Fe because of concerns, not felt in Europe, regarding emulsion stability, or infection enhancing risk [163]. Since Fe deficiency is one of the most common complications of long term PN (affecting 30–50% patients on HPN in different series [218,219], it is strongly recommended that regular Fe provision is maintained by use of a preparation that provides Fe as part of the PN regimen [217]. The ESPEN Micronutrient Guideline recommends that PN shall provide at least 1 mg/d of elemental Fe, or an equivalent amount at periodic intervals by separate infusion [164].

Daily I requirements in adults receiving PN are estimated to be 70–150 μg, but many PN formulations do not contain I at all or include it in low doses [220-222]. If chlorhexidine replaces I-containing disinfectants for catheter care, I deficiency may occur during long-term HPN, and periodic testing of thyroid functions may be prudent. This is especially important during pregnancy, in preterm and newborn in which I is necessary for central nervous system development [220]. Cases of hypothyroidism in adults dependent upon TPN are rare in the literature [223]. However, there are a number of cases reported in children. One prospective study examining the urinary I concentration of children from the onset of TPN found there to be a significant decrease in urinary I levels as time progressed [224]. There is also some evidence that adults with CIF on long-term HPN may be at risk of I deficiency [225]. The ESPEN Micronutrient Guideline recommends that PN shall provide the standard dose of 130 μg/d [164].

Although Mo is an essential trace element, only one case of Mo deficiency with long-term PN has been reported in the literature, probably because it is present as a contaminant in PN [192]. The ESPEN Micronutrient Guideline recommends that PN should provide 19–25 μg Mo per day [164].

Fl is not an essential element but amounts provided by contamination may be beneficial for bone strength. In patients on HPN for CIF (short bowel), high blood fluoride values have been objectivated in a series of 31 patients who developed osteoporosis and were explained by high Fl intakes from drinking water [226]. For PN, the need for adding Fl is debated, especially in the USA. However, Fl has been supplied for over 40 years as part of standard multi-element mixtures in European products at a dose of 0.95 mg without any side effects and may be continued in PN with the potential for beneficial effects on bones and teeth [164].

6.8. Parenteral trace elements products

The choices of trace element products vary from country to country, but in many countries only multi-trace 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.

6.9. Micronutrient monitoring: existing guidelines

There are recommendations for monitoring of vitamins and trace elements during HPN from different societies mostly based on expert opinion, since there is no good scientific evidence [2,163,227-230]. It is important to measure the micronutrient status at starting HPN, as some patients may need replenishment doses of some micronutrients because of malnutrition and refeeding risk.

In patients on long-term HPN, the ESPEN guideline recommends that clinical signs and symptoms as well as biochemical indexes of vitamin and trace metal deficiency or toxicity should be evaluated at least once per year (Grade of recommendation GPP, Strong consensus (95.7% agreement)). Serum ferritin and Fe should be evaluated every three to six months; serum folate, vitamins B12, A, E, 25-OH Vitamin D, Zn, Cu and Se every six to twelve months, and serum Mn yearly [2]. In special conditions, such as cholestasis or high gastrointestinal losses, these measurements can be done more frequently [164]. More frequent monitoring may be required during shortage periods.

6.10. How should intravenous micronutrient vial shortage be managed in patients on HPN for CIF?

6.10.1. Recommendation 45

In case of intravenous micronutrient shortage, the intravenous supplementation with multivitamin and multi-trace element vials should be prioritized for patients on exclusive/total HPN.

Grade of recommendation GPP- Strong consensus 100% agreement.

6.10.2. Recommendation 46

In patients on exclusive/total HPN, when the micronutrient shortage doesn't allow the daily IVS with multivitamin and multi-trace element vials, the micronutrients requirements should be met by single micronutrient supplementation through any other available route in the individual patient.

Grade of recommendation GPP- Strong consensus 100% agreement.

6.10.3. Recommendation 47

In patients on supplemental/partial PN, the micronutrient supplementation through sublingual, oral, enteral, intramuscular and subcutaneous route should be maximized.

Grade of recommendation GPP- Strong consensus 96% agreement.

6.10.4. Recommendation 48

During period of intravenous micronutrient vial shortage, a more frequent monitoring of serum micronutrient concentrations may be required to prevent micronutrient deficiency.

Grade of recommendation GPP - Strong consensus 96% agreement.

6.10.5. Recommendation 49

During period of intravenous micronutrient vial shortage, pediatric multivitamin and multi-trace element vials shall not be used for adult patients on HPN, if there is a risk of shortage of pediatric vials as well.

Grade of recommendation GPP - Strong consensus 93% agreement.

6.10.5.1. Commentary. In recent years, many countries have been faced with increasingly recurring shortages of intravenous vitamins and trace elements [231-233].

The COVID-19 pandemic further worsened the risk of shortage, because of the conversion of production chains, especially for intravenous multivitamins solutions, towards SARS-CoV2-vaccine. In 2021, ASPEN provided further considerations to assist clinicians in coping with PN vitamin and trace elements shortages [234].

The British Association for Parenteral and Enteral Nutrition (BAPEN) has developed similar recommendations [235].

After publishing the guideline on micronutrients [164], also ESPEN devised specific recommendations to deal with intravenous multivitamin and multi-trace element solutions for acute, prolonged acute and chronic IF [236]. The recommendations for CIF are reported in Table 15.

6.10.6. Recommendation 50 (recommendation #28 of the 2016 CIF GL)

The routine addition of individual amino acids (glutamine, cysteine, taurine) in the parenteral formula to decrease complications in adults on HPN cannot be recommended.

Grade of recommendation 0 - Strong consensus 100% agreement.

6.10.6.1. Commentary. Commercial amino acid formulations contain varying amounts of nonessential amino acids that may become conditionally essential under certain circumstances. Since 2015, no new data have been published to change this recommendation.

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/d in adults appears to be safe [237]. Very little information is available on the efficacy of glutamine-supplemented PN in home patients. In one study, five patients received glutamine at a dose of 0.285 g/kg for four weeks in their PN, and, in three out of five patients, glutamine administration was stopped because of elevations in liver enzymes [238]. In a randomized, controlled, 12-month cross-over study, 22 HPN patients received six months of PN containing glycyl-glutamine during the first or second six-month study period (0.14–0.15 g/kg/d dipeptide, 10 g glutamine). No differences were observed between study periods in infectious complications, nutritional status, intestinal permeability, plasma glutamine concentrations, or QoL [239].

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 [240,241]. The supplementation of taurine in adults on long-term HPN (10 mg/kg/d) normalizes plasma and blood cell taurine levels [242]. In a pilot study of adults on HPN for SBS, 32 patients were studied retrospectively and ten 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 [243].

7. Chapter 5 - Short bowel syndrome

7.1. What are the definitions and the criteria for the diagnosis, classification and reporting of short bowel syndrome?

7.1.1. Statement 10

In adults, SBS is defined as the clinical feature associated with a residual small bowel in continuity shorter than 200 cm.

Table 15
ESPEN recommendation do deal with intravenous multivitamin and multi-trace shortage in patients with chronic intestinal failure [236].

	Multivitamin Shortage	Multi-trace element shortage
Exclusive (total) PN with no oral/enteral intake:	One multivitamin product in each PN bag • Alternatively, administer individual parenteral vitamin entities with suggested daily IV doses of thiamine 6 mg, folate 0.6 mg, ascorbic acid 200 mg, and pyridoxine 6 mg, unless deficiency not suspected or otherwise clinically indicated. • IV vitamin K dosing is 0.5–1 mg/d or 5–10 mg per week. • Administer cyanocobalamin (B12) 100–1000 μg intramuscular or deep subcutaneous at least once monthly, 500 μg intranasal once weekly or 1000 μg sublingual once daily.	One multi-trace element product in each PN bag
Supplemental PN with oral/enteral intake:	One multivitamin in each bag and oral multivitamin on all non-PN days	One multi-trace element in each bag and oral TE provided on the day off of IV supplementation along with monitoring of nutrition status (Zn, Se, Cu).
When all options to maintain stock levels of adult IV multivitamin and multi-trace element products have been exhausted	Ration adult micronutrient infusions (e.g. give 2–3 times per week instead of daily and supplement with oral/enteral and/or intramuscular preparations.	Ration IV multi-trace element products in PN by reducing daily dose by 50% or giving one multi-trace element product infusion three times per week. Alternatively, consider administration of individual parenteral TE entities (e.g. Zn 5 mg per day and Se 100 g per day).
Monitoring of vitamin and TE status	Increased frequency is recommended depending on clinical status. Assessment should be performed on a monthly basis instead of 3–6 months (e.g. vitamin A, E, D, Folate, B12, B1, as well as prothrombin level).	Increased frequency is recommended depending on clinical status. Assessment of TE (Zn, Cu, Se) should be performed on a monthly basis instead of 3–6 months.

Abbreviations: IV, intravenous; PN, parenteral nutrition; TE, trace elements.

Strong consensus 92% agreement.

7.1.2. Statement 11

The presence of clinical feature of SBS notwithstanding a residual small-bowel length >200 cm is defined "functional SBS".

Strong consensus 100% agreement.

7.1.3. Statement 12

On the basis of the anatomy of the residual intestine in continuity, SBS is classified as SBS with end small bowel ostomy (or SBS type 1), SBS with jejuno-colic anastomosis (or SBS type 2) and SBS with jejunoileal anastomosis with intact colon and the presence of the ileocecal valve (or SBS type 3).

Strong consensus 96% agreement.

7.1.3.1. Commentary. In adults, normal small intestinal length, measured from the duodenojejunal flexure (ligament of Treitz) at autopsy or surgery, varies from about 275 to 850 cm [244,245]. A short bowel may be the result of extensive surgical resections or of congenital diseases of the small intestine [5,246,247]. The term SBS describes a "clinical condition associated to having less than 200 cm of residual small bowel in continuity, measured from the ligament of Treitz, with or without colon" [246,247]. This definition of SBS has been included in the International Classification of Diseases 11th Revision (ICD-11) of the WHO (DA96.04 Short bowel syndrome) [248]. The clinical feature of SBS is characterized by malabsorption, diarrhea, fatty stools, malnutrition, and dehydration [246,247]. SBS if the most frequent mechanism of CIF in adults [12]. Mesenteric ischemia, Crohn's disease, radiation enteritis, post-surgical intra-abdominal adhesions and post-operative complications are the most frequent underling diseases of SBS [249]. An SBS-CIF has been reported more frequent in women (60.7%) than men [249], possibly because women start with a shorter length of small intestine than men [244,245].

In some patients, SBS can occur despite a post-resection small intestine length >200 cm due to impairment of remnant bowel function, such accelerated motility or mucosal disease, which diminish the absorptive capacity of the bowel beyond what expected on the basis of the remnant small bowel [12]. To describe this condition the term "functional SBS" has been devised [247,249,250].

The anatomical classification of SBS categorizes three types, based on the anatomy of the remnant bowel in continuity: *SBS-type 1*) end-jejunostomy/ileostomy; *SBS-type 2*) jejuno-colonic anastomosis, where the remnant jejunum is in continuity with part of the colon, most frequently the left colon; *SBS type 3*) jejuno-ileo-colonic anastomosis with ileo-cecal valve and the intact colon in continuity [246,247,251]. The ESPEN survey on SBS-CIF in adults, reported that SBS-type 1, SBS-type 2 and SBS-type 3 accounted for 60.0%, 30.9% and 9.1% of total cases, respectively [249]. According to the pathophysiological consequences, the SBS can be categorizes into two groups, SBS with colon in continuity (SBS-type 2 or SBS-type 3) and SBS without colon in continuity (SBS-type 1) [246,247,250,252]. In adults, the likelihood of SBS-CIF reversibility with weaning off HPN, due to spontaneous adaptation and/or induced by diet, conventional drugs and non-transplant surgery has been shown to be around 20%, 40% and 80% in SBS-type 1, SBS-type 2 and SBS-type 3, respectively [24]. If the remnant bowel is healthy, the probability of SBS-CIF reversibility is higher when the length of the remnant small bowel in continuity is > 100 cm in SBS-type 1, >65 cm of small bowel in SBS-type 2 (provided that there is >50% of colon in continuity) and >30 cm in SBS-type 3 [24,251,252]. The percentage of the remnant colon is measured according to Cummings' criteria [253].

7.2. Which are the criteria for the appropriate oral/enteral nutrition for patients with short bowel syndrome?

7.2.1. Recommendation 51 (recommendation #30 of the 2016 CIF GL)

SBS patients should have dietary counselling 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 recommendation GPP – Strong consensus 100% agreement.

7.2.2. Recommendation 52 (recommendation #31 of the 2016 CIF GL)

The diet of SBS patients with a preserved colon in continuity can be high in complex carbohydrates, low in mono- and disaccharides and low in fat.

Grade of recommendation 0 – Strong consensus 97% agreement.

7.2.3. Recommendation 53 (recommendation #32 of the 2016 CIF GL)

The diet of SBS patients with a preserved colon in continuity should have a high content MCT, that confers a marginal benefit on overall energy absorption compared to a diet containing regular LCT.

Grade of recommendation B – Strong consensus 100% agreement.

7.2.4. Recommendation 54 (recommendation #31 of the 2016 CIF GL)

The diet of SBS patients without a preserved colon in continuity can have any fat:carbohydrate ratio, with a low mono- and disaccharides content.

Grade of recommendation 0 – Strong consensus 100% agreement.

7.2.5. Recommendation 55 (recommendation #33 of the 2016 CIF GL)

SBS patients consuming a low fat diet or where the LCT have been replaced by MCT should be monitored for the potential deficiency in EFA and fat-soluble vitamins.

Grade of recommendation GPP – Strong consensus 96% agreement.

7.2.6. Recommendation 56 (recommendation #34 of the 2016 CIF GL)

In patients with SBS, soluble fiber (e.g. pectin) may not be added to the diet to enhance overall intestinal absorption.

Grade of recommendation 0 – Strong consensus 92% agreement.

7.2.7. Recommendation 57 (recommendation #35 of the 2016 CIF GL)

Lactose may 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 recommendation 0 – Strong consensus 96% agreement.

7.2.8. Recommendation 58 (recommendation #36 of the 2016 CIF GL)

Isotonic oral nutritional supplements can be added to the diet of SBS patients at risk of malnutrition.

Grade of recommendation GPP – Strong consensus 100% agreement.

7.2.8.1. Commentary. The recommendations of the 2016 guideline on this issue have been confirmed, because no new data were published. Overall, the two criteria driving the oral feeding are the pathophysiological consequences of the presence or absence of the colon in continuity (as well as the length of remnant colon) and, in SBS type 1, the length of the remnant small bowel [246,247,250,252,254-256]. The bomb calorimetry method as gold standard to assess intestinal absorption has also been confirmed [257] Basically, SBS patients should consume regular whole food diets, and they are to be encouraged to compensate for malabsorption by hyperphagia [258-260]. 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 [261]. Compared to a high fat, low carbohydrate diet, a reduction in fecal energy excretion of approximately 2.0 MJ/d (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/d (1003 kcal) in these SBS patients [262]. 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 [252] may be seen in SBS patients with a preserved colon in relation to the intake of easy fermentable carbohydrates. 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 [261]. Another drawback of low-fat diets is the lower provision of EFA [97] and fat-soluble vitamins [104]. However, a low-fat diet may benefit the absorption of calcium, magnesium and Zn [263]. In patients with jejuno- or ileostomies, who consume a 10 MJ/d (2388 kcal) diet, the weight of the high carbohydrate, low fat diet was approximately 700 g/d higher than the iso-energetic, high fat diet and tended to increase stomal wet weight losses in the same magnitude [261]. Thus, in these patients, significantly higher fat intakes are possible but at the expense of an increased loss of divalent cations: calcium, magnesium, Zn and Cu. Altering the ratio between saturated and poly-unsaturated fatty acids had no consistent effect of divalent cation losses [264].

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 MCT fatty acids may share the ability of SCFA 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/d in SBS-patients with a preserved colon. No benefits in absolute energy absorption were detected in jejuno- or ileostomy patients [265]. 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 diarrhea. 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 with a preserved colon on the borderline of needing IVS.

In SBS type 1, the balance studies showed that oral food can consist of any fat:carbohydrate ratio, provided that it has a low mono- and disaccharides content [262,264-266].

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, $p = 0.15$); fecal wet weight (1582 vs 1689 g/d, $p = 1.00$) and urine production (1615 vs. 1610 mL/d, $p = 1.00$) remained constant [267]. 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 [268]. 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/d of lactose was well tolerated in patients with SBS but should be carefully titrated in case of previous intolerance [269]. In addition to restricting dietary choices, avoiding lactose potentially could diminish calcium intake and aggravate the development of osteoporosis commonly seen in these patients.

7.2.9. Recommendation 59 (recommendation #37 of the 2016 CIF GL)

The EN in combination with oral feeding can be prescribed in patients with CIF in whom the expected gain with EN could allow to wean off HPN.

Grade of recommendation GPP – Strong consensus 100% agreement.

7.2.10. Recommendation 60 (recommendation #38 of the 2016 CIF GL)

In patients with CIF treated with EN, the use of polymeric isotonic enteral diets may be the first choice.

Grade of recommendation 0 – Strong consensus 96% agreement.

7.2.11. Recommendation 61 (recommendation #39 of the 2016 CIF GL)

The addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process cannot be recommended.

Grade of recommendation 0 – Strong consensus 96% agreement.

7.2.11.1. Commentary. 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 EN 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 EN increases the absolute intestinal absorption compared to voluntary oral intake and even accelerates adaptation in the immediate post-operative 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 [260,270], 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 [270]. 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 EN, studies suggest that elemental and polymeric diets are similar in terms of nutrient absorption and fluid and electrolyte loss [266,271]. 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 fecal excretions of energy, wet weight, and electrolytes remained constant [272]. 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 [273].

A study in 15 adults with SBS (three to 130 months from last surgery, four without a colon in continuity) illustrated that continuous EN for seven days, alone or in combination with oral feeding, increased intestinal macronutrient absorption compared with oral feeding alone [274]. An energy gain of approximately 400 kcal/d was achieved by increasing the oral energy intake by approximately 4.2 MJ/d (1003 kcal). Thus, this treatment could be recommended in patients on the borderline with a low-level of HPN (i.e. PN and/or intravenous fluids and electrolytes) dependence and in whom the expected gain with EN could allow them to wean off HPN. Results on changes in abdominal symptoms, patient preferences, and fecal wet excretions were not reported in the study. This study also did not examine longer-term EN: many patients find it difficult to comply with long-term nasogastric feeding, although some patients only require nighttime drip.

Animal studies have suggested positive effects of glutamine on intestinal absorption and morphology. However, in an eight-week, randomized, placebo-controlled, cross-over study in eight SBS patients, no effects were found on bowel morphology, transit, D-xylose absorption, or stool losses [275]. 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 [276]. However, in children, cases of bacteremia with the ingested probiotic bacteria have been described in SBS patients depending on PN [277,278].

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 [279]. There are no data about supplementation with probiotics in adults with SBS.

7.2.12. Recommendation 62 (recommendation #40 of the 2016 CIF GL)

Patients with type 1 SBS (end jejunostomy) can use salt liberally and restrict the administration of oral fluids in relation to meals.

Grade of recommendation GPP – Strong consensus 96% agreement.

7.2.13. Recommendation 63 (recommendation #41 of the 2016 CIF GL)

SBS patients who have borderline dehydration or sodium depletion can use an isotonic high sodium oral rehydration solution to replace stoma sodium losses.

Grade of recommendation 0 - Strong consensus 100% agreement.

7.2.14. Recommendation 64 (recommendation #42 of the 2016 CIF GL)

SBS patients with net-secretion and a high output jejunostomy shall limit 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 the stoma output.

Grade of recommendation GPP – Strong consensus 96% agreement.

7.2.14.1. Commentary. The aim of providing SBS patients with ORS is to optimize 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 centers have the facilities, setup, analyzes, 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 [129].

In adult SBS patients, wet weight absorption (the difference between the weight of the oral intake minus the weight of fecal excretions) below 1.41 kg/d, sodium absorption of 50–100 mmol/d, urine production below 800–900 mL/d (normal >840 mL/d), and urine sodium excretion below 35 mmol/d (normal >35 mmol/d) are suggestive of inadequate intestinal water and sodium absorption [260,280,281]. 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 [282]. 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 [258-260]. 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 [132]. Some of these patients even experience losses of water and sodium when they take nothing by mouth ("secretors") [132]. 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 [283]. In a study of 14 patients with a jejunostomy and one patient with a jejuno-rectal anastomosis (jejunal lengths<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) [132]. Similar findings were observed in the study by Jeppesen et al. [260]. 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 [284], but its use has now become more widespread to include any acute diarrheal 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 [285]. 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 amino acids (solvent drag), whereas water movements are passive [286]. 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 [130,287]. Thus, jejunal sodium and water absorption may be dependent on the sodium and glucose concentration of oral intakes as well as the osmolarity [284,288].

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 [289]. 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, ORS are rarely indicated in SBS patients with a preserved colon [290].

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 [129,290-295]. In order to halt this, the general advice has been that the patients should restrict excessive habitual beverages and instead drink ORS [129]. 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 [129,291,294–305].

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 IF, 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 ten SBS patients out of whom two received supplemental IVS [306]. Therefore, the advice to restrict fluid intake at meal time cannot be considered a general rule for patients with SBS.

7.3. Which are the drug options for the treatment of short bowel syndrome?

7.3.1. Recommendation 65 (recommendation #43 of the 2016 CIF GL)

H_2-receptor antagonists or PPI may be used to reduce fecal wet weight and sodium excretion, especially during the first six months after surgery, mainly in those SBS patients with a fecal output exceeding 2 L/d.

Grade of recommendation 0 – Strong consensus 100% agreement.

7.3.2. Recommendation 66 (recommendation #44 of the 2016 CIF GL)

In the individual patient, H_2-receptor antagonists or PPI can also be used to reduce fecal wet weight and sodium excretion in the long-term.

Grade of recommendation GPP – Strong consensus 95% agreement.

7.3.3. Recommendation 67 (recommendation #45 of the 2016 CIF GL)

Especially in the short-term after intestinal resection, octreotide can be used for patients with high-output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments.

Grade of recommendation GPP – Strong consensus 91% agreement.

7.3.4. Recommendation 68 (recommendation #46 of the 2016 CIF GL)

Patients treated with octreotide should be carefully monitored to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects, fluid retention and potential negative interference with the process of intestinal adaptation during long-term use.

Grade of recommendation GPP– Strong consensus 91% agreement.

7.3.4.1. Commentary. Enterectomy is associated with gastric hypergastrinemia and hypersecretion [307]. The etiology 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 fecal losses. In addition, the associated hyperacidity may denature pancreatic enzymes and compromise bile salt function [308], which may further aggravate conditions for absorption.

The main treatments for gastric hypersecretion are H_2-receptor antagonists and PPI, 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 IF patients: in case of lack of effect of tablets and capsules, soluble forms or intravenous administration should be considered. H_2-receptor antagonists and PPIs have also been suggested to delay gastric emptying rates, which possibly also could benefit intestinal absorption in SBS patients [309].

Several clinical case series [310-313] as well as double-blind placebo-controlled studies [314,315] have demonstrated their effect on decreasing ostomy output and fecal excretions in patients with SBS. On average, the reduction in fecal wet weights and sodium excretions are in the range of 20–25%, whereas the effects on energy, macronutrients, 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 fecal wet weight excretions exceeding 2 kg/d. 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 diarrheal conditions. It has been suggested to decrease gastric [316], biliary, and pancreatic secretions [317-319]. In addition, it may inhibit secretagogue-induced water and electrolyte secretion in the jejunum and the colon [320], stimulate sodium and chloride absorption in the ileum [321], decrease intestinal motility [322], and inhibit the release of hormones that may contribute to diarrhea (e.g. Vasoactive intestinal peptide (VIP), Glucose-dependent insulinotropic polypeptide (GIP), gastrin) [323]. Although it has beneficial effects on intestinal absorption by reducing fecal wet weight losses in patients with diarrhea, 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 [324] and it may reduce the use of amino acids for splanchnic protein synthesis thereby interfering with the physiological process of adaptation to intestinal resection [325,326].

Somatostatin and the somatostatin analog octreotide have been shown to reduce ileostomy diarrhea and large volume jejunostomy output in several case series [326-335] and a single placebo-controlled trial [336]. No significant changes in the net absorption of potassium, calcium, magnesium, phosphate, Zn, nitrogen, or fat were seen in relation to these studies. The largest absolute effects are seen in patients with fecal wet weight excretions exceeding 2 kg/d. 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 postsynaptic enterocyte α2-adrenoreceptors [337,338]. 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 [339].

7.3.5. Recommendation 69 (recommendation #47 of the 2016 CIF GL)

Oral loperamide shall be used to reduce wet weight and sodium fecal excretion in SBS patients with an ostomy.

Grade of recommendation A - Strong consensus 100% agreement.

7.3.6. Recommendation 70 (recommendation #48 of the 2016 CIF GL)

Loperamide shall be preferred to opiate drugs, such as codeine phosphate or opium, because it is not addictive or sedative.

Grade of recommendation A - Strong consensus 100% agreement.

7.3.7. Recommendation 71 (recommendation #49 of the 2016 CIF GL)

In SBS patients with a high ostomy output, the use of loperamide may be guided by objective measurements of its effect.

Grade of recommendation 0 - Strong consensus 100% agreement.

7.3.7.1. Commentary. The use of anti-diarrheal 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 diarrhea. Eventually, this can also reduce the need for IVS. Apart from lessening of malabsorption and salt and water depletion, anti-diarrheals can also facilitate ostomy appliances, prevent accidental soiling and skin excoriation, and ease ostomy care. However, the evidence for the use of anti-diarrheals in SBS patients is mainly obtained from patients with normal intestinal anatomy but with diarrhea due to other causes. A few studies have also been performed in patients with an ileostomy or with minimal ileal resection [340]. 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-diarrheals 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-diarrheals (mainly codeine, diphenoxylate, and opium) may have central nervous system side effects, e.g. sedation, and they may have potential for addiction [341]. 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 centers.

Loperamide is chemically related to, but more potent, lacks central opiate effects, is more gut-specific, and has longer duration of action than diphenoxylate [342]. Loperamide is believed to inhibit the peristaltic activity of the small intestine and thereby prolong intestinal transit time [343]. 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 [344]. In general, loperamide, 4 mg given three to four 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 diarrhea of less than 1.5 kg/d [342,345-347]. In general, treatment reduced fecal 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/d in the patients studied [348,349]. Whether similar relative effects are obtained in patients with more pronounced diarrhea still remains to be investigated. The main side effects in relation to anti-motility drugs were nausea, vomiting, abdominal pain, and distension.

7.3.8. Recommendation 72 (recommendation #50 of the 2016 CIF GL)

SBS patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who are suspected with bacterial overgrowth, can benefit from occasional antibiotic treatment.

Grade of recommendation GPP - Strong consensus 97% agreement.

7.3.9. Recommendation 73 (recommendation #51 of the 2016 CIF GL)

The routine use of antibiotics in SBS patients with a preserved colon cannot be recommended, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to SCFA, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation.

Grade of recommendation GPP - Strong consensus 96% agreement.

7.3.9.1. Commentary. Very little is known about the presence of small bowel bacterial overgrowth in patients with SBS [350-355]. 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.

Which are the indication and the criteria for the selection of patients candidate for treatment with intestinal growth factors, as well as the criteria for treatment monitoring?

7.3.10. Recommendation 74

In SBS-IF patients, intestinal growth factors should be considered in an SBS patient requiring PN continuation, if that patient is stable after a period of post-surgery intestinal adaptation, which is usually the case twelve to 24 months after the last intestinal resection and in the absence of contraindications.

Grade of recommendation B - Strong consensus 100% agreement.

7.3.10.1. Commentary. In patients with SBS, post-surgery intestinal adaptation is a spontaneous process resulting in a more efficient absorption of nutrients per unit length of the remnant bowel. It is promoted by the presence of nutrients in the gut lumen, pancreatic and biliary secretions, gut hormones produced by the endocrine L-cells of the intestinal mucosa and changes in intestinal microbiota. The results are structural and functional changes represented by hyperplasia of the intestinal mucosa, slowing of the gastrointestinal transit, and increased SCFA production by colonic microbiota. This process appears to be absent or impaired in in SBS with end-jejunostomy (type 1), because of the reduced/absent secretion of gastrointestinal hormones. In some patients, an adaptive hyperphagia also takes place. The intestinal adaptation process progresses with time, reaching the full development within one, two and three years after surgery in SBS-type 1, SBS-type 2 and SBS-type 3, respectively [246,247,252].

In adults, those time frame, spontaneous adaptation, diet counselling, conventional anti-secretory and anti-diarrheal drugs and surgical procedures aimed to increase the bowel length has been shown to allow SBS-CIF reversibility with weaning off HPN, in 20% of SBS-type 1, in 40% of SBS-type 2 and in 80% of SBS-type 3 [24,251]. The probability of HPN weaning off depends also on the length of the remnant small bowel in continuity, provided it is healthy. The higher probability has been reported with >100 cm in SBS-type 1, >65 cm with >50% of colon in continuity in SBS-type 2, and >30 cm of small bowel in SBS-type 3 [24,251].

However, over the past decades, it has become increasingly clear that mucosal nerve endings and endocrine cells within the gastrointestinal tract as well as various systemic hormones and growth factors, regulate and highly coordinate the processes of nutrient assimilation [356].

These observations have promoted the use of hormonal factors in the intestinal rehabilitation programs for SBS-CIF, with the aim to enhance the function of the remnant bowel in addition to what obtained by spontaneous post-surgical adaptation and conventional medical and surgical care, described by the term “pro-adaptive treatment” [357,358].

Clinical research focused on those hormones with an intestinotrophic effect, thereby stimulating intestinal mucosal growth, for which the term intestinal growth factor is currently used. At this time, only two molecules have been approved for SBS patients, the human growth hormone (hGH) somatotropin (only in US) and the glucagon-like peptide-2 (GLP-2) analogue, teduglutide (in US and Europe).

A number of animal and human studies evaluating the effects of hGH on intestinal adaptation and absorption have demonstrated conflicting findings [359-365]. Five studies met the inclusion criteria of a Cochrane review to evaluate of the efficacy of hGH with or without glutamine supplementation for adult patients with SBS-CIF [366]. The results suggested a positive effect of hGH on weight gain and energy absorption. However, in the majority of trials, the effects are short-lived returning to baseline shortly after cessation

of therapy. Being a systemic hormone, its use was often associated with significant side effects, such as peripheral edema, light muscle and joint stiffness, generalized arthralgias, fatigue, and transient gynecomastia [359-366].

GLP-2 is a trophic hormone secreted by intestinal L cells of the lower small and large intestinal mucosa in response to the presence of nutrients in the gut lumen. GLP-2 enhances intestinal capacity to absorb nutrients by promoting intestinal crypt cell proliferation, inhibiting enterocyte apoptosis and gastric acid secretion, decreasing small intestinal motility, and increasing mesenteric blood flow [367-369]. 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 [370-373], Teduglutide is a recombinant GLP-2 receptor agonist, administered subcutaneously, resistant to *in vivo* degradation by dipeptidyl peptidase IV; this results in an extended half-life as compared to native GLP-2 (1.3 h vs. 7 min) [367].

A systematic review showed the GLP-2 analogue, teduglutide, an efficacious, safe, and well-tolerated therapy by which to reduce PN dependency in adult patients with SBS, after a period of post-surgery intestinal adaptation [374]. A single center cohort of 79 patients with SBS-CIF was investigated to know the candidacy for teduglutide treatment [375]. According to indications, contraindications, special warnings, and precautions for use of the drug, listed in the drug monographs and in the phase-III trial protocol, patients were categorized in three groups: 34.2% non-candidates because of contraindications to the treatment; 30.4% potential candidates because of special warnings and precautions conditions but no contraindications; 35.4% straight candidates for the treatment, because of neither contraindications nor warnings and precautions. Interestingly, the straight candidates group showed the lowest requirement of IVS, of number of days of infusion per week and the lowest amount of IVS energy and volume. The results highlighted that a systematic analysis of SBS-CIF patient candidate for GLP-2 analogue therapy would allow HPN/IF centers to make a homogeneous patient selection and would facilitate the worldwide comparison of the results of clinical practice and research.

7.3.11. Recommendation 75

In case of intestinal growth factors consideration, colonoscopy (if remnant colon and/or rectum), abdominal ultrasound, and gastroscopy shall be performed on all patients before initiation of treatment, to assess for the presence of polyps and to exclude neoplastic disease, as well as to clarify unclear anatomic situations (e.g. suspected strictures, blind loops, and unclear anastomotic sites) or disease activity in the gastrointestinal remnant (e.g. Crohn's disease).

Grade of recommendation GPP - Strong consensus 100% agreement.

7.3.11.1. Commentary. Since GLP-2 stimulates crypt cell proliferation and exerts antiapoptotic effect, survey for the risk of intestinal neoplasia is mandatory for patients receiving treatment with GLP-2 analogues [376].

The Teduglutide Effectiveness in Parenteral Nutrition Dependent SBS Subjects (STEPS)-2 was a two-year, open-label extension study designed to evaluate long-term safety and efficacy of teduglutide in adults [377]. Fifty of the 65 patients who completed the study underwent 51 colonoscopies. Gastrointestinal polyps were reported in nine patients, adenoma (n = 5), hyperplastic polyp (n = 1), and rectal inflammatory polyp (n = 1) and unclassified (n = 2). There were no cases of intestinal dysplasia or malignancy [377]. A systematic review reported that teduglutide treatment for up to 30 months did not increase risk in patients without any known pre-existing cancer and promoted growth of pre-existing neoplasia in rodents [378]. In randomized (RCT)/extension teduglutide studies, including 173 patients for a total of 222 person-years exposure to the drug, colonic polyps, rectal polyps and small intestinal polyps were reported in 1.7%, 1.2%, and 0.6% of patients, respectively [379]. Furthermore, three events of cancer were observed, one gastrointestinal adenocarcinoma, considered drug-related, and two lung cancers, not considered drug-related [379]. Case reports of *de novo* development of duodenal and small intestinal polyps in patients who were not considered at increased risk [380,381], were also reported.

The four year interim data analysis of the SBS-IF registry (NCT01990040; EUPAS7973) promoted by Takeda and initiated in 2014 reported the safety of teduglutide treatment by comparing adult patients who received the treatment (ever treated, n = 540; SBS type 1 28.9%, type 2 or 3 71.1%) with those who did not received it (never treated, n.756, SBS type 1 22.2%, type 2 or 3 77.8%). During the study period: no occurrences of new colorectal cancer were recorded in either patient group; new or worsening diagnoses of colorectal polyps were observed in 3.0% of ever-treated patients and in 0.7% of never-treated patient; however, a higher proportion of ever-treated patients underwent colonoscopy than never-treated patients (25.4% vs 9.7%) [382].

Patients with suspected or active malignancies, as well as those with a history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas should not be treated with intestinal growth factors. Colonoscopy, gastroscopy, and abdominal ultrasound should be performed prior to commencing treatment, after one year of treatment and then every three to five years. The detection of non-malignant gastrointestinal polyps before starting the treatment would not be an absolute contraindication to the therapy, but would represent a worning and precaution condition requiring tighter monitoring [378,383].

7.3.12. Recommendation 76 (recommendation #52 of the 2016 CIF GL)

Patients with CIF due to SBS should be carefully informed of the potential benefits and risks associated with intestinal growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of QoL 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 recommendation GPP - Strong consensus 100% agreement.

7.3.12.1. Commentary. The main criteria to define candidacy of patients with SBS-CIF for GLP-2 analogue therapy are the time elapsed since the last intestinal resection, and the absence of contraindication for the treatment. The time from the last surgery should be long enough to ensure that the spontaneous post-resection intestinal adaptation has entirely developed. Contraindications are the presence or the actual risk of gastrointestinal, hepatobiliary or pancreatic cancer. The presence of other conditions listed as warnings or precautions should also be carefully considered during the decision process [375,383].

Patients should actively participate in the decision on to start the treatment [384]. The information to be given to the candidate patients have been reported in a review based on the data available up to 2018 [385]. Efficacy of the treatment is defined as $\geq$20% stable reduction in IVS volume with respect to baseline. RCT showed a clinical response in 65% of patients, with additional days per week off IVS from baseline observed in 58% and complete independence from IVS observed in 20%. Efficacy was greater in SBS requiring high

baseline IVS volume and in SBS type 1. SBS with colon showed a slower response, but a higher probability of weaning off IVS. Crohn's disease was associated with a non-significant trend of increased response [386]. A recent systematic review and meta-analysis confirmed these data [387]. Furthermore, observational studies identified the presence or development of hyperphagia as an independent predictor for reduction and weaning off IVS [388].

Patients should be aware of the high probability of a life-long duration of treatment and of returning to baseline IVS requirements, in case of treatment cessation [385].

Treatment-emergent adverse events were reported in 95% of patients, mostly of mild or moderate severity. The most common included abdominal pain, nausea and abdominal distension, more frequently earlier in the course of treatment, with their frequency declining over time [379,385]. The risk for new gastrointestinal, hepatobiliary and pancreatic benign or malignant neoplasia as the consequent need to undergo the appropriate follow up screening should be clearly highlighted [379,382,385].

The first study investigating the effects of teduglutide treatment on patient QoL did not demonstrate any significant improvement in comparison to placebo [389]. A subsequent study using a validated SBS specific QoL scale assessed the impact of teduglutide among patient subgroups stratified by IVS volume requirement at baseline, disease etiology, and bowel anatomy [390]. Nonsignificant improvement in SBS-QoL scores were observed in the teduglutide group compared with placebo, in the patients treated with teduglutide with the highest baseline IVS volume and in those with IBD as underlying disease [390]. These results fit with those of an international, cross-sectional survey on patients with CIF, not receiving any GLP-2 treatment, using a validated self-assessment tool for the measurement of QoL in patients receiving HPN (HPNQOL). QoL scores were significantly better with the longer duration of HPN, with Crohn's disease and mesenteric ischemia as underlying disease, with living with family, and with lower days of IVS infusion per week [391]. The latter results were confirmed in another multicenter study [392]. Altogether, these data indicated an association between better QoL scores and lower number of IVS infusion per week and/or lower volume of the IVS infusion.

A study on direct medical cost concluded that teduglutide is not cost-effective in adult patients with SBS-IF, when compared with no treatment [393]. No data are still available on the potential positive implications for employment and activities of daily living related to the additional time off IVS due to successful treatment with teduglutide.

Patients candidate for the treatment should be clearly informed of the need to undergo careful and regular monitoring. Close monitoring while receiving the drug is crucial to prevent and timely treat adverse event and risk of the treatment. Patients who cannot comply with regular monitoring should not be treated with intestinal growth factors [383,385].

7.3.13. Recommendation 77 (recommendation #53 of the 2016 CIF GL)

For carefully selected SBS patients who are candidates for intestinal growth factor treatment, the GLP-2-analogue which is the only one approved by FDA and EMA so far, teduglutide, shall be the first choice.

Grade of recommendation A - Consensus 87% agreement.

7.3.14. Recommendation 78 (recommendation #54 of the 2016 CIF GL)

The efficacy of growth factor treatment shall be done according to standardized protocols measuring fluids, electrolytes and energy balance.

Grade of recommendation GPP - Strong consensus 100% agreement.

7.3.15. Recommendation 79 (recommendation #55 of the 2016 CIF GL)

Intestinal growth factors shall be 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 recommendation GPP - Strong consensus 100% agreement.

7.3.15.1. Commentary. Teduglutide is the only recombinant analog of physiologic GLP-2 so far approved in the United States and Europe (adults and children aged $\geq$1 year) for the treatment of patients with SBS-CIF.

Three RCT [371-373], one controlled trial [377], and four cohort studies [388,394-396] demonstrated the efficacy and the safety of the treatment supporting the grade A of the recommendation #77. Similar results have been described by other single center reports [397-400]. Substitution of glycine in the native peptide for alanine makes teduglutide resistant to degradation, thereby extending half-life and facilitating daily dosing [367,370]. Novel GLP-2 receptor agonists with longer half-life are also under clinical development. Phase three RCTs are ongoing for Glepaglutide which administered once/twice weekly [401-404] and Apraglutide administered once weekly [405,406].

Also, GLP-1 receptor agonists, successfully used in type 2 diabetes and obesity, may have a putative role in SBS by reducing gastric emptying and hypersecretion. Exenatide and liraglutide showed encouraging results in small case series [407,408] but no RCT has yet been performed in SBS patients.

Efficacy of the intestinal growth factor treatment is defined as $\geq$20% stable reduction in IVS volume with respect to baseline. Body weight and composition, electrolyte balance and renal function should remain stable in spite of the reduction of the IVS. A careful monitoring of the treatment is mandatory, performed by expert multidisciplinary team and according to standardized protocol [374,383]. Healthcare professionals without appropriate knowledge and expertise on CIF, SBS and intestinal growth factor therapy should timely refer patients to CIF/intestinal rehabilitation centers.

7.3.16. Recommendation 80 (recommendation #56 of the 2016 CIF GL)

To patients with SBS, oral drugs should be prescribed on an individual basis, 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 recommendation GPP - Strong consensus 100% agreement.

7.3.16.1. Commentary. Pharmacotherapy in SBS patients remains a difficult clinical problem, as drug absorption from the gastrointestinal tract may be considerably impaired in such patients [409-412]. The impairment of absorption of orally administered drugs shows significant interpatient 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.) [409-412].

There is limited and dated literature regarding absorption of oral drugs in SBS [413-423]. 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 [409-412]. 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 (LMWH) should be considered an option when appropriate [413-423].

Omeprazole is commonly used in SBS patients to slow gastric acid hypersecretion secondary to loss of inhibitory enteral hormones. PPI and H_2 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 [369-371]. 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 fecal losses, suggesting a reduction of its bioavailability in such patients [409-412]. 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 intravenous formulation may be necessary [409-412,422]. 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 [419]. 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 therapeutic efficacy and levels of plasma concentration, when available and appropriate.

7.4. Which are the options for non-transplant surgical procedures to improve remnant intestinal function in patients with short bowel syndrome?

7.4.1. Recommendation 81 (recommendation #66 of the 2016 CIF GL)

In patients with SBS, during intestinal resection, bowel length should be conserved to the fullest extent possible to avoid dependence on HPN.

Grade of recommendation B - Strong consensus 100% agreement.

7.4.2. Recommendation 82 (recommendation #67 of the 2016 CIF GL)

In patients with SBS, restoration of intestinal continuity should be realized whenever possible, to decrease HPN dependency.

Grade of recommendation B - Strong consensus 100% agreement.

7.4.3. Recommendation 83 (recommendation #68 of the 2016 CIF GL)

Regarding non-transplant surgery in patients with SBS, bowel lengthening procedures may be considered in selected patients.

Grade of recommendation 0 - Strong consensus 100% agreement.

7.4.4. Recommendation 84 (recommendation #69 of the 2016 CIF GL)

In patients with SBS, management should be performed through a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome.

Grade of recommendation GPP - Strong consensus 100% agreement.

7.4.4.1. Commentary. 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, reconstruction of gastrointestinal continuity should be prioritized whenever feasible by ostomy reversal and recruitment of distal unused bowel. In a large series of 500 patients with PN dependent IF from a highly specialized center definitive autologous gut reconstruction was achieved in 378 (82%) patients - often requiring complex and combined procedures including primary reconstruction, interposition of alimentary-conduits, intestinal/colonic lengthening and reductive/decompressive surgery. These authors also introduced a model for the prediction of restoring nutritional autonomy by anatomy of reconstructed gut, TPN requirements, cause of gut failure, and serum bilirubin [424]. Restoring bowel continuity may resolve PN induced chronic cholestasis in about 50% by reducing need for PN [425]. Even in ultra-SBS (median length 18 cm) nutritional autonomy may be achieved by gastrointestinal reconstruction in 44% - average of 20 months with special regard to those with intact colon and ileocecal valve [426]. Following progression to IF, surgical management of SBS depends on the symptoms and anatomical characteristics of the individual patient. There is an increasing prevalence of patients with IF after bariatric surgery which may afford Roux-en-Y gastric bypass reversal and restoration of gastric tract continuity [427]. A retrospective analysis of a prospective database for CIF includes 88 patients with SBS undergoing

autologous gastrointestinal reconstruction surgery [428]. At initial evaluation the SBS anatomy was type 1 in 78 patients, type 2 in three and type 3 in seven patients. After autologous gastrointestinal reconstruction surgery, it was type 3 in 59 patients, type 2 in 26 and type 1 in three patients. Treatment with teduglutide was offered to a group of eight patients who had achieved the plateau for intestinal rehabilitation and were destined to be PN-dependent for life. Freedom from PN was achieved in 83% of patients. Variables identified at the logistic regression analysis led to a novel formula to predict intestinal rehabilitation, including postsurgical intestinal length, presence of ileocecal valve, and use of teduglutide as part of postsurgical treatment [428].

Surgical options in patients with long-term IF fall into four main categories: operations to correct slow transit [429], operations to improve intestinal motility in cases of dilated bowel [430], operations to slow intestinal transit in the absence of bowel dilatation [431], and operations to increase mucosal surface area [432].

7.5. 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 [428]. These are often sequelae of the underlying disease leading to SBS, such as Crohn's disease or radiation enteritis, and often require meticulous investigation to diagnose and treat appropriately [431].

7.6. 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 [432,433]. 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 [434]. 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 [435] 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 two “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 seven of nine survivors attaining enteral autonomy from PN at a mean follow-up of 6.4 years [436-437]. LILT should be applied with extreme caution in patients with ultrashort bowel and in the presence of liver disease [436,437].

Tapering without loss of surface area is accomplished effectively and relatively simply by the serial transverse enteroplasty (STEP) procedure described by Kim et al. [438] 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 twelve pediatric patients who underwent STEP, eight (67%) patients remained alive and transplant-free at a median follow-up of 5.7 years. Of those eight patients, seven achieved independence from PN. In addition, the dilated segment showed an 87% increase in median length and a 67% decrease in mean internal diameter [439].

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. [440] 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 two 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 ITx 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 yr for STEP) [441].

7.7. 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 [442]. SRSB creates an antiperistaltic segment of bowel approximately 10–12 cm in length, located approx. 10 cm proximal to an end-stoma or small bowel-colon anastomosis [433-443]. 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 three 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 [444]. A case control study evaluated intestinal absorption in a large series of patients with SRSB 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/d [445]. 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 [445].

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 [446]. The largest available study included six infants who were followed for 24–84 months. Three patients achieved enteral autonomy from PN within four months of surgery. The remaining

three patients were not weaned from PN, and all died, at an average of 20 months post-surgery [447].

7.8. 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 [448]. 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 [449]. The Manchester experience with CTE, limited to only ten cases, is nevertheless noteworthy for having reached the goal of performing LILT procedures in all ten patients and, more important, for accomplishing enteral autonomy in nine of the ten patients. A more immediate application of these principles is the demonstration of the feasibility of repeat intestinal lengthening with the STEP procedure [450]. 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 [451].

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 [452-454]. The surgical approach should integrate the age of patient, intestinal status (dilated or non-dilated small bowel remnant), and experience of the center.

8. Chapter 6 - Chronic small intestinal dysmotility

8.1. What are the definitions and the criteria for the diagnosis, classification and reporting of chronic small intestinal dysmotility

8.1.1. Statement 13

Chronic small intestinal dysmotility is defined as “impaired gastrointestinal propulsion of the gut content in the absence of fixed occluding lesions causing chronic/recurrent obstructive type symptoms and intolerance to oral or EN”.

Strong consensus 100% agreement.

8.1.2. Statement 14

Chronic small intestinal dysmotility is diagnosed by the clinical features of recurrent/chronic episodes of intestinal occlusion with abdominal pain, nausea and/or vomiting and intolerance to oral or enteral nutrition, with or without radiological features of dilated intestine with air/fluid levels and/or, where feasible, manometric evidence of gastro-intestinal dysmotility.

Consensus 77% agreement.

8.1.3. Statement 15

Chronic small intestinal dysmotility is classified as CIPO, when there are radiological features of dilated intestine with air/fluid levels, or ED when no radiological features of a dilated intestine are present.

Both CIPO and ED are categorized as primary/idiopathic, when no underlying disorder can be demonstrated, or secondary, when related to underlying gastrointestinal or systemic diseases, either sporadic or familial, or other known factors such as side effects of medications.

Strong consensus 100% agreement.

8.1.3.1. Commentary. Historically, chronic small intestinal dysmotility has primarily comprised patients with CIPO, where a patient has a dilated small intestine with the modifier “pseudo” used to underline the absence of occluding lesions. CIPO may be congenital or acquired, due to a variety of diseases [455]. It is apparent, however, that chronic small intestinal dysmotility also includes patients with ED, who have manometric evidence of dysmotility but without radiological features of a dilated intestine [19-21,456-458]. Hence, since ED is not an infrequent cause of CIF, the generic term chronic small intestinal dysmotility is now used to describe the conditions of CIPO and ED. Indeed, a recent ESPEN-led international survey of expert clinicians published by Vasant and colleagues revealed that over 90% of respondents felt that CIPO and ED should be considered as separate entities within the classification of small intestinal dysmotility, particularly in reference to the need for HPN [21]. Supporting this opinion, data from a national UK IF reference center recently demonstrated that distinguishing between CIPO and ED carries prognostic significance for those placed on HPN, with patients in the latter group more likely to cease PN in the long term compared to those with CIPO [460].

While the diagnosis of CIPO can be readily made using radiological studies to demonstrate a dilated small bowel in the absence of a mechanical cause, the diagnosis of ED can be more challenging given the requirement for antro-duodenal manometry, which is not readily available to many clinicians and can be poorly tolerated by patients; indeed, antro-duodenal manometry was noted to be requested in fewer than a quarter of potential cases of ED in the international survey by Vasant [21]. There has been a recent increased number of patients with hypermobile Ehlers Danlos Syndrome [461] referred to IF centers; however, the formal diagnosis of ED in this condition is difficult due to the aforementioned issues with antro-duodenal manometry tolerance [21]. Full-thickness small bowel biopsy has been used to aid in the diagnosis of chronic small intestinal dysmotility, with myopathic changes being more common in CIPO and neuropathic changes more common in ED [462]; however, again, this is an invasive procedure that the majority of clinicians do not necessarily feel influences onward management [21]. The further development of novel techniques such as wireless motility capsule or cine-MRI may prove beneficial in the future, possibly obviating the need for antro-duodenal manometry or full-thickness biopsy [463]. The management of chronic small intestinal dysmotility relies primarily on nutritional and medical approaches, ensuring optimal nutritional intake, with medical therapies to promote motility and treat complications such as bacterial overgrowth.

8.2. Which nutritional support should be provided to patients with chronic small intestinal dysmotility?

8.2.1. Recommendation 85

Dietary counselling can be used as the first-line management in patients with chronic small intestinal dysmotility; patients can be encouraged to eat according to individual tolerance and may benefit from frequent small meals of low-fiber and low-fat content alongside texture modified food and liquid supplements as well as minerals and micronutrients to prevent specific deficiencies.

Grade of recommendation 0 - Strong consensus 100% agreement.

8.2.1.1. Commentary. The main goals of chronic small intestinal dysmotility management are to reduce the major symptoms by improving intestinal propulsion and maintaining adequate nutritional status. Nutritional support 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 [464-467].

Dietary actions should be used as first-line management [468,469]. They are influenced by the disease phenotype and intended to provide sufficient oral micro- and macronutrients in line with the patient's needs. The oral intake of patients with chronic small intestinal dysmotility is influenced by the extent of gastrointestinal disease [470]. For instance, patients with gastroparesis often complain of early satiety, bloating, and nausea and liquid meals may be better tolerated than solids [458]. A low-fiber, low-residue diet is helpful in minimizing intestinal gas, cramps, and potential bezoar formation; furthermore, a recent guideline from the British Society of Gastroenterology suggests that patients may benefit from frequent small meals of low-fiber and low-fat content alongside liquid supplements [458]. Indeed, food with high concentrations of fat should be avoided in order to limit the delay in gastrointestinal transit [466,471]. Patients with chronic small intestinal dysmotility may also be at risk of developing vitamin and trace element deficiencies, therefore, multivitamin combined with trace element preparations should be added to their diet. Evaluation of micronutrient status at least once a year with supplementation as needed should prevent deficiency. In order to meet an adequate caloric intake, hypercaloric formulae are available on the market and can be helpful if tolerated [466,471,472]. To summarize, oral intake should be divided into five to six 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 formation; liquid meals may also be better tolerated than solids as symptoms progress. Associated multivitamin and trace element 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.

8.2.2. Recommendation 86

Any decision to escalate from oral nutrition to EN or PN should involve careful multidisciplinary team consideration of the potential risks and benefits with the patient.

Grade of recommendation GPP - Strong consensus 100% agreement.

8.2.3. Recommendation 87 (recommendation #58 of the 2016 CIF GL)

EN should be considered as a first step in patients with chronic gastrointestinal dysmotility who are not able to meet their energy needs with oral nutrition alone and who continue to lose weight, before using HPN.

Grade of recommendation GPP - Strong consensus 96% agreement.

8.2.4. Recommendation 88 (recommendation #59 of the 2016 CIF GL)

HPN shall not be delayed in malnourished patients with chronic gastrointestinal dysmotility when oral/enteral nutrition is obviously inadequate.

Grade of recommendation GPP - Strong consensus 100% agreement.

8.2.4.1. Commentary. In patients with severe gastrointestinal dysmotility who are not able to meet their caloric needs with oral nutrition alone and continue to lose weight, EN may be appropriate. Given the inherent risks of percutaneous enteral tube placement, it is important that the patient, dietetic team and wider multidisciplinary team are in agreement that escalation to EN is required [462]. Furthermore, before placing a permanent enteric feeding tube, it is important to perform a trial of naso-enteric feeding in order to confirm that the patient is able to tolerate the formula and the rate of formula delivery; indeed, it is advisable to ensure that the patient is able to absorb the formula and achieve nutritional gain before placing a permanent feeding tube [458,468,473,474]. Percutaneous endoscopic gastrostomy can be performed in patients without significant gastroparesis following a successful trial of naso-gastric feeding [462]. Alternatively, an artificial feeding device that bypasses the stomach may be required in those with evidence of gastroparesis. Temporary or permanent small bowel access can be achieved by endoscopic, surgical, or radiological placement [468,474]. Percutaneous endoscopic gastrostomy/jejunostomy is a dual system in which a jejunal tube is passed via a gastrostomy tube to the small bowel.

An advantage of gastro-jejunostomy EN is that the gastric port can be used to vent the stomach if necessary while also allowing post-pyloric feeding [458,474]. A recent British Society of Gastroenterology guideline suggests that percutaneous endoscopic or radiological gastro-jejunostomy tubes are preferred to a direct jejunostomy since the latter typically requires surgical placement and may also lead to more complications such as leakage [458].

As with EN, it is important that any decisions to escalate to PN involve a multidisciplinary team such that only patients remaining at nutritional risk despite EN be considered for long term PN. As with all decisions in healthcare, the patient should be at the center and, of course, fully informed of the risks of HPN. The large international multi-center study by Pironi et al. evaluating one-year outcomes of nearly three thousand HPN-dependent adults demonstrated that patients with CIPO had a higher CRBSI rate than other underlying diseases leading to CIF [13]; notably, in that study, the proportion of patients included with ED was not specified. While respondents completing Vasant and colleagues' international survey also felt that, in their experience, CRBSI rates are also higher in HPN-dependent patients with chronic intestinal dysmotility than those with other IF disease mechanisms [21], a single-center study from the UK assessing outcomes over a 16-year period demonstrated that patients with ED had a non-significantly higher rate of CRBSIs than those with CIPO [460]. The latter study also demonstrated that patients with ED were more likely to wean off PN than those with CIPO, with recurrent CRBSIs predicting the ability to cease PN [460]. The majority of clinicians surveyed recently by Vasant reported greater psychological comorbidity in patients with ED than those with CIPO [21], such that it is possible that a considered multidisciplinary team approach, including support from pain specialists to facilitate opioid reduction as well as from psychologists, can ultimately help patients with ED enhance their enteral tolerance and wean PN.

8.3. Which are the drug options for the treatment of chronic small intestinal dysmotility?

8.3.1. Recommendation 89 (recommendation #60 of the 2016 CIF GL)

Trials with prokinetics can be attempted in patients with chronic small intestinal dysmotility.

Grade of recommendation 0 - Strong consensus 95% agreement.

8.3.1.1. Commentary. Treatment of chronic small intestinal dysmotility can be disappointing and frustrating for the clinician and the patient, and remains extremely challenging even in tertiary referral centers [458,467]. Many patients report significant delays in diagnosis, which can lead to psychological harm [475].

The management goals of chronic small intestinal dysmotility include improving gastrointestinal motility, relieving symptoms, and restoring nutritional status and hydration. The therapeutic

approach also require input from a multidisciplinary team including psychology support and advice from a chronic pain team, perhaps reflecting the limitations of pro-motility agents in treating severe pan-enteric dysmotility. Indeed, the recent international survey of experts found that the majority of clinicians opined that most pharmacological therapies were not usually beneficial in treating ED or CIPO [21]. The medications felt to be most efficacious were antibiotics for bacterial overgrowth, particularly for CIPO [21]. While a trial with prokinetic agents can be considered, a fundamental strategy to managing chronic small intestinal dysmotility involves minimizing opioid therapy to avoid exacerbation of dysmotility and associated narcotic bowel syndrome [458,459,462,467].

8.4. Motility agents and antiemetics

The main drugs used include metoclopramide, domperidone, prucalopride, erythromycin, amoxicillin-clavulanate, octreotide, and pyridostigmine [458,467].

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 [476].

The long-term use of metoclopramide and domperidone has also been limited due to their neurologic and cardiac adverse effects [477].

Erythromycin and derivates, including azithromycin, possess potent motilin receptor agonist activity, enhancing gastric emptying and antro-duodenal coordination, but treatment does not appear to be effective in the long term [467,462,478].

Prucalopride is a highly specific serotonin receptor agonist with enterokinetic effects. It has been tested in seven CIPO patients and only four patients completed the study, three of whom experienced a pain improvement but without significant functional changes [479] Octreotide, a somatostatin analogue 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 μg/d (a dose much lower than that used to inhibit peptide secretion in neuroendocrine tumors) [479-481].

The anticholinesterase drug, pyridostigmine may also be used. A small study including seven patients with recurrent pseudo-obstruction demonstrated some benefit [360], although more extensive supportive data are limited [463].

Other non-prokinetic antiemetics such as cyclizine and ondansetron have been used for the often troublesome nausea experienced by patients with intestinal dysmotility. However, the recent British Intestinal Failure Alliance (BIFA) guideline highlighted concerns with the use of cyclizine because of risks of dependence and hallucinatory effects [482]. The BIFA committee recommended avoidance of the long-term use of cyclizine, noting a potential increased risk of catheter infections in those taking cyclizine whilst on PN.

8.5. Analgesic drugs

Abdominal pain is one of the main symptoms of chronic small intestinal dysmotility. This pain has many mechanisms, making treatment difficult. In severe cases, patients may have been commenced on opioids prior to referral to specialist centers, but it is important to recognize that these medications will exacerbate intestinal dysmotility and risk narcotic bowel syndrome, whereby abdominal pain and hyperalgesia may worsen with opioid continuation [458,467]. Hence, strategies to avoid or reduce opioids, wherever possible, are vital. Indeed, opioid use was shown in a large single-center study to place HPN-dependent patients at increased risk of CRBSIs, possibly as a result of the inherent immunosuppressive effect of these medications and/or due to the cerebral effects of opioids, impacting on the care required when handling a CVC [26]. Indeed, it is noteworthy that the same center reported a lower CRBSI rate in HPN-dependent patients with systemic sclerosis, where opioid use is less prevalent than patients in primary CIPO [460,483].

Enhanced understanding of the role of gut-brain neuromodulation in the etiology of chronic abdominal pain has facilitated the use of alternative medications to opioids, such as tricyclic antidepressants, as well as selective serotonin or serotonin-norepinephrine reuptake inhibitors. Gabapentin or pregabalin can be particularly helpful for neuropathic pain [458,462]. Engagement of a chronic pain team can be particularly useful when reducing opioids and seeking alternative approaches. Furthermore, psychological support can be equally helpful, not least given the psychological distress identified in those with chronic abdominal pain resultant from intestinal dysmotility [475].

8.5.1. Recommendation 90 (recommendation #61 of the 2016 CIF GL)

Antibiotic therapy can be used to treat intestinal bacterial overgrowth and to reduce malabsorption in patients with chronic small intestinal dysmotility.

Grade of recommendation 0 - Strong consensus 100% agreement.

8.5.2. Recommendation 91 (recommendation #62 of the 2016 CIF GL)

Periodic antibiotic therapy can be used to prevent intestinal bacterial overgrowth in patients with chronic intestinal dysmotility who have frequent relapsing episodes.

Grade of recommendation GPP - Strong consensus 95% agreement.

8.5.2.1. Commentary. Intestinal bacterial overgrowth has often been described in digestive motility disorders [484] and it has been shown that improvement of digestive motility reduces bacterial overgrowth [467,485]. Sequential antibiotic therapy is very effective in treating intestinal bacterial overgrowth and in reducing malabsorption [485]. Correlation between bacterial translocation and absence of MMC activity has been demonstrated and can result in a worsening of digestive motility disorders [486]. A potential life-threatening consequence of bacterial overgrowth relates to bacterial translocation [487-488].

The rationale for the use of antibiotics is the treatment and prevention of small intestinal overgrowth due to intestinal stasis in CIPO patients. Notably, this seems to be less of an issue in those with ED [460]. The treatment of bacterial overgrowth should be evaluated individually. Sequential antibiotic therapy can be very effective in treating intestinal bacterial overgrowth and reducing malabsorption. It has also been shown to improve nutritional status and sometimes bloating. Poorly absorbable antibiotics such as aminoglycosides and rifaximine are preferred, but alternating cycles with metronidazole and tetracycline may be necessary to limit resistance [489]. In clinical practice, the most commonly used antibiotics are metronidazole, amoxicillin-clavulanate, doxycycline, and norfloxacine [467].

8.6. Which surgical procedures should be used to improve gastrointestinal function, and oral/nutrition feeding and to relieve symptoms in patients with chronic small intestinal dysmotility

8.6.1. Recommendation 92 (recommendation #70 of the 2016 CIF GL splitted)

Surgery should be avoided in chronic small intestinal dysmotility patients, whenever possible, due to the risk of postoperative

worsening of intestinal function and need for subsequent reoperation.

Grade of recommendation GPP - Strong consensus 100% agreement.

8.6.2. Recommendation 93 (recommendation #70 of the 2016 CIF GL, splitted)

In patients with chronic small intestinal dysmotility, venting ostomy (either endoscopically or surgically), can be performed to diminish symptoms in case-by-case selected patients.

Grade of recommendation GPP - Strong consensus 95% agreement.

8.6.2.1. Commentary. Surgery plays a limited role in the management of patients with chronic small intestinal dysmotility, 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 three procedures per patient. Surgery was performed in half of the cases in emergency situations in a series of 63 patients. The overall rate of postoperative mortality was 7.9% and the overall rate of morbidity was 58.2%. 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 one year and 66% at five years) [490]. Furthermore, surgical procedures should only be used after achieving improvement of nutritional status and bowel distension. A more recent UK retrospective evaluation of 45 HPN-dependent patients with chronic small intestinal dysmotility found that patients with CIPO had undergone a mean of 1.6 surgeries, while those with ED had still undergone a mean of 0.9 surgeries/patient [460].

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 [474,491,492]. Chronic postprandial bloating, abdominal distension, and pain may be treated with a venting gastrostomy or jejunostomy in patients with CIPO. This simple intervention can substantially reduce the number of hospital admissions and emergency room visits in selected patients with intermittent obstructive symptoms [493]. However, extreme caution should be observed in selecting patients for these procedures with careful assessment of the patient's symptoms and parts of the gastrointestinal 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 who 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 [494]. 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. Such surgeries are, of course, unlikely to be beneficial in those with ED, where small intestinal dilatation is, by definition, not as severe as for patients with CIPO.

The last surgical option is ITx. That is indicated in case of life-threatening HPN-related or underlying disease-related complications [495,496]. 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 [27]. Non-transplant or transplant surgery should be performed only in a highly selected, well-characterized subset of patients, or in cases of life-threatening complications [466,497]. The role of ITx in patients with ED is currently ill-defined, particularly since, as noted earlier, HPN weaning in patients with ED has been shown to occur more often than in those with CIPO [460].

9. Chapter 7 - Radiation enteritis

9.1. Which nutritional support should be provided to patients with chronic radiation enteritis?

9.1.1. Recommendation 94 (recommendation #64 of the 2016 CIF GL)

In patients with chronic radiation enteritis EN may be used if oral nutrition, including use of oral nutritional supplements, is inadequate.

Grade of recommendation 0 - Strong consensus 96% agreement.

9.1.2. Recommendation 95 (recommendation #65 of the 2016 CIF GL)

In malnourished radiation enteritis patients, HPN should not be delayed, if oral nutrition/EN is obviously inadequate.

Grade of recommendation GPP - Strong consensus 100% agreement.

9.1.3. Recommendation 96 (recommendation #63 of the 2016 CIF GL)

In patients with chronic radiation enteritis, the PN regime should follow the same criteria for the HPN of patients with other causes of CIF.

Grade of recommendation GPP - Strong consensus 100% agreement.

9.1.3.1. Commentary. Chronic radiation enteritis is a severe complication of pelvic radiotherapy [498-503]. The damage of radiation enteritis 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 [501-502]. A 2015 ESPEN international multicenter survey on CIF in adults, reported chronic radiation enteritis to be the underlying disease in 7.8% of patients [12]. This feature was similar to the 8% observed in 1993 [504] and confirmed that radiation enteritis is still unsolved issue. Data from the UK annual survey on HPN, indicated that radiation enteritis accounted for approximately 4% of new HPN registrants [505].

In radiation enteritis, CIF is usually the result of stricturing and/or fistulizing disease, often with associated surgical complications [502]. Small bowel syndrome is the most frequent pathophysiological mechanism [12,22]. 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 [502].

The overall survival probability on HPN of patients with radiation enteritis has been reported to be 83% (range 58–100), 78% (60–100), 62% (36–90), and 56% (41–90), at one, three, five, and ten

years, respectively [23,29,506-514]. There are no prospective studies. In an early RCT comparing PN with elemental diets, Loiudice and Lang [515] 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 radiation enteritis in the context of IF is limited [502,516]. 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 [506,513,517,518]. Otherwise, there is the indication for surgery. After abdominal radiation surgically placed feeding tubes bear a higher risk for complications which has been retrospectively observed in 122 pediatric and adolescent cancer patients [519]. In 92 retrospectively analyzed patients with radiation enteritis bioelectrical impedance spectroscopy, combined with nutritional assessments (NRS, PG-SGA) were appropriate to measure the nutritional status which correlated with inflammatory status (CRP, neutrophil/lypmphocyte ratio) [520].

9.1.4. Recommendation 97

No recommendation can be made for or against the use of glutamine to prevent or treat radiation enteritis.

Grade of recommendation 0 - Strong consensus 97% agreement.

9.1.4.1. Commentary. A meta-analysis [521] of 13 RCTs investigating the protective efficacy of glutamine versus placebo in preventing occurrence of radiation enteritis or curative efficacy of glutamine versus placebo in cancer patients with radiation enteritis after receiving pelvic and/or abdominal radiotherapy. The results showed that: a) the total efficacy of glutamine was higher for patients with radiation enteritis compared with that in control group, however, there was no statistically significant difference (OR 3.07; 95%CI 0.79–11.96; $p > 0.05$); b) the combined ORs for all five grades (from grade 0 to grade 4) of radiation enteritis in patients receiving glutamine were 2.06, 1.35, 0.55, 0.62 and 0.59, respectively ($p > 0.05$ for all); c) glutamine failed to significantly improve the symptoms of radiation enteritis in terms of tenesmus, abdominal cramping and blood in bowel movement ($p > 0.05$).

An RCT including 69 adult patients undergoing abdominal or pelvic radiotherapy due to a neoplasm investigated the effects of oral glutamine during abdominal radiotherapy on chronic radiation enteritis [522]. Patients were assigned to receive either glutamine (glutamine, 30 g/d) or placebo. Chronic enteritis was developed by 14% of patients: glutamine 16.7% vs. placebo 11.1% (RR 1.33, 95%CI 0.35–5.03, $p = 0.540$). Most cases of enteritis were grade I (75.0%), with no differences between groups. The stool frequency increased post-radiotherapy in patients who received glutamine (from 1 ± 1 to 2 ± 2 stools/d, $p = 0.012$), but remained unchanged with placebo (1 ± 1 stools/d, $p = 0.858$; difference between groups $p = 0.004$). There were no differences between the two groups in terms of weight, fat mass or fat-free mass index, or between patients with enteritis and those without intestinal toxicity. A prospective RCT investigated perioperative alanyl-glutamine -supplemented PN (0.4 g/kg d) versus isonitrogenous control in patients undergoing surgery due to intestinal obstruction. Significantly increased CD4/CD8-positive T-lymphocyte ratios were observed in both groups, there was also a significant intergroup difference ($p < 0.001$; glutamine -PN, baseline 1.36 ± 0.32 vs 1.82 ± 0.30 on POD14, $p < 0.001$; control, baseline 1.37 ± 0.25 vs 1.63 ± 0.31 on POD14, $p < 0.001$). However, no significant differences were found for parameters of nutritional status and intestinal permeability [523].

10. Chapter 8 - Entero-cutaneous fistulas

10.1. What are the definition and the criteria for the diagnosis and classification and reporting of chronic entero-cutaneous fistulas

10.1.1. Statement 16

The ECF is classified by anatomic location (proximal: jejunum and more proximal; distal: ileum or more distal), fasting output volume (low: <200 mL/d; medium: 200–500 mL/d; high: >500 mL/d), location in the open abdomen (deep vs superficial) and number of fistula openings (single opening, multiple in close proximity; multiple distant from each other).

Strong consensus 95% agreement.

10.1.1.1. Commentary. ECF is defined as an abnormal connection between the gastrointestinal tract and the skin. Enteroatmospheric fistula (EAF) is a connection without a cover from the abdominal wall and the atmosphere, usually associated with open abdomen. ECF and EAF may cause acute IF, which may become CIF if the fistula does not close spontaneously within a few weeks. Spontaneous closure is very rare in EAF [524,525].

The great majority of ECF are iatrogenic (75–85%), between 15 and 25% occur spontaneously [524]. Among 649 adult patients with open abdomen 58 (8.9%) developed EAF. Indications for open abdomen were peritonitis (51.2%) and traumatic-injury (16.8%) [526]. In case of open abdomen negative pressure wound therapy may be a risk factor for the development of EAF [527,528]. Sepsis is the major cause of mortality [529].

According to Di Saverio et al. [530] the fistula may be classified by anatomic location (proximal: jejunum and more proximal; distal: ileum or more distal), output volume (low: <200 mL/d; medium: 200–500 mL/d; high: >500 mL/d), location in the open abdomen (deep vs superficial) and number of fistula openings (single opening, multiple in close proximity; multiple distant from each other). Risk factors for persistent fistula are: foreign body, radiation, inflammation or infection, epithelialization of the fistula tract, neoplasm, and distal obstruction [531].

While there is consent that serum proteins may not be considered a nutritional marker [532], decreased plasma concentrations of serum albumin, transferrin, retinol binding protein, and prealbumin may be a consequence of fistula -related inflammation and have prognostic significance. Increased serum albumin concentration in patients undergoing PN may be associated with significantly less fistula output and improved rate of spontaneous closure [525].

10.2. Which nutritional support and drug therapy should be provided to patients with entero-cutaneous fistulas?

10.2.1. Recommendation 98

Withholding EN cannot be of benefit regarding fistula closure, whereas some oral/enteral nutrition may protect the integrity of the mucosal barrier as well as the immunologic and hormonal function of the gut.

Grade of recommendation GPP - Strong consensus 96% agreement.

10.2.2. Recommendation 99

Optimizing nutrition and wound care may stabilize ECF and potentially allow spontaneous closure.

Grade of recommendation 0 - Strong consensus 100% agreement.

10.2.2.1. Commentary. There are no studies showing a benefit of withholding EN with regard to fistula closure. EN or PN supplementation does not differ in principle for fistula compared to other

causes of intestinal insufficiency or IF [525]. There is consent that oral and enteral nutrition are the preferred method of feeding in order to maintain the structural and functional integrity of the gastrointestinal tract [526].

Adequate nutrition, careful and timely surgical management of the underlying abdominal situation and special wound care have been identified as determining factors to control ECF and allow spontaneous closure or surgical revision, which is usually delayed until six to twelve months [524,530,533].

The ASPEN/FELANPE Clinical Guideline from 2017 recommends with low evidence: "After stabilization of fluid and electrolyte balance oral diet or EN may be feasible and tolerated in patients with ECF output <500 ml/d (suggesting no distal obstruction). However, patients with high-output ECF (>500 mL/d) may require PN to meet fluid, electrolyte, and nutrient requirements to support spontaneous or surgical closure of the fistula" [525].

The ASPEN/FELANPE guideline also recommends on expert consensus the provision of protein at 1.5–2.0 g/kg/d and energy intake appropriate to the patient's energy requirements based on results of nutrition assessment. More protein is recommended (up to 2.5 g/kg/d) in patients with prolonged acute IF due to EAF and high fistula output [525]. Recent data from a multicentric trial in critically ill patients showed that such a high amount of protein was without favorable impact on outcome but may be harmful with regard to those patients with impaired renal function [534]. Concerning patients with CIF, the ESPEN guideline on HPN recommend not to exceed 0.8–1.4 g/kg/d [2]. In line with the ASPEN/FELANPE guideline HPN is recommended when the patient is medically stable and the fistula output is manageable, as well as in patients with high-output ECF (>500 mL/d) when surgical repair is not yet appropriate [2,525].

10.2.3. Recommendation 100

Refeeding enteroclysis (chyme reinfusion) may be recommended in double enterostomies high output fistulas.

Grade of recommendation 0 - Strong consensus 96% agreement.

10.2.3.1. Commentary. In order to avoid losses of trophic chyme refeeding enteroclysis is a method for patients with proximal enteral fistula or stoma. Furthermore, it makes EN feasible and may wean the patient from PN [525,535,536]. Enteric succus refeeding can be self-administered. In a retrospective study of 306 patients with SBS chyme reinfusion started in median after five days and was continued for 64 days. Nutritional status improved with regard to weight gain (+3.5 ± 8.4%) and albumin (+5.4 ± 5.8 g/L). Intestinal output decreased by 2096 ± 959 ml/d, accompanied by an increase in absorption of nitrogen (32 ± 20%) and lipids (43 ± 30%), and the improvement of citrulline 13.1 ± 8.1umol/L [537]. Similar positive results were reported by an Indian study on a case series of 30 patients [538].

A new device has been developed for reinfusion and proven feasible in ten patients [539]. Enteroclysis using water and electrolytes instead of chyme (hydration enteroclysis) is also feasible and reduces intravenous energy and volume/electrolyte requirements [540].

Based on a systematic review of 15 level IV studies with high risk of bias and the lack of RCTs there is no clear evidence for topical management in order to induce fistula closure [529]. Topical interventions were categorized as isolating, intubating, or occluding the fistula. In all studies negative pressure wound therapy with a great variability was used, applied directly to the fistula orifice or surrounding a pouching system. While there is a risk for new fistula formation, these authors do not endorse the use of negative pressure wound therapy over any other topical management system. The guideline group agrees with these authors to consider negative pressure wound therapy only as part of a comprehensive plan of care topical management. Pain, odor control, mobility, and independence as important quality-of-life issues and patient reported outcomes should be prioritized for the selection and evaluation of appropriate interventions [529].

10.2.4. Recommendation 101

Drug therapy for ECF can be the same used for SBS.

Grade of recommendation 0 - Strong consensus 100% agreement.

10.2.4.1. Commentary. As in IF in general, acid suppressive therapy, preferably with a PPI decreases fistula output [531,524]. Antimotility agents appear to have the same effect as in other etiologies of IF or intestinal insufficiency [341]. Two meta analyzes report that somatostatin analogues provide an improved rate of fistula closure [541,542]. The ASPEN/FELANPE Clinical guideline recommends with moderate evidence from their meta-analysis to use a somatostatin analogue in adult patients with high-output (>500 mL/d) ECF in order to reduce effluent drainage and enhance spontaneous closure [525].

A practical approach may be to try a course of somatostatin analogue for three days and to continue, if fistula output is decreased in meaningful way [524]. The ASPEN/FELANPE Clinical guideline also recommends with low evidence the combination of PN with oral glutamine [525].

10.3. Which are the options for non-transplant surgical procedures for chronic entero-cutaneous fistulas?

10.3.1. Recommendation 102

Surgical intervention with regard to the restoration of continuity may be individualized and only performed by experienced surgeons in specialized interdisciplinary units.

Grade of recommendation 0 - Strong consensus 100% agreement.

10.3.1.1. Commentary. So far, no evidence based standardized recommendations for management and intestinal reconstruction have been developed. A recent systematic review of 15 level-IV case-based publications has not revealed evidence for standardized treatment. Interventions should be based on practical considerations, resources, and clinical skills [529]. In case spontaneous fistula closure will not be achieved by appropriate nonsurgical management, it is an indication for surgery in order to restore bowel continuity. For the surgical management consensus-based recommendations of the European Society of Coloproctology have been available from 2016 [543]. Because there is a high risk for complications including further deterioration and loss of bowel there is strong consensus that surgical interventions should be very carefully prepared in specialized interdisciplinary units and performed by surgeons with special expertise in the field in CIF centers [525,529,543]. Surgery should not be performed before the inflammatory response has resolved, the nutrition status has been optimized and the general condition improved [525,543].

11. Chapter 9 - Intestinal transplantation

11.1. Which patients with CIF should undergo assessment for candidacy for intestinal transplantation and which patients should be listed for transplantation?

11.1.1. Recommendation 103

Patients with CIF should be assessed for candidacy for ITx, when they have been evaluated by a multidisciplinary team,

rehabilitation options have been explored, and a state of permanent/irreversible or life-limiting CIF and one of the following exist.

- Evidence of advanced or progressive IFALD, as described below:
  - Hyperbilirubinemia >75 μmol/L (4.5 mg/dL) despite intravenous lipid modification strategies that persists for >2 months
  - Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio (INR)), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 month in the absence of a confounding infectious event(s)
- Thrombosis of three out of four discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular)
- Invasive intra-abdominal desmoids
- Acute diffuse intestinal infarction with hepatic failure
- Failure of first intestinal transplant
- Any other potential life-threatening morbidity.

Grade of recommendation B - Strong consensus 96% agreement.

11.1.2. Recommendation 104 (recommendation #73 of the 2016 CIF GL)

Patients with advanced or progressive IFALD and those with an invasive intra-abdominal desmoid tumor should be listed for a life-saving ITx (with or without liver transplantation).

Grade of recommendation B - Strong consensus 100% agreement.

11.1.3. Recommendation 105 (recommendation #74 of the 2016 CIF GL)

Patients with CVC related thrombosis of two or more central veins (internal jugular, subclavian or femoral) may be listed for a life-saving ITx on a case-by-case basis.

Grade of recommendation GPP - Strong consensus 100% agreement.

11.1.4. Recommendation 106 (recommendation #75 of the 2016 CIF GL)

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 should not be listed for a life-saving ITx.

Grade of recommendation B - Strong consensus 93% agreement.

11.1.5. Recommendation 107 (recommendation #76 of the 2016 CIF GL)

Patients with CIF with high morbidity or low acceptance of HPN may be listed for a rehabilitative ITx on a careful case-by-case basis.

Grade of recommendation GPP - Strong consensus 96% agreement.

11.1.6. Recommendation 108 (recommendation #77 of the 2016 CIF GL)

Whenever possible, patients listed for ITx should undergo the procedure while they are in a stable clinical condition, as represented by being able to stay at home and not requiring hospitalization while waiting for transplant.

Grade of recommendation GPP - Strong consensus 100% agreement.

11.1.7. Recommendation 109

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 awaiting and after transplantation.

Grade of recommendation GPP - Strong consensus 95% agreement.

11.1.7.1. Commentary. Safety and efficacy data support HPN as the primary treatment for CIF and ITx as an option for patients with a high risk of mortality on HPN [23,35,37].

The 2019 report of the Intestinal Transplant Registry includes 4103 worldwide patients who have undergone ITx, with and without a liver graft from 1985 to 2017 [544].The data show that the numbers of ITx decreased from 270 during the peak year of 2008 to 149 in 2017 and that pediatric cases prevailed in the first decades, while adult cases comprised the majority in the last decade of the Registry [544]. The proportion of combined liver-small bowel transplants (LITx) decreased in children, where isolated small bowel ITx currently comprises the majority. On the contrary, the numbers of LITx increased in adults, where it is currently prevailing [544]. The global decrease in the annual number of ITx, as well as the aforementioned changes in the types of transplants performed, likely reflect advances in CIF knowledge and management that have occurred in the last 20 years and the resultant improved prognosis of patients with CIF.

The indications for ITx were initially developed in 2001 by an expert consensus of the American Society of Transplantation 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 [545]. Those indications were based on retrospective analyzes of national and international registries and individual center cohorts of patients, with an emphasis on children who were receiving the majority of transplants at that time, mainly because of the higher risk of IFALD-related liver failure relating to physiological liver immaturity and episodes of sepsis.

Subsequent surveys on adult and pediatric patients have better clarified the natural history of CIF and indications for a life-saving ITx. In 2004, ESPEN's Home Artificial Nutrition and Chronic Intestinal Failure working group (HAN&CIF group) carried out a prospective comparative study to evaluate the appropriateness of the 2001 indications for ITx [31-33]. 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 five-year survival rate on HPN was 87% in non-candidates. However, the five-year survival rate for ITx candidates 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 compared well with those of the International ITx Registry report on patients included from 2000 to 2013 [38]; notably, patients included in the latter report had a one-year conditional survival and actuarial five-year patient and graft survival of 58% and 50%, respectively (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) [38]. The 2019 International ITx Registry report including patients up to 2017, shows an actuarial graft survival around 70% in both children and adult recipients at one year, and 70% in children and 50% in adults at five years. During the last decade, graft survival rate has appeared stable in adults, while demonstrating an increase in children; it also appeared to be grater in patients undergoing LITx [544].

In the European survey [32,33], analysis of the risks and causes of death on HPN associated with each indication revealed that only patients with liver failure due to IFALD (RR 3.2) or those with invasive intra-abdominal desmoids (RR 7.1) had a statistically significant increased risk of death on HPN. In these patients, almost all (91.7%) of the deaths on HPN were related to the indication for ITx. A non-statistically significant increase in the risk of death on HPN

was also observed in patients considered to be candidates due to multiple CVC-related thromboses (RR 2.1, p = 0.058). None of the other indications for ITx demonstrated 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. Thus, these data indicated that only liver failure due to IFALD and invasive intra-abdominal desmoids could be considered indications for a direct referral for a life-saving ITx. Appropriately-selected patients with CVC-related thrombosis of ≥2 central veins could be also considered for a life-saving ITx. 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 [33].

The 2001 indications for ITx were also challenged by a retrospective survey on two groups of CIF children, the "old era"— children treated between January 1, 1999 through to December 31, 2005 (n = 99) and the "current era"— children treated between January 1, 2006 through to December 31, 2012 (n = 91) [546]. The results showed that two 2001 criteria had poorer predictive values for the risk of death and need of transplantation in the current era: advanced cholestasis (PPV 64% old vs. 40% current era; sensitivity 84% vs. 65%, respectively) and ultra SBS (PPV 100% old vs. 9% current era; sensitivity 10% vs. 4%, respectively). The data showed that three new criteria had high predictive values: ≥2 intensive care unit (ICU) admissions (OR 23.6, 95%CI 2.7–209.8, p = 0.0001), persistent bilirubin >75 mmol/L despite lipid strategies (OR 24.0, 95%CI 3.2–177, p = 0.00054), and loss of ≥3 CVC sites (OR 33.3, 95%CI 18.8–54.0, p = 0.0003). There was 98% probability of needing ITx when two of these new criteria were present.

The outcome of patients with CIF has also been enhanced by the development of guidelines and expert centers for IF. The presence of a specialist team has been reported to be a factor independently associated with a better outcome on HPN [23,35-38]. Improvement of strategies to prevent and treat IFALD, including the newer intravenous lipid emulsions, have decreased the risk of liver failure [118,119,547,548]. The risk of CVAD related sepsis has been decreased by the use of taurolidine to lock the CVAD [2,549]. The chance of intestinal rehabilitation and weaning from HPN in patients with SBS has been increased by post-resection intestinal reconstruction procedures [454] and also by therapy with intestinal growth factors [385].

On the other hand, increasing experience in ITx has suggested that its potential benefits lie beyond transplantation just offering a life-saving option to those at risk of death from CIF-related complications, primarily as a result of better long-term survival after transplant [38,544] and potential improvements in both QoL and cost-effectiveness after successful transplantation [550-556]. However, limitations of immune suppression and the ever-present risk of rejection mean that actual QoL gains remain to be established, and that the decision for a pre-emptive ITx (i.e., before the onset of HPN-related complications) should be carefully taken on a case-by-case basis [554].

As a result of these changes in practice and outcomes in CIF and ITx since the publication of the 2001 position paper, a working group of the Intestinal Rehabilitation and Transplant Association convened and re-evaluated the indications for ITx in 2015 [39] (Table 16).

Advances in HPN care have modified management approaches for CIF, moving from the direct referral for ITx of any patient with a potential risk of death from HPN to the practice of earlier patient referral to intestinal rehabilitation centers with expertise in both medical and surgical treatments for CIF. This represents a key step to maximize the chance of weaning off HPN, preventing HPN-failure, improving QoL and ensuring timely assessment for listing for the appropriate type of ITx [23,35-38]. A document devised by IRTA in 2008 on 'strategies to reduce mortality and morbidity in patients with CIF' recommends that patients requiring 50% or more of their energy requirements via the intravenous route within three months of HPN commencement should be referred to expert CIF centers [35]. Expert centers can also help optimize and stabilize the patient's clinical condition while on the transplant waiting list. Moreover, a previous report from the International ITx Registry demonstrated that patients able to reside at home rather than in-hospital when awaiting transplantation achieve better outcomes following transplantation [38].

Identifying the progression of hepatic fibrosis to irreversible cirrhosis is a key issue for the timing of referral, as well as for the type of transplant required. Today, serial liver biopsy remains the gold standard for assessing IFALD. Indeed, while fish oil emulsions [547,548] may improve liver function tests in patients with IFALD cholestasis, there is a risk of continued hepatic fibrosis, highlighting the need to perform a liver biopsy in those at risk of hepatic fibrosis resultant from IFALD [557-560].

It has been suggested that patients with Metavir stage II fibrosis (perisinusoidal and portal/periportal fibrosis) should be considered for an isolated intestinal transplant, whereas those with stage III (bringing fibrosis) or IV (cirrhosis) should be considered for LITx [39].

Attenuation or reversal of liver fibrosis has been reported after successful isolated ITx in adults with SBS, with preserved hepatic synthetic function and the absence of portal hypertension [561,562]. Successful isolated liver transplant has been reported in children with IFALD-related liver failure with portal hypertension as a result of SBS, with full enteral adaptation and complete HPN weaning HPN after transplantation [563,564].

Mortality on the waiting list for those awaiting combined liver-ITx is higher compared to patients who do not have CIF awaiting an isolated liver transplant [247,565]. Adult and pediatric end-stage liver disease models (MELD and PELD) can be used to risk stratify waiting times for LITx, with an adjustment applied to incorporate an additional sliding scale of 10% mortality at three months [35]. Over time, this approach has reduced waiting times for LITx and increased the number LITx performed, narrowing the gap between isolated liver and LITx in both pediatric and adult populations [565,566].

12. Chapter 10 - Prevention/treatment of CVAD-related complications

12.1. Which are the procedures for the prevention, diagnosis and management of CVAD-related infections?

12.1.1. Recommendation 110

For the prevention of CVAD-related infections, the infusion line and CVAD care shall be in keeping with recommendations #19–38 of the ESPEN guideline on HPN (Table 10).

Grade of recommendation A - Strong consensus 100% agreement.

12.1.1.1. Commentary. The HPN guideline [2] recommendations #19–38 are listed in Table 10. For the underlying evidence, please consult the original guideline (https://doi.org/10.1016/j.clnu.2020.03.005).

It is highlighted that all the recommendations of the 2016 guideline on CIF [1] for the primary prevention of CRBSI were confirmed and that new evidence on taurolidine supported the upgrade of the grade of recommendation about its use for CVAD lock.

The 2016 guideline on CIF recommendations for the prevention of CRBSI are summarized below.

Table 16
Old and revised criteria for placement on a wait list for intestinal transplantation, presuming that patients will have been assessed by a multidisciplinary team, rehabilitation options have been explored, and a state of permanent or life-limiting intestinal failure exists [adapted from references 33,39,546,554,560].

2001 criteria	2019 criteria	*Comments*
Evidence of advanced or progressive IFALD		
• Impending (total bilirubin above 3–6 mg/dL, progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of PN-liver injury.	• Hyperbilirubinemia >75 μmol/L (4.5 mg/dL) despite intravenous lipid modification strategies that persists for more than 2 months • Any combination of elevated serum bilirubin, reduced synthetic function (sub-normal albumin or elevated INR), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count persisting for more than 1 month in the absence of confounding infectious event(s)	• *This is confirmed as the major criterion for direct listing for combined liver-ITx.* • *Liver biopsy is the gold standard test to identify the stage of liver disease, the timing of transplantation and the type of transplant required (isolated ITx or combined liver-ITx)*
Thrombosis of central veins:		
• Central venous catheter related thrombosis of two or more central veins	• Children: thrombosis of three out of four discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) or occlusion of a brachiocephalic vein. • Adults: on a case-by-case basis	• *This criterion for children was based on a survey that showed a statistically significant increased risk of death associated with the loss of ≥3 CVAD sites (right and left internal jugular vein, right and left subclavian vein, right and left femoral vein).* • *This criterion for adults refers to the loss of right and left internal jugular vein, right and left subclavian vein, or right and left femoral vein; a survey showed that it was not associated with a statistically significant the risk of death.*
Other HPN/IF-related major complications		
• 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.	• Children: two admissions to an intensive care unit (after initial recovery from the event resulting in intestinal failure) because of cardio-respiratory failure (mechanical ventilation or inotrope infusion) due to sepsis or other complications of intestinal failure. • Adults: on a case-by-case basis.	• *For children, this criterion was supported by the above mentioned single center retrospective survey.* • *For adults, this criterion is on a case-by-case basis, because recurrent episodes of CRBSIs or of severe dehydration were demonstrated not to be associated with an increased risk of death.*
Underlying disease related complication		
• Desmoid tumors associated with familial adenomatous polyposis.	• Invasive intra-abdominal desmoids in adolescents and adults	• *This is a criterion for direct listing for ITx;* • *Case reports of ITx for other intestinal premalignant and malignant conditions have been published: malignant tumors including hepatoblastoma, hepatocellular carcinoma, neuroendocrine tumors, and gastrointestinal stromal tumors have been considered for ITx, often in conjunction with chemotherapy; high-grade dysplastic polyps in Peutz-Jeghers syndrome, and other multiple intestinal polyposis syndromes when malignant and premalignant lesions are identified sufficiently early.*
	• Acute diffuse intestinal infarction with hepatic failure	• *Urgent multivisceral transplantation should be considered in case of complicated acute splanchnic venous thrombosis with failure of initial attempts of revascularization.*
	• Failure of first intestinal transplant	• *Re-transplant is the primary treatment.* • *The optimal timing for re-transplantation, the decision to remove the failed graft prior to the next transplant, and sensitization of re-transplant candidates due to high titers of circulating anti-HLA antibodies are major concerns affecting post-transplant outcome.*
• 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).	Not included in the list	• *These scenarios do not need a lifesaving ITx, but they require an early referral to a center with experience in intestinal rehabilitation.* • *Tufting enteropathy may improve during childhood and beyond, up to weaning off HPN.* • *Multiple intestinal fistulas, frozen abdomens, radiation enteritis, IF after bariatric surgery also require early referral to expert centers.*
• Intestinal failure with high morbidity (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).	Not included in the list	• *Even though ITx appears to achieve worthwhile gains in QoL for children and adult recipients, the risks related to immunosuppression and the risk of graft rejection must be taken into account if a preemptive ITx is considered (i.e., before the onset of complications of therapy related to HPN).* • *Survival on HPN of patients with dysmotility is similar to that of patients with SBS.*

Abbreviations: CRBSI, catheter related bloodstream infection; CVAD, central venous access device; HLA, human leukocyte antigen; HPN, home parenteral nutrition; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; ITx, intestinal transplantation; PN parenteral nutrition; SBS, short bowel syndrome.

a) recommend education of staff and patients/caregivers; implementation of an adequate policy of hand washing and disinfection by patients and staff; handwashing and disinfection by patients and caregivers before touching CVAD as well as after CVAD 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, CVAD exit site, stopcocks, catheter hubs and other sampling ports and regular change of intravenous administration sets.
b) suggest performing site care, including catheter hub cleaning on at least a weekly basis; changing CVAD dressings at least once weekly; avoiding CVAD care immediately after changing or emptying ostomy appliances and disinfecting hands after ostomy care.
c) not recommend the use of in-line filters; routine replacement of CVADs; antibiotic prophylaxis and heparin lock.

Catheter locking protocol is a key step for the prevention of CRBSI. 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.

Locking with sodium chloride 0.9% has been demonstrated to be superior to heparin solution for the prevention of CRBSI. 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 biofilm growth [567-569]. An RCT in >750 cancer patient with a newly inserted port compared low-dose heparin (300 U/3 mL) versus 0.9% saline locking. CRBSI rate was 0.03/1000 catheter days in the saline group versus 0.10/1000 catheter days in the heparin group [570]. Several meta-analyzes showed that CVAD patency is not prolonged in catheters that are not used for blood processing by intermittent flushing with heparin when compared with normal saline [571-573].

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 [574,575]. The earliest non-controlled study with taurolidine as a catheter lock in the setting of HPN reported a decreased infection rate from 10.8 infections per 1000 catheter days pre-treatment to 0.8 thereafter [576].

The first prospective controlled trial randomizing HPN patients after treatment for CRBSI to receive either 2% taurolidine (n = 16) or heparin (150 U/mL, n = 14) 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 ($p < 0.0001$) [577]. 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 [578]. In 2013, Liu and co-workers [579] 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 (RR, 0.27, 95%CI 0.11–0.65, $p = 0.004$), and was associated with a non-significant decrease in Gram-positive infections (RR, 0.41, 95%CI, 0.15–1.09, $p = 0.07$). No association was observed with taurolidine locks and catheter-associated thrombosis. On the other hand, the same group performed a systematic review on taurolidine-citrate lock solution, including two studies on adult hemodialysis patients and one study on pediatric patients with hematological malignancies and catheters used for chemotherapy and intravenous medication/alimentation. They observed a reduced risk of CRBSI but an increased risk of vein thrombosis with taurolidine-citrate lock solution (1.35% taurolidine and 4% citrate) in comparison with standard heparin lock solution (5000 U/mL) [580].

Several recent studies with various taurolidine formulations have bolstered the available evidence on use of taurolidine to prevent CRBSIs, all in the setting of HPN support for adult benign CIF. Tribler et al. investigated CVAD locking with taurolidine 1.4%-citrate-heparin in comparison to control (low-dose heparin 100 IE/mL) in a single center study in 41 high-risk Danish HPN patients who had been stratified according to their prior CRBSI incidence. In 20 patients who received the taurolidine-containing formulation, no CRBSIs occurred in contrast to CRBSIs in seven out of 21 controls (incidence 1.0/1000 CVC days; $p < 0.05$). Costs in the taurolidine arm were lower because of fewer admission days related to CRBSI treatment [581].

Since locking with heparin solutions has been suspected of promoting CRBSI, Wouters et al. compared a pure taurolidine 2% lock to another control (saline 0.9%) in a multicenter trial. Patients were stratified in a new catheter group and a pre-existing catheter group. Overall 102 patients were analyzed. In the new catheter group, CRBSIs/1000 catheter days were significantly lower (0.29 vs 1.49) in the taurolidine arm while in patients who entered the trial with a pre-existing catheter CRBSI rates were also lower in the taurolidine arm (0.39 vs 1.32; $p > 0.05$ due to under-powering). Mean costs per patient were significantly lower for taurolidine. Drug-related adverse events were rare and generally mild [549].

A retrospective survey 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. CRBSI rates were 1.1/yr for heparin and 0.2/yr for taurolidine-locked catheters, while occlusion incidence rates were 0.2/yr for heparin and 0.1/yr 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 [582].

A retrospective study compared CRBSI rates twelve months before and twelve 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 [583].

Wouters et al. analyzed long-term complications and adverse events in this cohort of HPN patients during a more recent period (2006–2017) while all patients used taurolidine locks [584]. In 270 HPN patients who used taurolidine during 338,521 catheter days, CRBSIs, CVAD-related vein thrombosis (CRVT) and occlusions occurred at rates of 0.60, 0.28, and 0.12 events per 1000 catheter days, respectively. In 24 (9%) patients, mild to moderate adverse events resulted in discontinuation of taurolidine. A subsequent switch to 0.9% saline resulted in an increased CRBSI rate (adjusted rate ratio 4.01, $p = 0.02$). Several risk factors were identified for CRBSIs, including lower age and increased infusion frequency.

To identify the most effective catheter locking solution formulation in patients receiving HPN these authors also conducted a systematic review and individual-patient data meta-analysis (IPDMA) [585]. Primary outcome was the number of CRBSIs/1000 catheter days for each catheter locking solution. Three studies comprising 162 HPN patients and 45,695 catheter days were

included. CRBSI rates were significantly decreased in patients using taurolidine (rate 0.13) when compared with saline (rate 0.74, $p = 0.002$) or heparin (rate 2.01, $p < 0.001$). Taurolidine was the most effective catheter locking solution formulation in HPN patients for the prevention of CRBSIs, since the cumulative proportion of CRBSI-free patients using taurolidine, saline, and heparin after one year was 88%, 56%, and 14%, respectively. Three risk factors for CRBSIs were identified: type of catheter locking solution, intestinal dysmotility as underlying condition, and use of CVC [585].

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 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.

Other CVAD lock solutions are under investigation for CRBSI prevention. A retrospective crossover cohort study observed that 4% tetrasodium ethylenediaminetetraacetic acid (EDTA) solution, which has nonantibiotic antimicrobial, antibiofilm, and anticoagulant effects, was effective in reducing central line-related bloodstream infections (CLABSI) and catheter occlusions in 20 pediatric patients with long-term CVAD [586]. Similarly, a pre- and post-intervention study carried over 36 months including 20 adults on long-term HPN reported a significant reduction in the CLABSI rate after introducing CVAD lock with 4% EDTA solution ($p = 0.04$) [587]. No RCT in patients with CIF have yet been carried out.

12.1.2. Recommendation 111 (recommendation #91 of the 2016 CIF GL)

The creation of arterio-venous fistulas to prevent CVAD-related infections may be considered in carefully selected patients.

Grade of recommendation 0 - Strong consensus 100% agreement.

12.1.2.1. Commentary. Arterio-venous fistulas or shunts were the earliest type of central venous access when HPN was first used. A retrospective review of practice in the Netherlands, where some hospitals have continued to use these shunts, showed that while bloodstream infections were extremely rare for arterio-venous fistulas compared to tunneled CVCs, occlusion was more frequent [588]. It was recently shown that using autologous venous grafts instead of prosthetic materials to create arterio-venous fistulas lowers this risk for occlusion [589].

12.1.3. Recommendation 112 (recommendation #92 of the 2016 CIF GL)

Catheter locking with 70% ethanol should not be used to prevent CVAD-related infections, because its use is associated with systemic toxicity, catheter occlusion and catheter damage.

Grade of recommendation B - Strong consensus 100% agreement.

12.1.3.1. Commentary. 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 [590-595]. Benefits over antibiotics include the lack of development of microbial resistance, potent bactericidal and fungicidal properties, and low cost. Opilla et al. [592] studied nine HPN patients with a crossover design using ELT. Patients developed 81 CRBSIs before ELT and nine 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 [593]. A study from the US that evaluated hospital readmissions for CRBSI in home patients found that there was no length of stay 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%) [594]. A meta-analysis estimated the pooled effectiveness and safety of ELT in comparison with heparin locks with regard to CRBSI rate and CVAD replacements for pediatric patients with CIF. Fifty-three studies were included. In comparison with heparin locks, ELT reduced the CRBSI-rate per 1000 catheter days by 7.67 events and CVAD replacements by 5.07. ELT decreased the CRBSI rate by 81% and replacements by 72% [595]. However, a 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 [596]. Wolf et al. carried out a randomized, double-blind, placebo (heparinized saline)-controlled superiority trial to evaluated ethanol (70% ethanol) lock therapy as treatment and secondary prophylaxis for CRSBI in children with cancer or hematological disorders [597]. The results showed that ethanol lock therapy did not prevent CRBSI treatment failure, while it increased catheter occlusion. These data do not allow us to recommend ethanol lock for the prevention of CRBSI in patients on long-term HPN.

12.1.4. Recommendation 113 (recommendation #93 of the 2016 CIF GL)

Re-education of the patient and/or caregiver shall be made in patients who repeatedly present with CVAD-related infections.

Grade of recommendation GPP - Strong consensus 100% agreement.

12.1.4.1. Commentary. CVAD 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 [53]. Implementation of an adequate written policy and education of healthcare personnel and patients is necessary for the prevention of complications [598,599]. A randomized trial has provided evidence that interactive video-based education of both staff and patients reduces CRBSI in HPN patients and improves problem-solving capacities and QoL [600]. Such training of all individuals who are involved in HPN care is a key strategy for preventing CRBSI.

12.1.5. Recommendation 114 (recommendation #86 of the 2016 CIF GL)

CVAD-related infections should be managed according to current guidelines on long-term CVAD and as described in the comment section: a conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections; CVAD removal should be the first choice in case of tunnel infections or blood cultures positive for virulent bacteria; CVAD removal is mandatory for port abscesses, complicated infections, persistent hemodynamic instability, or blood cultures that are positive for fungi.

Grade of recommendation B - Strong consensus 100% agreement.

12.1.5.1. Commentary. Available data on the diagnosis of CVAD-related infections 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 bacteremia. A diagnosis of CRBSI should be achieved (a) by quantitative or semiquantitative culture of the catheter (when the CVAD is removed or exchanged over a guide wire), or (b) by paired quantitative blood cultures or paired qualitative blood cultures from a peripheral vein and from the CVAD, with continuous monitoring of the differential time to positivity (if the CVAD is left in place) [598,499,602,603]. A probable CRBSI is characterized by a colonized catheter in association with clinical signs suggesting septicemia, 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 CRBSI [599,604].

Clinical assessment is recommended to evaluate whether the CVAD is the source of the CRBSI [605]. It is not always necessary to remove a CVAD in case of a CRBSI, as was confirmed by a high mean CVAD-salvage rate of 55% (depending on infection type and causative microorganism) in a Danish HPN cohort of adult patients, although the risk of a CRBSI relapse (7,5%) or recurrence (7,3%) was increased [606]. A conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections due to *Staphylococcus aureus*, coagulase-negative staphylococci, and Gram-negative bacilli, before removing the CVAD [40,598,599]. CVAD 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 [598]. For salvage of CVAD in patients with uncomplicated infections, antibiotic lock therapy should be used for two 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 [251,598]. Reinsertion of long-term CVAD 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 CVAD in a stable patient ideally should be done after a systemic antibiotic course of therapy is completed, and repeat blood samples drawn five to ten days later yield negative results [598]. Successful salvage of infected implanted ports by antibiotic treatment is rare and most of these devices have to be removed [607]. Antibiotic locks may have limited efficacy due to the presence of fibrin deposits that harbor bacteria inside the port reservoir [608]. 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 [601,608].

While thrombolysis with urokinase, streptokinase, or tissue plasminogen activator has been successfully used to unblock clogged CVAD, 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 [601,609].

While prophylactic use of antibiotic locks is not recommended, this strategy appears effective for attempted CVAD salvage upon infection, as was suggested by a review of available data on outcomes of three treatments: systemic antibiotics, antimicrobial lock therapy, and catheter exchange [610]. In 28 studies comprising 4911 CRBSIs it was found that to achieve successful catheter salvage, the addition of an antimicrobial lock solution was superior to systemic antibiotics alone (OR 1.75, $p = 0.003$). Also, CRBSI recurrence was less common for antimicrobial lock therapy compared to systemic antibiotics alone (OR 0.26, $p = 0.002$). Successful salvage rates were highest for coagulase-negative staphylococci, followed by Gram-negative rods and *S. aureus* [610].

A Dutch study investigated the efficacy of chronic nasal mupirocin use on *S. aureus* eradication and prevention of CVAD related infections in 266 patients on HPN who were screened for *S. aureus* carriage [611]. In case of carriage, the patient was instructed to apply mupirocin nasal ointment monthly. *S. aureus* nasal carriage was found in 143 (54%) of patients. Eradication was successful in 66% of patients treated with mupirocin. Overall *S. aureus* catheter-related infection rates decreased by 50%. The decrease was mostly due to a drop in CRBSI rates (0.26 versus 0.1/1000 catheter days). Overall CRBSI rates decreased as well (incidence ratio rate 0.43). Low-level mupirocin resistance was observed in four patients [611].

S. aureus bacteremia is a feared complication in patients with a CVAD, because of its association with septic thrombosis. As a standard for this diagnosis was lacking, the value of Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography ([18F]FDG-PET/CT) imaging to establish septic thrombosis was evaluated in 93 patients with a CVAD-related *S. aureus* bacteremia, 54 of whom were on HPN. It was found that this technique can detect septic thrombosis since a ratio of 1.6 between tracer uptake in the thrombus versus blood allowed differentiation between septic and non-septic thrombosis (sensitivity of 92%; specificity 89%). Based on these data a decision rule-based algorithm was developed to guide clinical management of CVAD-related *S. aureus* bacteremia [612].

12.2. Which are the procedures for the prevention, diagnosis and management of CVAD-related occlusion/thrombosis?

12.2.1. Recommendation 115 (recommendation #94 of the 2016 CIF GL)

Treatment of CVAD-related venous thrombosis should be made with anticoagulation, the duration of which to be chosen on an individual basis.

Grade of recommendation B - Strong consensus 100% agreement.

12.2.2. Recommendation 116 (recommendation #94 of the 2016 CIF GL)

In CRVT, the decision to maintain the CVAD should depend on individual factors (e.g. necessity of a central line, lack of infection, clinical outcome).

Grade of recommendation GPP - Strong consensus 100% agreement.

12.2.2.1. Commentary. Since the 2016 guideline for CIF, no studies endorsing changes or upgrade of the recommendations about CRVT have been published.

Development of CRVT 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, where the blood clot that adheres to the vessel wall and can occlude the tip of the catheter but does not completely occlude the vein, to venous thrombosis totally occluding the vein lumen [613].

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 [39]. 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 [52,111,609,614-616]. These data were confirmed by a recent meta-analysis reporting a range of 0.02–1.5/1000 catheter days [617]. 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 [618].

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 [619].

A prospective study of the HAN&CIF group in 62 patients on HPN, the incidence of CRVT with serial Color Doppler Duplex Sonography evaluations for twelve months after catheter insertion was 0.045/catheter/yr, quite similar to that found in retrospective studies [620]. 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, edema, warmth, erythema, and the development of regional collateral vessels, usually along with catheter malfunction, although these symptoms and signs are nonspecific. The gold standard method for CRVT diagnosis is venography, but it is invasive and requires exposure to intravenous contrast 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 [621]. 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 [621]. In this review, only one study evaluated the value of the clinical findings, D-dimer, MRI, rheography, and plethysmography and found a wide range of sensitivity and specificity [621]. Reliable data on the accuracy of ultrasound in CRVT are limited [622]. 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 computed tomography, or MRI may be useful and of potential interest, but are not yet validated [622]. According to the results of a recently published prospective study, Color Doppler Duplex Sonography is not recommended for routine screening of CRVT in asymptomatic patients with benign diseases on HPN [620].

The optimum management of CRVT is controversial as there are few prospective studies on this topic [622,623]. CRVT is usually treated with anticoagulation, usually 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 [624]. 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 three to six months and in some cases forever [625–627].

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 [598]. Moreover, there is a risk of 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 [625–627].

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 ten days long). In some cases, it may be necessary to place a superior vena cava 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 [625–627].

12.2.3. Recommendation 117 (recommendation #95 of the 2016 CIF GL and R #14 of the ESPEN GLs 2020 on HPN)

For the primary prevention of CVAD-related venous thrombosis, insertion of the CVAD should be made using ultrasound guidance with placement of the tip at the superior vena cava-right atrium junction.

Grade of recommendation B - Strong consensus 96% agreement.

12.2.4. Recommendation 118 (recommendation #96 of the 2016 CIF GL)

Routine thromboprophylaxis with drugs (heparin, warfarin) should not be made for the primary prevention of CVAD-related venous thrombosis for all adults on HPN based on the risk/benefit balance.

Grade of recommendation B - Strong consensus 91% agreement.

12.2.4.1. Commentary. 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 [600]. CVC composed of silicon or polyurethane are less often associated with local thrombosis than the old ones made of polyethylene [624]. 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 [628]). Left-sided catheters also have been associated with higher thrombosis risk [624]. In a systematic review, peripherally inserted central venous catheters (PICCs) and insertion of CVCs at femoral sites increases CRVT when compared with other catheter types or insertion sites, respectively [629]. These general recommendations are included in some clinical guidelines on prevention of CRVT [600,630,631].

An association between CRBSI and CRVT has been reported [624]. In recent studies, an increased risk has been described for vein thrombosis associated with ethanol lock therapy in the pediatric HPN population [630].

In the prevention of CRVT, 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-analyzes 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) [567,632-640]. Based on the current evidence, previous published guidelines have not recommended the use of routine prophylactic anticoagulation in patients with CVC [628,640].

At least five 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 [641–645]. 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/d) 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 [646]. Three studies evaluated warfarin prophylaxis in HPN adults [646]. In a prospective non-randomized trial of 2 mg of warfarin given to 23 HPN patients, the incidence of venous thrombosis was one in 1617 catheter days compared with one in 251 days prior to the study [647]. In a retrospective review of 47 HPN patients with HIV/AIDS, the thrombosis rate was 0.016 per patient per month in nine patients receiving 1 mg/d warfarin compared with a rate of 0.09 thromboses per patient per month in 38 patients on no prophylaxis [648]. Finally, in a retrospective review of HPN patients who already had one thrombotic event, the use of therapeutic warfarin resulted in a significantly decreased thrombosis rate (one in 18 patient months vs one in 184 patient months) [649]. 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 [650].

Barco et al. performed a systematic review on the efficacy, safety and feasibility of anticoagulant use for preventing and treating CRVT during short-term PN. The seven interventional studies of short-term PN (adult population, n = 5) were included showing that intravenous unfractionated heparin did not prevent catheter-related thrombosis if compared to saline [651]. No interventional studies were conducted in patients on long-term HPN.

Two recent single center retrospective studies addressed the role of anticoagulation in preventing CRVT in adults with CIF. The study by Barco et al. included 236 patients, 136 of whom received anticoagulants at HPN onset. Only a mild protection for anticoagulation was observed: the rate of first CRVT was 10.1/100 patient-years (n = 31, 95%CI 19.1–25.9/100 patient-years) for patients on anticoagulants and 13.3/100 patient-years (n = 27, 95%CI 15.4–29.8/100 patient years) for those off anticoagulants [652].

More recently, Gillis et al., compared CRVT risk in 389 patients in the presence or absence of anticoagulants [653]. In total, 84 patients developed a primary CRVT during the observation period. A secondary CRVT occurred in 14% of the patients who started anticoagulants after a primary CRVT and in 60% of those who did not receive anticoagulants. Multivariate analysis showed that anticoagulant use was associated with a decreased CRVT risk (OR 0.53, 95%CI 0.31–0.89, p = 0.02), whereas left-sided CVAD insertion (OR 2.00, 95%CI 1.36–2.94), a history of venous thrombosis (OR 1.73, 95%CI 1.05–2.84), and a shorter period postinsertion (OR 0.78, 95% CI 0.65–0.92) were independently associated with an increased CRVT risk [653].

A UK survey on the use of anticoagulation in the current practice to prevent CRVT in patients on HPN showed that 80% of the 41 responders anticoagulated patients who had previous line thrombosis and 65% anticoagulated those who had any deep vein thrombosis or pulmonary embolus. The most commonly used anticoagulant was dose-adjusted warfarin aiming for an INR of two to three [654]. Based on this evidence, the decision to use anticoagulation therapy to prevent CRVT 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 meantime, the decision to start thromboprophylaxis should be decided on an individual basis.

12.2.5. Recommendation 119 (recommendation #97 of the 2016 CIF GL)

Pulsatile flushing of catheters with saline can be made instead of flushing with heparin solution to prevent CVAD occlusion.

Grade of recommendation 0 - Strong consensus 100% agreement.

12.2.5.1. Commentary. 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/yr (0.059–0.083) [655]. 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 [656].

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 [600].

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 [657]. 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 limited, 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 [657]. However, many of the studies included in this systematic review included short-term catheters and hospitalized patients, and therefore these results possibly cannot be extrapolated 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.

12.2.6. Recommendation 120 (recommendation 98 of the 2016 CIF GL)

Irrigation of the CVAD with saline can be made as the first attempt to restore catheter patency in intra-lumen CVAD occlusion.

Grade of recommendation GPP - Strong consensus 100% agreement.

12.2.7. Recommendation 121 (recommendation #99 of the 2016 CIF GL)

Fibrinolytic drugs can be used for the treatment of acute CVAD occlusion likely caused by blood clotting.

Grade of recommendation GPP - Strong consensus 100% agreement.

12.2.7.1. Commentary. 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) [656]. 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 [658]. 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 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 NaOH [658]. 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 [615].

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 six to 8 h.

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 partial 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 [659].

Another chemical agent used for catheter clearing is sodium hydroxide. In a retrospective study that included data from six 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 [660].

Allan et al. published a report on the safe and effective use of endoluminal brushing to manage occluded CVCs in patients requiring long-term HPN [661]. In this study, those patients admitted with a CVC occlusion to one of the two national IF centers 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.

13. Chapter 11 - Prevention/treatment of intestinal failure-associated liver disease

13.1. Which are the tools to prevent the development of IFALD

13.1.1. Recommendation 122 (recommendation #100 of the 2016 CIF GL)

The following intervention should be made to prevent the development of IFALD.

- prevention of sepsis or managing it, if present
- preservation of small intestinal length and retainment/restoration of the colon in continuity with small bowel;
- maintenance of oral/enteral intake and, where feasible, considering distal EN/chyme reinfusion in patients with non in continuity small intestine;
- cycling PN infusion;
- avoiding PN overfeeding;
- limiting the dose of soybean-oil based lipid to less than 1 g/kg/d
- avoiding any hepatoxic insults wherever possible (e.g. alcohol)

Grade of recommendation B - Strong consensus 100% agreement.

13.1.1.1. Commentary. 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 [52]. 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 auto-immune), 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 [115,116,662-666]. As a result, study definitions are heterogenous, including terms such as ‘abnormal liver function tests’, ‘chronic cholestasis’ and ‘advanced’ or ‘severe liver disease’ [115,116,662-666]. However, reliance on biochemistry alone for definition can lead to inconsistent reports of the true incidence and prevalence of IFALD [667].

Indeed, a position statement from the HAN&CIF group of ESPEN published in 2018 reaffirmed the importance of liver biopsy as still the gold-standard modality to diagnose IFALD, although this must be balanced against the risks inherent to such an invasive procedure [547]. Thus, there remains a requirement for a consensus definition, that sets parameters of biochemical and histological abnormality, to truly standardize the use of the term IFALD, both in clinical and research spheres.

Histological abnormalities associated with IFALD include steatosis, portal inflammation, portal edema, ductal reaction, ductopenia, and portal and perivenular fibrosis [668]. 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 [668]. 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 [668]. However, liver biopsy carries risks including hemorrhage 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 [669]. Proton magnetic resonance spectroscopy was used to quantify liver fat content in a pilot study of 15 adults with CIF who had received HPN for more than six months and found that patients with steatosis had higher alanine aminotransferase values than those without steatosis [670]. A recent systematic review included four studies assessing two serum (vitamin B12, fibroblast growth factor (FGF) 21) and two imaging tests (Fibroscan, computer-aided ultrasound) and found that, while vitamin B12 did not correlate with liver injury, fibroscan correlated with cholestasis rather than fibrosis and FGF 21 correlated with steatosis [670]. In addition, several computer-aided ultrasound parameters correlated with the degree of steatosis as assessed by proton magnetic resonance spectroscopy. However, the authors of the systematic review concluded that the limited data do not confirm the diagnostic value of these non-invasive assessments of IFALD [670]. 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 [35]. A consensus categorization appropriate to adults is now required that ideally incorporates defined histological and/or radiological parameters [547].

The incidence or prevalence of IFALD cannot be accurately gauged against a standardized consensus definition. The prevalence 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, such that previous studies have reported the prevalence of abnormal liver tests and/or cholestasis with rates ranging from 19% to 95% [115,116,662-666]. Notably, a recent single-center study evaluated the use of nine criteria based on liver function tests and ultrasound to diagnose IFALD in 113 patients and found that IFALD prevalence can vary from 13 to 40% cholestasis, 27–90% steatosis, 2–5% fibrosis and 8–75% 'unclassified', depending on the diagnostic criteria chosen [667]. Micic and colleagues performed a retrospective analysis of liver biopsies performed in 53 individuals undergoing ITx and found that the fibrosis-4 (FIB-4) index positively correlated with the stage of liver fibrosis on biopsy, suggesting that the FIB-4 may be useful in identifying liver fibrosis in IFALD [671]. A prospective longitudinal evaluation of 20 HPN-dependent adults demonstrated that dynamic liver function assessment using the 'Liver Maximum Capacity' (LiMAx) test may be more sensitive in detecting early changes in liver function than other modalities including fibroscan, indocyanine green test and FIB-4 index, although clearly larger studies will be required to validate these findings [672]. Similarly, a small cross-sectional study of 32 patients in children suggested that the aminotransferase-to-platelet-ratio-index and transient elastography correlated better with known risk factors for IFALD than did the enhanced liver fibrosis score, although the authors also concluded that larger studies are required into the diagnostic value of these non-invasive tools in IFALD [673].

Moreover, the incidence of clinically-advanced liver disease also varies in published studies from 0% to 50% [115,116,662-666]. Two cohort studies exemplify this variation [130,115]. 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 six years [115]. By contrast, Luman and colleagues evaluated 107 patients receiving HPN for a median of 40 mo (range 4–252), 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 [115]. Furthermore, mortality in patients with IFALD has been reported to range from 0 to 22% in various studies [115,116,662-666]. Thus, a more accurate estimate of IFALD incidence, prevalence, morbidity, and mortality can only be ascertained once a consensus regarding definition is reached.

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

13.2. Sepsis

Evidence for sepsis as a risk factor for IFALD derives from two retrospective studies of PN in pediatric patients [674,675]. 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 [676]. 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 [677,678]. Indeed, there is emerging evidence that intestinal microbes may play a role in the progression of liver disease in non-IF related liver disease [679]. There are, however, no large prospective, randomized controlled data supporting the prophylactic use of antibiotics to prevent IFALD in CIF.

13.3. Intestinal anatomy

Cavicchi et al. [115] and Luman et al. [666] 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 [662] 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 [662]. More recently, Cazals-Hatem et al. [680] demonstrated that ultra-short bowel (<20 cm) and alcohol consumption were independent risk factors for the development of liver fibrosis in 32 adults dependent on HPN [680]. In a larger study of 135 adults with CIF, low levels of plasma citrulline levels (a surrogate marker of small bowel mass and function) FGF 19 were associated with chronic cholestasis; patients with chronic cholestasis were also noted to have a reduced five-year survival rate compared to those without chronic cholestasis, leading the authors to devise a scoring system incorporating citrulline levels, FGF 19 and the number of intravenous infusions per week to predict overall survival [681].

13.4. Oral/enteral nutrition

Earlier studies in infants and neonates receiving short-term PN have demonstrated the benefit of EN on liver outcomes [682,683]. More recently, a large multi-center international study demonstrated that the severity of CIF, as reflected by the type and volume of parenteral support required, was associated with the occurrence of IFALD in adults [13]. While it is likely that both increased PN requirements and reduced EN play a synergistic role in the development of IFALD, further mechanistic insight has been provided by studies demonstrating the beneficial effects on liver function of chyme reinfusion in patients with double enterostomies and ECF or EAF probably via restoration of the enterohepatic circulation of bile salts, subsequent recovery of the bile salt-FGF 19 axis and activation of the farnesoid x receptor [684,685].

13.5. PN infusion modality

A two-week prospective study of adults receiving PN demonstrated that cycling improved bilirubin levels [686]. Clearly, cyclic PN yields greater freedom and improved QoL for patients requiring long-term PN.

13.6. Nutrient deficiency

Protein and/or EFA deficiency is associated with steatosis in animal studies [687]. Deficiencies in methionine metabolites (choline, carnitine, and taurine) can result in hepatic steatosis and chronic cholestasis in premature infants [688]. Taurine supplementation has been shown to be effective in decreasing cholestasis in neonates and infants [689], but there are no comparable studies in adults. Carnitine deficiency did not influence IFALD in an intervention study in adults [690]. Small studies have shown that choline replacement can improve liver transaminases in adults [691,692]; however, sufficient quantities are unstable in PN solutions, complicating delivery [692].

13.7. 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 [693,694]. Excessive lipid can also have a deleterious effect on hepatic function; soybean-based lipid emulsions in excess of 1 g/kg/d have been shown to be detrimental to liver function, with associated morbidity and mortality [115]. A four-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 [695]. More recently, Klek and colleagues conducted a twelve-month RCT in 67 HPN-dependent patients and found no difference in liver enzymes between groups receiving LCT, medium/long-chain triglycerides, olive oil/LCT and a mix of soybean/MCT/olive oil/fish oil; the authors noted that the use of olive oil may have been associated with a drop in serum bilirubin levels, although the group receiving olive oil emulsions had with higher bilirubin levels at the start of the study [696]. In this study, no patients developed EFAD. The authors subsequently published five-year open-label follow-up study and again found no difference between groups in liver function tests other than, this time, a significant reduction in medium bilirubin concentration in the soybean/MCT/olive oil/fish oil group compared to baseline [697]. A recent systematic review evaluating the effects of different HPN lipid formulations identified ten studies (including RCTs, prospective cohort and cross-sectional studies) comparing lipid emulsions and one study comparing lipid emulsions with lipid-free HPN and found that emulsions containing olive and/or fish oil were associated with lower ω-6:ω-3 fatty acid ratio and positive reductions in makers in liver function; the authors concluded, however, that further studies are needed before drawing definitive conclusions on the clinical value of olive and/or fish oil emulsions in the HPN population [65]. Another recent systematic review that included six RCTs comparing two or more intravenous lipid emulsions also concluded that there is insufficient evidence to determine superiority of one formulation over another, although they also highlighted that no studies reported EFAD [106]. Thus, while data are promising, larger 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.

13.8. Which are the tools for the treatment of IFALD

13.8.1. Recommendation 123 (recommendation #101 of the 2016 CIF GL)

Treatment of IFALD should rely on:

- re-consideration of all the measures to prevent IFALD
- revising the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω-6/ω-3 PUFA ratio
- revising any potential inflammatory/infective foci
- excluding/managing any other causative factors of abnormal liver function

Grade of recommendation B - Strong consensus 100% agreement.

13.8.1.1. Commentary. As outlined in the ESPEN position statement on IFALD, it is important to exclude other causative factors, that should be investigated and managed in patients with CIF presenting with abnormal liver function along standard lines; this may include serological and radiological investigation, where indicated, as well as avoiding concomitant hepatotoxic agents if possible [547]. In addition, approaches to managing IFALD include nutritional, pharmacological and transplantation.

13.9. Nutritional approaches

Since overfeeding can be deleterious [115,694], energy requirements should be tailored to the individual, with optimization of oral/enteral nutrition, wherever possible. A prospective, non-randomized study evaluating adults with hyperbilirubinemia receiving PN demonstrated an improvement in liver function following cycling of the infusion [686]. A recent study in patients with mesenteric ischemia demonstrated an improvement in

abnormal liver biochemistry in the majority of patients one-year following restoration of bowel continuity [425]. Furthermore, and as mentioned earlier, it is apparent that chyme re-infusion and distal EN can have beneficial effects on liver function [685,698,684].

While there are no RCTs 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/d [115]. 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 normalization of bilirubin levels [699]. There are currently no data to support the role of lipid-free regimens to treat IFALD. Equally, while there are case reports [114,698,700-703], case series [559,704], and reviews [65,548,705,706], to support the role of pure fish oil emulsion, olive 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.

13.10. 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 [707], 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 [708]. Based on the evidence outlined earlier, the use of choline, taurine, or carnitine cannot currently be recommended to treat IFALD in adults with CIF [689-692]. GLP-2 analogues may have a role in improving liver function in patients with CIF; teduglutide use has been associated with an improvement in recorded liver function particularly in those patients achieving larger reductions in parenteral support [377], while glepaglutide was recently shown to be associated with an increase in FGF 19 levels and reduction in alkaline phosphatase levels in a small double-blind study of 18 patients with SBS-IF, leading the authors to suggest that glepaglutide may stimulate the bile acid/farnesoid x receptor/FGF 19 axis [709]. While GLP-2 analogues can be used to reduce PN requirements in SBS-IF and may prove to be of circumstantial benefit to IFALD, their singular use to treat IFALD as a sole indication warrants further evaluation.

13.11. Transplantation

Impending or overt liver failure is an indication for small intestinal/multivisceral transplantation (see: relevant section in this CIF Guideline). 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.

14. Chapter 12 - Prevention/treatment of gallbladder sludge and stones

14.1. Which are the tools to prevent/treat gallbladder sludge and stones

14.1.1. Recommendation 124 (recommendation #102 of the 2016 CIF GL)

Maintenance/resumption of oral feeding can be made be considered to prevent/treat of gallbladder sludge.

Grade of recommendation 0 - Strong consensus 96% agreement.

14.1.2. Recommendation 125 (recommendation #103 of the 2016 CIF GL)

Cholecystectomy and/or endoscopic procedures should be performed in the case of biliary complications as for the general population.

Grade of recommendation B - Strong consensus 100% agreement.

14.1.3. Recommendation 126

Cholecystectomy during abdominal surgery for other indications can be considered in patients with CIF known to have gallstones at the time of surgery, providing this additional procedure is felt to have a low risk of morbidity and the risk vs. benefit of cholecystectomy is carefully considered with the patient.

Grade of recommendation GPP - Strong consensus 91% agreement.

14.1.3.1. Commentary. Patients on PN have been recognized as at risk of developing biliary sludge or cholelithiasis [40,710,711]. In a prospective study that included 23 selected adult patients on TPN, serial ultrasonographic studies indicated that the percentage of sludge-positive patients during PN increased from 6% during the first three weeks to 50% during the fourth and the sixth week and reached 100% after six weeks [712]. In a retrospective study that included 119 patients on long-term HPN, the same team reported that the probability of developing cholelithiasis during HPN was estimated to be 6.2%, 21.2%, and 38.7% at six, twelve, and 24 months, respectively [713]. 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 [714]. In two retrospective studies that included patients with a short bowel, the prevalence of cholelithiasis was 31% (n = 35) and 43% (n = 38), respectively [74,715]. In the Dray's study, biliary complications developed in 7% of the patients during follow-up [713]. More recently, Appleton and colleagues reported the outcomes of 81 patients from the UK who were dependent on home parenteral support for more than five-years; notably 17/63 (27%; 13/17 were symptomatic) patients with no pre-existing gallstones on imaging went on to develop gallstones after commencing HPN after a median time of 133 months. Subsequent incidence at ten years was 21%, 38% at 20 years and 47% at 30 years [711].

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 [74], an absent ileocecal junction [716], the duration of PN, increased weekly energy content and the provision of parenteral lipids, and Crohn's disease but risk is mostly attributable to nil or negligible ingesta [710,712,716,717]. This is probably due to bile stasis during fasting that is due to lack of cholecystokinin hormone that usually empties the gallbladder [712,718,719]. It has been also suggested that bile composition may be altered by fasting [720] or lipid infusion [721], or, more likely, by MCT/LCT [722], or the use of narcotics or anticholinergics [719].

In the eighties, prophylactic cholecystectomy was advocated by some authors [723] but has never been confirmed in a prospective trial. Indeed, since the majority of HPN-dependent patients in the long-term series reported by Appleton did not actually develop gallstones after commencing HPN, prophylactic cholecystectomy in any patient with type 3 IF and an apparently healthy gallbladder is unlikely to be justified [711]. However, given that 13/17 of those who developed gallstones after HPN initiation became symptomatic, it may be reasonable to consider ‘en-passant’ cholecystectomy

during abdominal surgery for other indications in patients with type 3 IF known to have asymptomatic gallstones at the time of surgery, providing this additional procedure is felt to have a low risk of morbidity and the risk vs. benefit of cholecystectomy is carefully considered with the patient [711].

There were a few randomized studies in humans (very limited number of patients) that showed that rapid intravenous administration of amino acids [724] or ω-3 fatty acids [725] could reduce the risk of developing biliary stones. Sinealide (cholecystokinin) that was used in five human studies, failed to show long-term effects in preventing and treating PN-associated gallbladder disease [726-728]. In animal studies it has been observed that intravenous chenodeoxycholate prevents calcium bilirubinate gallstones [729] and glutamine-enriched TPN prevents the lithogenic effect of PN [730]. In practice, the major recommendation for preventing biliary sludge or stone formation is to encourage oral and/or enteral nutrition 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 four weeks after resuming oral feeding [712]. Besides the effect of resuming oral feeding on biliary sludge, and consideration of 'en-passant' cholecystectomy during abdominal surgery in patients with type 3 IF, treatment of biliary stones is similar to that in the general population [710-731].

15. Chapter 13 - Prevention/treatment of intestinal failure-associated renal failure and stones

15.1. Which are the strategies to prevent/treat renal failure and renal stones

15.1.1. Recommendation 127 (recommendation #104 of the 2016 CIF GL)

For the primary prevention of renal failure and of renal stones in patients with CIF, regular monitoring shall be performed of renal function and fluid balance as well as a timely adjustment of fluid supplementation in order to avoid episodes of dehydration.

Grade of recommendation GPP - Strong consensus 100% agreement.

15.1.2. Recommendation 128 (recommendation #105 of the 2016 CIF GL)

For the primary prevention of renal failure, acute and chronic infections as well as acute and chronic dehydration shall be timely addressed by the relevant clinical intervention.

Grade of recommendation GPP - Strong consensus 100% agreement.

15.1.3. Recommendation 129 (recommendation #106 of the 2016 CIF GL)

For the primary prevention of oxalate renal stones, a low oxalate and low fat diet, in addition to an increase of oral calcium, should be prescribed to reduce the risk of oxalate stone formation in patients with SBS with a colon in continuity.

Grade of recommendation GPP - Strong consensus 95% agreement.

15.1.4. Recommendation 130 (recommendation #107 of the 2016 CIF GL)

Avoiding metabolic acidosis and giving citrate supplementation can be recommended, to reduce the risk of uric acid stones.

Grade of recommendation GPP - Strong consensus 96% agreement.

15.1.5. Recommendation 131 (recommendation #108 of the 2016 CIF GL)

In patients with CIF, renal failure and renal stones shall be treated according to the standards for these conditions.

Grade of recommendation GPP - Strong consensus 100% agreement.

15.1.5.1. Commentary. Renal complications, reduced kidney function, and renal stones are among the metabolic complications that patients with CIF on long-term HPN are up against. For the clinician, this is a challenge since the possible end-stage scenario with chronic kidney disease 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 chronic kidney disease is scarce and very little medical evidence on renal failure and renal stones related to CIF is at hand.

An early retrospective study testing the change in glomerular filtration rate, measured as creatinine clearance in 33 long-term HPN patients [732], showed that renal clearance decreased by 3.5 ± 6.3% per year, greater than expected from increasing age alone. A retrospective study compared renal function, evaluated by estimated glomerular filtration rate (GFR) of 33 patients on HPN with that of 22 patients who underwent ITx. The annual decline in renal function and a five-year probability of retaining normal renal function were 2.8% and 84% respectively in patients on HPN and 14.5% and 44% in the transplanted group [733]. More recently, Chalencon et al. investigated the GFR of 40 adult patients with CIF by measured GFR, observing a decline of 2.1% per year [734]. The study demonstrated that estimated GFR by creatinine-based equations overestimated renal function in patients with CIF, probably because of low serum creatinine concentration due to the presence of sarcopenia [734].

Two cross sectional studies reported a decreased GFR in 52–56% of patients on HPN [45,735]. In a retrospective and prospective study on 72 adults, it was observed that chronic kidney disease (estimated GFR <60 mL/min/1.73 m^2 body surface) was present in 10.0% patients at initiating HPN and in 35.9% at the end of the follow up, indicating that, in patients with CIF, renal function may be already impaired at starting HPN and may worsen during the treatment [736].

The mechanism of decreased renal function in patients with CIF is multifactorial. Chronic dehydration caused by high stomal losses [735,736], repeated episodes of CRBSI [732,736], the use of nephrotoxic medications [732], existing urologic disease [735,736] and aging [736] have been reported to be associated with decreased renal function in adult patients.

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 [74]. The risk of development of renal stones in SBS without a colon in continuity has historically considered very low [74]. They derive from calcium oxalate crystallization in the collecting system. Renal colic, urinary tract infections and an obstructive uropathy with an associated risk of irreversible renal damage can develop. Calcium oxalate may also be deposited in the renal parenchyma (nephrocalcinosis) and may cause a chronic renal failure [737,738].

Renal stones and nephrocalcinosis are linked to increased absorption of oxalate and hypovolemia and dehydration [737]. 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; however, in patients with SBS, 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 [126,252]). The prevalence and incidence of renal damage caused by this mechanism is unknown [738]. In prevention, one should focus on sufficient IVS 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 [739]. A low-fat diet or replacing with MCT and oral calcium supplementation at meal time have also to be considered [126,252].

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 [126,252].

A recent single center observational retrospective study including 459 patients with SBS on HPN reported the development of kidney stones in 24% of patients, with no difference in the incidence between patients with a colon in continuity and those with an end stoma [740]. Stone composition, evaluated in ten patients was of calcium oxalate monohydrate/dihydrate, a mixture of calcium oxalate and calcium hydrogen phosphate dihydrate in two, and magnesium ammonium phosphate (struvite) [740]. In patients treated with PN and limited oral feeding, the risk of urolithiasis was twice as high as in patients receiving PN only. No association with the length of residual small bowel and the severity of CIF was found [740].

No data on the risk of renal stones in patients with CIF due to mechanisms other than SBS have been provided so far.

16. Chapter 14 - Prevention/treatment of intestinal failure-associated metabolic bone disease

16.1. Which are the strategies to prevent/treat metabolic bone disease

16.1.1. Recommendation 132 (recommendation #109, 110 of the 2016 CIF GL)

Patients with CIF should be routinely monitored for MBD by bone densitometry scanning, biochemistry, and clinical history.

Grades of recommendation GPP - Strong consensus 100% agreement.

16.1.2. Recommendation 133 (recommendation #111 of the 2016 CIF GL)

General risk factors for developing MBD 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, should be addressed promptly in all patients with CIF.

Grades of recommendation GPP - Strong consensus 100% agreement.

16.1.3. Recommendation 134 (recommendation #112 of the 2016 CIF GL)

Optimization of PN admixture with the required supplements of vitamin D, calcium and phosphate can be the initial step in management of MBD in patients with CIF. Further, medical treatment can be used to stabilize/increase BMD and lower fracture risk.

Grades of recommendation 0 - Strong consensus 96% agreement.

16.1.3.1. Commentary. MBD consists of a group of disorders that result in defective bone density (osteopenia, osteoporosis, etc.) and/or bone mineralization (osteomalacia, renal osteodystrophy, etc.) and is quite common in patients on HPN. An ESPEN multicenter cross-sectional survey [741] of 165 patients evaluated the prevalence of MBD by dual-energy X-ray absorptiometry (DEXA). In 84% of the patients, the BMD T-score of the femoral neck or spine was lower than one (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. A prospective study of 60 adults from China with SBS who had been weaned from PN noted that 96.6% (58/60) had a BMD T Score of < -1.0 as measured by DEXA [742]. Osteopenia was noted in 68.3% while 28.3% of patients had osteoporosis. An HPN cohort from Northern Alberta, Canada noted that out of 62 patients who underwent DEXA, 16 (25.8%) had osteopenia and 17 (27.4%) had osteoporosis [172]. Other groups have also reported similarly high rates of osteopenia and osteoporosis that are significantly higher than noted in matched controls without CIF [173,743]. 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 [744-746] 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.

The pathogenesis of MBD is most likely related to the underlying disease, malabsorption, chronic inflammation, or the use of medications, in particular corticosteroids. In retrospective review of HPN patients from Canada, 50% were noted to have 25-hydroxy vitamin D level between 20 and 30 ng/mL while 25.8% had level less than 20 ng/mL [172]. In a cohort of 167 patients from Denmark with intestinal insufficiency (n = 71) and IF on HPN (n = 97), a multivariate analysis noted that BMI and vitamin D deficiency were independent predictors of BMD for the spine and hip [173]. Additionally, a study of 75 patients on HPN noted that both spinal and hip BMD was significantly reduced in patients with Crohn's disease compared to those without IBD at initiation of HPN therapy, indicating significant impact of underlying disease on BMD [245]. Treatment with PN may also affect bone health with possible PN-related factors including toxicity from aluminum contamination of the nutrition formula, increased sensitivity to vitamin D suppressing parathyroid hormone (PTH) secretion, and hypercalciuria induced by the intravenous infusion of nutrients. HPN 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, Cu, Fl, B, 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 [747-750].

Although gathering clinical factors such as loss of height, bone pain, smoking history, and history of fracture are important, the gold standard for diagnosing MBD remains DEXA scan. Measurement of bone density however 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. 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 [747-750]. A histomorphometric study approach noted that out of 16 adults followed for seven to 89 months on PN, twelve had osteomalacia [751]. 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.

Taking into account general factors, disease-specific causes, and impact of PN, it is important to optimize the PN formula prior to initiation of specific treatment. Aluminum contamination of PN fluids must be reduced to a minimum and be less than 25 μg/L [752]. 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 [747-749]. 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 [747-749]. 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 [753]. 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) [748].

The recommended intravenous dose of vitamin D is 200 IU/d. Consider withdrawing vitamin D temporarily in patients with low BMD, low serum PTH, and low 1,25-dihydroxyvitamin D concentrations associated with normal 25-hydroxyvitamin D [754]. In the case of elevated PTH and low 25-hydroxyvitamin D, additional parenteral supplementation with vitamin D is indicated [755]. The use of higher doses of oral vitamin D supplementation (20,000–50,000 IU per week) whether provided once a week or divided into daily doses has also been studied in CIF population in small case series [172,756]. 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.

Bisphosphonates provided intravenously at regular intervals (Clodronate, Pamidronate, or Zolendronic 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 RCT of bisphosphonate treatment has been carried out in patients on HPN [757]. Intravenous clodronate decreased the urinary excretion of markers of bone resorption, and BMD of the lumbar spine was maintained in patients on HPN after twelve months, but a significant increase in BMD was not observed. Anecdotal reports suggest that intravenous pamidronate is also useful [758,759]. Subcutaneous denosumab, a monoclonal antibody that neutralizes RANKL has also been evaluated in the HPN population and noted to be efficacious and fairly tolerated in this cohort [760]. An 18-month course of teriparatide, a PTH analogue, was utilized in a 65-year-old female HPN patient with SBS and renal disease resulting in significant increase in spinal BMD [761].

For monitoring purposes, we recommend repeated DEXA measurements at yearly intervals, although the benefit of this routine is not well supported by studies [744,746,750]. 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.

17. Chapter 15 - Pregnancy and breast feeding

17.1. How should a safe pregnancy be management in patients on HPN for CIF?

17.1.1. Recommendation 135

Attempts shall be made to optimize the nutritional status of those considering pregnancy, ensuring adequate vitamin and trace element supplementation with particular emphasis on ensuring adequate oral or parenteral folate.

Grade of evidence GPP - Strong consensus 100% agreement.

17.1.2. Recommendation 136

Close monitoring of pregnant patients with CIF, at least on a four-weekly basis, shall be made by the IF multidisciplinary team, maintaining close dialogue with, and close overview from, a 'high-risk' obstetric service throughout all trimesters.

Grade of evidence GPP - Strong consensus 100% agreement.

17.1.3. Recommendation 137

Strategies to optimize maternal underlying disease and minimize HPN-related complications, with a pre-emptive approach to tailored macronutrient and adequate micronutrient support shall be implemented.

Grade of evidence: GPP- Strong consensus 100% agreement.

17.1.4. Recommendation 138

Individualized birth plans shall be devised for patients with CIF, as per the general population and dependent on the underlying disease, with caesarean section reserved for obstetric indications or in the presence of active perianal Crohn's disease.

Grade of evidence GPP - Strong consensus 100% agreement.

17.1.5. Recommendation 139

Breast feeding should be considered wherever possible, with mindful consideration of any concomitant medications that may be secreted into breast milk as per other diseases.

Grade of evidence GPP - Strong consensus 100% agreement.

17.1.6. Recommendation 140

The patient shall be monitored closely by the CIF NST team during lactation to ensure adequate nutritional status.

Grade of evidence GPP - Strong consensus 100% agreement.

17.1.6.1. Commentary. While there are multiple reports describing the safe use of short-term PN in hospitalized pregnant women, for example with hyperemesis gravidarum, there are relatively fewer data in pregnancies occurring in patients on HPN with CIF. Around 15 pregnancies had been reported in the literature up until 2015, with no fetal deaths reported and the majority of cases describing an uncomplicated vaginal delivery [762]. Most babies were healthy, although there were reports of vitamin K deficiency embryopathy and cataracts in two neonates [762]. Since 2015, there have been three cases series reporting outcomes in 21 pregnancies occurring in 15 women cared for in four centers in France [763], 5 pregnancies in 5 women from a single UK center [764] and nine pregnancies in five women from two centers in Israel and Poland [765].

There are no data to provide a clear evidence base to fertility risk and pre-conception care in CIF. It is reasonable to adopt a comparable approach to that in individuals who do not suffer from CIF. Thus, patients should be counselled on an individual basis by IF clinician and obstetric team regarding their fertility and potential risks of pregnancy. In general, patients of child-bearing age should be supported in their decision making when considering pregnancy, highlighting that successful pregnancy can be both safe and feasible for the mother and baby. Fertility therapy may be appropriate if necessary, noting that two of the 21 pregnancies reported by Billiauws and colleagues required *in vitro* fertilization [263].

Again, there are limited data to provide categoric recommendations in the management of patients with CIF during pregnancy. However, it is clearly important to consider the patient's underlying disease as well as the individual's associated HPN and nutritional requirements, while providing close obstetric monitoring. In the

largest series to-date from France, the median duration of HPN prior to pregnancy was around eight years, with most women suffering from underlying SBS or CIPO [763]. In this series, the median BMI pre-pregnancy was 19.4 kg/m^2 and women gained a median of 10 kg, with only one-third gaining more than 12 kg in weight [763]. The authors highlighted that there was close monitoring with supplementation of all vitamins and micronutrients during pregnancy, particularly noting the importance of folate, vitamins D, K and A as well as Fe and Zn [763]. Patients generally required increased HPN calorie provision during their pregnancy, particularly in the second and third trimester, with some requiring more nights of PN through the week. In the French series, all patients received lipid with a mixture of olive oil and soybean-based emulsions, with no patients solely receiving fish oils [763]. Similarly, in the UK series reporting five pregnancies, all mothers received a combination of lipid (less than 20% intralipid or Clinoleic) and aqueous PN bags and needed an increase in calorie and nitrogen provision during pregnancy [764]. Theilla et al. also note that their pregnant patients all received lipid-based PN (intralipid or clinoleic) without significant complication [765]. Thus, close clinical and dietetic overview is required during pregnancy to ensure nutritional requirements are met, particularly since oral intake may diminish in the second and third trimesters, perhaps as a result of worsening gastroesophageal acid reflux [763].

It is important that patients are reviewed by the multidisciplinary CIF team on a frequent basis to monitor the underlying disease and observe for HPN-related complications. In addition, patients should ideally be referred to a 'high-risk' obstetric clinic for equally close overview for pregnancy-related complications. In the French series, maternal complications unrelated to pregnancy included intestinal obstruction in nine patients, cholestasis in one and CRBSI in five patients, one of whom was subsequently treated with a taurolidine-based lock [763]. The authors also highlighted severe complication in twelve patients with CIPO involving multiple sepsis, obstruction and uterine rupture in one and obstructive uropathy with renal failure in another, which led them to suggest that this group of patients warranted particularly close follow-up [763]. Other underlying diseases also require monitoring and optimization, with standard approaches to inflammatory bowel diseases and associated medication use as described in established international guidelines [766]. While it may be difficult to disentangle the occurrence of IFALD from pregnancy-related liver issues, the latter may be more likely if noted as a new occurrence in pregnant women, as seen in one patient in the UK series, with resolution of abnormal liver function tests after delivery [764]. Six pregnancy related complications – pre-eclampsia in one patient, post-partum hemorrhage in three and thrombosis in two – were noted in the French series [763].

Of the 21 pregnancies reported by Billiauws and colleagues, there was one intra-uterine death at 36 weeks of unknown cause, while six newborns were said to be hypotrophic at birth, three of whom suffered from respiratory distress syndrome and one from a cardio-pulmonary arrest; all six survived with no long-term complications [763]. The median infant follow-up in this cohort was four years and two children were suspected of having CIPO [763]. In the UK series, two of the five neonates were pre-term and both suffered from respiratory distress with full recovery [764]. One baby was born with a cleft palate after an unplanned pregnancy [764]. There are no data to inform recommendations on breast feeding. Breast feeding should be considered wherever possible, with mindful consideration of any concomitant medications that may be secreted into breast milk as per other patient groups. It is important that the patient is always monitored closely by the CIF multidisciplinary team during both pregnancy and lactation to ensure adequate nutritional status.

18. Chapter 16 - Quality of life assessment

18.1. How and when should quality of life be assessed in patients with CIF?

18.1.1. Recommendation 141 (recommendation #9 of the 2016 CIF GL)

The QoL of CIF patients should be regularly measured using validated tools as part of standard clinical care.

Grade of evidence GPP - Strong consensus 96% agreement.

18.1.2. Recommendation 142

Validated tools to measure QoL of CIF patients should be able to distinguish factors depending on the HPN program from those depending on the underlying disease.

Grade of evidence GPP - Strong consensus 100% agreement.

18.1.2.1. Commentary. Patients on HPN for CIF due to benign underlying disease identified incidence of CRBSI, survival, and QoL as the top three quality of care indicators [43]. QoL is defined by the WHO as a state of complete physical, mental, and social wellbeing and not merely the absence of disease and infirmity [767] and, as such, is a subjective mindset belonging to the patient.

In patients with CIF, QoL is not only affected by the IVS but also by the underlying disease, presence or absence of a stoma, and frequency of hospital readmission [34]. Studies acknowledge the difficulty of trying to identify the effects of the underlying illness, resulting in the need for HPN, and the HPN itself [768,769]. Use of different QoL instruments, scales, and lifestyle domains limit comparison among studies [770]. It is recognized that reporting QoL should be patient-based rather than the clinician's perspective. The ESPEN working group on CIF developed and tested the HPN-QoL®, a treatment specific questionnaire for patients with CIF due to benign underlying disease, consisting of 48-items that focuses on physical, emotional, and symptomatic issues [771]. The results of an international multicenter survey including 699 adult patients from 14 countries showed that HPN-QOL® scores were significantly associated with HPN duration (better in long-term), underlying disease (better in Crohn's disease and mesenteric ischemia) and living status (worse in living alone) and, after adjusting for the other factors, with the number of days of HPN infusion per week [391].

Other instruments have been recently developed, such as the HPN patient-reported outcome questionnaire (HPN-PROQ) [772], the Short-Bowel Syndrome Quality of Life Scale (SBS-QoL) [773], the Parenteral Nutrition Impact Questionnaire (PNIQ) [392,774] and the New QOL [775].

The negative impact on QoL of the number of the days of IVS infusion per week has been confirmed by several recent studies [392,773,776-780]. Association of QoL with the underlying disease, presence of a stoma, social, employment and status were also consistently reported [392,773,776-784]. The capturing of social and personal data to measure QoL has traditionally been used in clinical trials, but current evidence indicates the need to include QoL assessment in routine practice.

19. Chapter 17 - Cost analysis

19.1. How should cost analysis of disease and treatment be performed in patients with CIF?

19.1.1. Recommendation 143

Studies on CIF costs and the cost associated with its treatment (HPN, ITx, teduglutide, etc.) should include at least the direct healthcare and non-health care costs.

Grade of recommendation GPP - Strong consensus 100% agreement.

19.1.2. Recommendation 144

Full economic evaluations, including cost-utility analyzes can help inform resource allocation decisions across different health care settings.

Grade of recommendation GPP - Strong consensus 96% agreement.

19.1.2.1. Commentary. Studies on HPN costs are encouraged, which should include at least the category of direct healthcare and non-health care costs (HPN provision, complications, and outpatient monitoring). Other costs that should be considered include personal costs and productivity costs [785]. Even if each institution carries out its own cost study, even with a limited number of patients, it will allow them to know the cost of HPN in their center or hospital. These data are of great value both at an economic and scientific level. On top of that, the analysis of personal and productivity costs would allow us to understand different dimensions of the lives of patients receiving HPN, such as their jobs, hobbies and so on. Additionally, the economic evaluations of HPN, such as the cost utility analysis, not only includes both the economic and the quality-of-life perspective.

Most studies investigated costs of HPN treatment from a healthcare perspective, therefore including direct costs. The items included in this category were mainly HPN bags cost, followed by personnel cost, consumables cost, follow-up cost and other. A limited number of studies evaluated personal costs for the patient and family. These charges included medical equipment, supply and freight charges, clinic visits and standard laboratory tests [786], ambulatory visit expenses (transportation, meals, parking, and accommodation) [787] or out of pocket expenses [788]. One study had a societal perspective, apart from direct costs and personal costs for the patient and family, also including productivity costs [789]. The majority of the studies focused on patients with benign disease [786], although some of them included patients with both benign and malignant disease [790-795]. In the latter case, the choice of such a heterogeneous patient population impedes the comparison of costs between studies, especially when costs are not presented separately. There are no RCTs published in the literature regarding HPN costs. The data comes from observational studies (cross-sectional, cohort longitudinal) and modelling studies. The first three HPN cost studies were published in the 1980s, their number remaining stable in the following decades and reaching a peak of eleven studies in the 2010s. Most of the studies have been published in the USA, followed by the Netherlands. Other countries were partial economic evaluations on HPN have been carried out include Canada and Spain [789].

According to a recent systematic review [789], which reviewed the existing scientific literature of full or partial economic evaluations associated to HPN, the cost of HPN in adult patients during first year, in Europe, hovered between €13,000 per year (pricing year 2017) and €71,000 per year (pricing year 2015), with a minimum reported of €8000 per patient per year (pricing year 2015) and a maximum of €77,000 per year (pricing year 2012). Whereas, in the USA, the costs are higher, some studies reporting costs of $103,000 per year (pricing year 1996), $176,000 per year (pricing year 1992) and approximately $253,000 (pricing year 1982–1983) [789].

There are two papers reporting full economic evaluations on HPN, specifically a cost-utility analysis. One of them was published in Canada and the other in the UK. According to Richards et al. [796], the cost per quality adjusted life year (QALY) for an average patient was approximately £68,975. The value for patients under 44 years was reduced to £58,233 (due to higher utility scores), while for those above 55 years was increased to £126,865 (due to lower utility scores). The cost per QALY for hospital care was approximately £190,000. The current practice of home care is about 65% more cost-effective than hospital care [796].

Detsky et al. showed that, for the entire cohort of patients (both chronic and acute), the baseline estimates of the difference in cost between the HPN and alternative strategies showed a net savings of $19,232 per patient (pricing year 1981–1982) over a 12-year time frame, if the alternative for acute patients was in-hospital PN. Additionally, if the alternative strategy for the acute cohort of patients was no nutritional support, with full nutritional support for the chronic patients as needed, the baseline estimate of the incremental cost for the entire cohort would be $27,375 per quality-adjusted life-year gained [797].

Canovai et al. [798] performed a retrospective unicenter analysis in order to report the total annual costs of long-term adult CIF patients with benign underlying disease and to assign them to a specific category. Total costs of CIF patients were the sum of: 1) HPN and associated complications costs: direct costs (HPN bags, additional nutrition/fluids, transport, needles, lines, pumps, nursing, and clinical follow-up) and complications (metabolic disorders, fluid/electrolyte disorders, line complications due to infection, mechanical or thrombosis); 2) underlying disease; 3) unrelated diseases costs [798]. The study included 37 CIF adult patients with a median age of 59 yr (34–85) and 67% were female. The median duration of HPN was 5.3 yr and the number of infusions per week was 4.3 d/wk (1.5–7). The type of access was tunneled catheter (81%) and totally implantable venous access device (ports) (19%). The causes of CIF were short bowel (59%), chronic severe dysmotility (30%), mechanical obstructions (8%) and mucosal disease (3%). The total costs of the first year was a median of €83,503 (min–max €35,364–256,780) (pricing year 2015). HPN and associated complications accounted for 69% of total costs, €57,970 (min–max €29,078–145,900), the underlying disease accounted for 27% of total costs, €22,505 (min–max €402–194,766) and the unrelated diseases accounted for 4% of total costs €3028 (min–max €754–6721). In the second year, total costs dropped by 15%, to a total of €71,311 (min–max €31,955–136,657, $p = 0.002$), due to fewer hospital admissions and fewer HPN complications. HPN and associated complications accounted for 78% of total costs, €55,795 (min–max €39,622–118,555, $p = 0.16$), the underlying disease accounted for 19% of total costs, €13,616 (min–max, 617–83,413), and the unrelated diseases accounted for 3% of total costs €3028 (min–max, 754–6721). In the third year, total costs decreased by a further 17%, to a total of €57,593 (min–max €29,161–238,136, $p = 0.02$). HPN and associated complications accounted for 77% of total costs, €45,079 (min–max €32,400–75,992, $p < 0,0001$), the underlying disease accounted for 19% of total costs, €11,407 (min–max €0–158,240), and the unrelated diseases accounted for 4% of total costs €2460 (min–max €849–6455). Costs for fourth and fifth years were similar: €58,791 (min–max €22,686–124,008) and €58,186 (min–max €25,049–143,988), respectively ($p = 0.398$). The fifth year was 40% cheaper overall compared to first year (€58,186 vs €83,503, $p = 0.001$). There were no differences in costs between the underlying conditions. The authors concluded that HPN related costs accounted for the majority of the total expenses in IF patients [798].

Fletcher et al. [799] recently reported the costs of CVAD repairs carried out in a cohort of IF patients. The results showed that there is a potential cost saving of £2766 for repair compared to replacement of damaged CVADs, even though when CVAD repair failed costs were increased slightly for individuals, where patients had both a repair attempt followed by a replacement [799].

Siu et al. [800] documented the cost of CIF within the hospital system from the time of initial admission, including each hospital readmission, and to compare incurred costs with current government reimbursement. This retrospective study carried out in Australia, included 25 patients commencing HPN over a seven-year time period. Twenty-one patients were aged 40 years or older, and 17 patients were female. The median starting age for PN in this study group was 55 years (IQR 43–67 years). The majority of the study group (72%) had SBS leading to IF. The median cost of inpatient per admission was $36,675 (IQR $23,196–$67,439). The main contributor to costs in the initial hospital admission was staff time (75.33%), with a median cost of $27,617 (IQR $15,862-$49,692) and PN costs (12.36%) with a median cost of $4532 (IQR $2715-$9260), respectively [800].

Over the study period, 15 patients required between one and ten readmissions into hospital, with a median readmission rate of two (IQR 1–6). The median total cost per patient per admission was $13,893 (IQR $11,151–$32,130). The main contributors to costs in the readmission(s) period were staff time (50.80%), with a median cost of $74,443 (IQR $26,013-$120,099), PN costs (46.44%), with a median cost of $68,047 (IQR $25,921-$107,702) and costs of laboratory/pathology tests (1.93%), with a median cost of $2830 (IQR $661-$11,268). The median incurred cost for initial hospital admission patients ($n = 24$) was significantly higher than reimbursement: $36,675 (IQR $23,196– $67,439) and $19,247 (IQR $7485-$41,090), respectively ($p < 0.001$). Similar results were observed in the readmissions period, with median costs per readmission(s) of $13,893 (IQR $11,151-$32,130) compared with reimbursement of $8469 (IQR $5625–$13,078) per readmission ($p = 0.001$). The authors concluded that the results indicate that type III IF patients have high inpatient costs, which substantially outweigh current reimbursement. Sustainable funding models and newer health policies for patients with IF may improve clinical service provision and patient outcomes and ensure hospitals that accept the management challenge of type III IF patients are not unduly penalized [800].

Siddiqui et al. [801] analyzed the Nationwide Inpatient Sample database from 2005 to 2014 to assess the trends in SBS-related hospitalizations and in-hospital mortality and to estimate the healthcare burden associated with SBS-related hospitalizations in the USA. A total of 53,040 SBS-related hospitalizations were identified. The overall mean length of stay was 14.7 days, with a mean hospital cost of $34,130. The hospital cost increased between 2005 and 2009 and thereafter remained stable in the last few years. Also, patients with sepsis ($41,502 vs $25,198, $p < 0.01$), liver disease ($38,136 vs $31,521, $p < 0.01$), and severe malnutrition ($39,639 vs $31,053, $p < 0.01$) showed costs of care significantly higher [801].

Recently, Canovai et al. [802] performed a study aimed to perform a detailed cost analysis of ITx and HPN and to investigate the cost-effectiveness of ITx compared to HPN for the treatment of CIF. In stable HPN patients, the costs were €83,402 (€35,364–169,146) in the first year, €70,945 (€31,955–117,913) in the second year, and stabilized to €60,242 (€29,161–238,136) in the third year. Costs before ITx were €69,160 (€60,682–90,891) in year −2, and €104,146 (€83,854–186,412) in year −1. After ITx, costs were €172,133 (€122,483–351,407) in the first year, €40,619 (€3905–113,154) in the second year, and dropped to €15,743 (€4408–138,906) in the third year. The authors concluded that, although initially ITx is a very expensive treatment, as costs continued to decline in the years after, ITx became cost-effective compared to HPN in adults by year four, and cost-saving by year five [802].

Raghu et al. [393], used a Markov model to evaluate the costs (in US dollars) and effectiveness (in QALYs) of treatment compared with no teduglutide use, with a presumed starting age of 40 years, in US adult patients with SBS. In the base scenario, teduglutide cost $949,910/QALY gained. In 1-way sensitivity analyzes, only reducing teduglutide cost decreased the cost/QALY gained to below the typical threshold of $100,000/QALY gained. Specifically, teduglutide cost would need to be reduced by >65% for it to reach the threshold value. Probabilistic sensitivity analysis favored no teduglutide use in 80% of iterations at a $100,000/QALY threshold. However, teduglutide therapy was cost-saving in 13% of model iterations [393].

Pliakos et al. [803] evaluated the cost-effectiveness of antimicrobial locks for the prevention of CLABSI in three settings: hemodialysis, cancer treatment, and HPN. A decision-analytic model was constructed to assess the cost-effectiveness of antimicrobial lock solutions for the prevention of CLABSI. In the base-case analysis for patients receiving HPN, the use of antimicrobial locks prevented 1.8 CLABSIs per 1000 patients treated and was associated with savings of $78,513.83 per CLABSI averted (ICER, -$78,513.83 per CLABSI averted) compared to a heparin lock. In the probabilistic analysis of the HPN setting, the mean estimated cost was $5781.24 (95%CI $3721.65–$7840.83) for antimicrobial locks and $5922.86 (95%CI $3861.62–$7984.10) for the heparin lock. At a willingness to pay of $50,000, antimicrobial lock solutions had a 96.24% chance of being cost-effective, compared with heparin locks in the hemodialysis setting, an 88.00% chance in the cancer treatment setting, and a 92.73% chance in the HPN setting [803].

Lannoy et al. [804] conducted a monocentric mirror-image design study to evaluate the cost-effectiveness of long-term taurolidine locks in preventing recurrent CRBSI in a cohort of adult patients receiving HPN. Considering both proven and probable CRBSI requiring hospital management, long-term taurolidine locks reduced by mean −2.63 (−3.26 to −2.06) infections per patient (from 2.89 (2.31–3.49) before to 0.26 (0.13–0.41) after). This corresponds to an average reduction in total cost per patient of €-7258 (€-10,450 to −4016; from €11,176 (€8004–14,968) before to €3918 (€2390–5445) after) [804].

Arnoriaga et al. [805] carried out a retrospective study to determine if taurolidine lock is a cost-effective intervention in patients on HPN. The total cost of CRBSI in the pre-taurolidine period was €151,264.14 vs €24,331.19 in the per-taurolidine period [805].

20. Chapter 18 - Transition from pediatric to adult centers

20.1. How transition of pediatric patients with CIF to adult centers should be managed?

20.1.1. Recommendation 145

The transition from pediatric to adult care in patients with CIF should be carefully prepared and should cover medical care and logistics concerning the treatment of the underlying disease and the HPN.

Grade of evidence GPP - Strong consensus 100% agreement.

20.1.2. Recommendation 146

In the transition process from pediatric to adult centers, the care should be transferred from the adult caregiver to the patient.

Grade of evidence GPP - Strong consensus 96% agreement.

20.1.3. Recommendation 147

The transition process should start at least one year before the patient adult birthday and can last a couple of years during which the referring pediatric center and the referral adult CIF center should cooperate.

Grade of evidence GPP - Strong consensus 92% agreement.

20.1.3.1. Commentary. A survey on home artificial nutrition in Italy reported that pediatric patients with CIF represented around 20% of

total patients on HPN for CIF [806]. An ESPEN international survey including 558 pediatric patients with CIF, showed that 17.9% of them were in the age of transition (14–18 years) [22]. Their CIF mechanism was SBS in 37.9%, intestinal dysmotility in 38.9%, and congenital mucosal disease in 23.2%. This data would suggest that most of adolescent with CIF facing transition from pediatric to adult care service were affected by CIF with a low probability of weaning from HPN [22].

"Transition is the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from a child-centered to an adult-centered healthcare system" [807]. Transition is not just a simple 'transfer' of patients from a pediatric service to an adult care one. Transition medicine actually represents a complex scheduled process, which starts early with pediatric specialists, and aims to make patients independent in managing their own health (and disease) [808]. The difference between pediatric and adult healthcare services and the typical psychological distress of the transition age are two key problems that need to be addressed during the transitioning process. Psychological issues are of great importance for the transition process. One third of respondents, consisting of pediatric and adult home PN care providers, identified confusion around care [5]. Usually, a commercial homecare company provide HPN during childhood. Parents or caregivers, who have completed a formal training program, administer the PN, and are in charge of supervising their child's activities and well-being, administering additional drugs, going to doctor's appointments, and so forth [809]. Such caring of their child has been reported to be highly stressful for some parents and to influence their daily functioning [810]. Patients receiving HPN are aware of their condition and do experience a variety of activity constraints as they grow up, but they are also able to develop a degree of resilience, preserve a positive attitude, and deal well with illness-related demands [811]. Children attend school and engage in typical childhood activities (e.g. school camps, birthday parties, sports, swimming, horse riding), usually avoiding contact sports. However, once they take on the task of managing the PN themselves as adults, they face some challenges. They will require training in the managing of HPN, as well as knowledge of what poses a risk to their health and wellbeing. The young person may be moving away from their home to work or attend university while also dealing with the typical difficulties of taking on responsibilities. They are a vulnerable population who have to learn to manage a chronic and life-threatening illness that affects their physical and mental well-being, QoL, interactions with peers and family, school, and employment, in addition to the typical challenges of young adulthood. This population is at high risk for complications and loss to follow-up when they leave pediatric care. For the above reasons, transition is a potentially dangerous time for young people with complex health needs and can be associated with excess mortality [811]. Collaboration between the pediatric- and adult team is key in creating a safe transition. Although this can be challenging in medical centers not providing both, a more systematic approach will contribute to this process. This can include effective information transmission through written, telephone and/or face-to-face consultations.

BAPEN carried out a survey to know the current practices and experience of transition of young people on long term HPN. Twelve adult and 18 pediatric centers filled out an anonymized questionnaire [809]. A high variability in the practices and processes of transition was observed. Time taken to achieve transition ranged from under six months up to two years. The most frequent concerns were confusion around care routines and psychological problems at the time of transition [809]. The Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) and the Italian Society of Artificial Nutrition and Metabolism (SINPE) elaborated a position statement on transition in CIF [812]. The main objectives of the transition process for CIF were summarized as "5 M": 1) Motivate independent choices which are characteristics of the adult world; 2) Move towards adult goals (e.g. self-management of his/her pathology and sexual issues); 3) Maintain the habitual mode of care; 4) Minimize the difficulties involved in the transition process and 5) Modulate the length of the transition so as to fully share with the adult's team the children's peculiarities. The devised recommendations highlighted that: clinicians should approach the issue of transition with patient and family/caregiver from 13 to 15 years of children age; the age range between 18 and 21 would be the most appropriate for actual referral to adult centers; the overall transition plan should last two years; adult and pediatric centers should have similar characteristics, organization, and way of CIF management, and should identify a facility that will provide emergency care; adult and pediatric teams should share at least two to four consultations with patient and families; consultations should involve physicians, nurses, dietitians, psychologists and social workers of each hospital team; the transition process should be documented with the help of schedules and tools that explain the steps of the process [812]. Besides, assessment of transition readiness with the help of transition-readiness questionnaires can give more insight into the longitudinal development of this process [813]. Most recently, in the US, Kinberg et al. [814] reviewed the literature on transition in children with chronic illnesses and discussed barriers to transition in SBS-CIF to identify the key constituents of the transition process and provide recommendations for the successful and smooth transition of the pediatric patient to the adult healthcare environment for SBS-CIF patients. The final recommendations were in agreement with those of the Italian group, even if discussed in a more extensive and detailed way [814].

21. Chapter 19 - Patient associations

21.1. Which should be the role of patients' association to improve the outcome of patients with CIF?

21.1.1. Recommendation 148 (recommendation #10 of the 2016 CIF GL)

Patients with CIF should be informed about the possibility to join non-profit groups that provide HPN education, support and networking among members.

Grade of evidence: GPP- Strong consensus 100% agreement.

21.1.2. Recommendation 149

Patient support groups should play a complimentary role to healthcare professionals, on the recognition of CIF as a medical condition and practical aspects of living with HPN.

Grade of evidence: GPP- Strong consensus 96% agreement.

21.1.2.1. Commentary. The first known organization for people using home parenteral and enteral nutrition was the Oley Foundation, started in 1983 by Lyn Howard and her HPN patient Clarence "Oley" Oldenburg in the United States. The goal was "enriching lives of those requiring home IVS and tube feeding through education outreach and networking" of patients/consumers, their families, clinicians, and the public in general [815].

The UK organization PINNT (Advocacy and support for people on home artificial nutrition, UK), was formed in 1987 [816]. These two associations were followed by other non-profit groups that support people who require Home Artificial Nutrition (Table 17). Each non-profit group will support their members to support in activities and information, which is necessary for their specific group or country. Some of these groups are associated with the

Table 17
Non-profit organizations for caregivers and patients on home parenteral nutrition and for clinicians.

Country	Non-profit organizations for caregivers and patients on home parenteral nutrition and for clinicians	web address
Australia/ New Zealand	PNDU – Parenteral Nutrition Down Under	https://pndu.org
Austria	Die-chronischen-experten	https://www.die-chronischen-experten.at
Belgium	Hello TPN	https://www.vzwhellotpn.be
Belgium	La Vie par un Fil	http://www.lavieparunfilbelgique.be
Croatia	1. Croatian Disabled ILCO Societies Association 2. HUCUK Croatian Crohn's and Ulcerative Colitis Association,	1. https://www.ilco.hr 2. https://hucuk.hr
Czech Republic	Život bez střeva	https://zivotbezstreva.cz
Denmark	HPN-foreningen - en frivillig patient organisation	https://hpn.dk
France	La Vie par un Fil	https://www.lavieparunfil.com
Germany	Selbsthilfe Kurzdarmsyndrom.	http://selbsthilfe-kurzdarmsyndrom.de
Germany	Kinder in Schwieriger Ernährungssituation	http://kise-ev.de
Germany	Koordination Kurzdarmsyndrom	https://www.koordination-kurzdarmsyndrom.de
Italy	Un filo per la vita.	http://www.unfiloperlavita.it
Netherlands	Informal Dutch IF group under the structure of Crohn & Colitis NL	https://www.facebook.com/CCUVNsbsdarmfalen https://www.crohn-colitis.nl/over-crohn-colitis/wat-is-short-bowel
Norway	Norsk Intravenøsforening	https://www.nifo.no
Poland	Stowarzyszenie 'Apetyt na Życie'.	https://apetytnazycie.org
Spain	Asociación de niños, adultos y familias con fallo intestinal, nutrición parenteral y trasplante múltiple	https://somosnupa.org
Sweden	Svenska HPN-Föreningen	https://www.hpn.se
United Kingdom	PINNT (Advocacy and support for people on home artificial nutrition)	https://pinnt.com
United Kingdom	Short Bowel Survivor & Friends	https://www.shortbowelsurvivor.co.uk
United States	Oley Foundation	https://oley.org
European	ERNICA, European Reference Network for rare Inherited and Congenital (digestive and gastrointestinal) Anomalies.	https://ern-ernica.eu/about/ernica/
International	PACIFHAN International Alliance of Patient Organizations for Chronic Intestinal Failure and Home Artificial Nutrition International Association	http://pacifhan.org

respective parenteral/enteral nutrition organizations in their country, which can contribute to shared learning and provide a platform for the voice of those on HPN. The International Alliance of Patient Organizations for Chronic Intestinal Failure and Home Artificial Nutrition (PACIFHAN) was established in 2014 to promote international sharing of information and resources, to improve awareness and the QoL of patients on home artificial nutrition, to do research and to increase global awareness of CIF and home artificial nutrition [817].

Support groups offer patients and caregivers the opportunity to talk to and learn from others who have similar experiences [818]. There are common topics such as adjusting and coping, building support networks, finding out about travelling with HPN and seeking ambulatory feeding equipment to enhance QoL [819]. Such engagement may be beneficial to people with CIF in respect to their QoL, psychosocial effects, such as depression, isolation, fatigue, anxiety, financial stress, and therapy-induced complications while also learning some coping techniques [818-820]. An additional important role is advocacy through government groups, non-government organizations, and elected officials to help improve the survival and QoL [820]. A friendly, informal, supportive atmosphere really helps to boost confidence, provide insight and establish long-lasting friendships for all involved.

Patient's associations can also contribute to address research priorities. Sowerbutts et al. [821] investigated the research agenda of patients receiving HPN, their family members and healthcare professionals, by the James Lind Alliance methodology. The aim was to determine the questions that patients, family members and healthcare professionals want answered by research around HPN for CIF due to benign disease and HPN used in people with cancer. For CIF with benign disease, 18 questions were discussed in two workshops attended by 13 patients and seven healthcare professionals. The top research priorities were prevention and treatment of liver disease, improving central infusion lines, oral absorption, avoiding long-term negative consequences, vascular access, side effects, line infections, decreasing stoma output, QoL and sleep [821].

CIF clinicians should introduce the patient organization (support group) to patients when the need for HPN is established and prior to hospital discharge.

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Disclaimer

This guideline has been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using this guideline shall do so only after consultation with a health professional and shall not mistake this guideline as professional medical advice. This guideline must not substitute seeking professional medical and health advice from a health professional.

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Conflicts of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

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Appendix A. Supplementary data

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