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ESPEN Guideline

ESPEN practical guideline: Clinical nutrition in chronic intestinal failure

Cristina Cuerda [a, *, 2], Loris Pironi [b, c, 2], Jann Arends [d], Federico Bozzetti [e], Lyn Gillanders [n], Palle Bekker Jeppesen [f], Francisca Joly [g], Darlene Kelly [o], Simon Lal [h], Michael Staun [f], Kinga Szczepanek [i], André Van Gossum [j], Geert Wanten [k], Stéphane Michel Schneider [l], Stephan C. Bischoff [m], the Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN[1]

[a] Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[b] Alma Mater Studiorum – University of Bologna, Department of Medical and Surgical Sciences, Italy
[c] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Centre for Chronic Intestinal Failure – Clinical Nutrition and Metabolism Unit, Italy
[d] Department of Medicine I, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[e] Faculty of Medicine, University of Milan, Milan, Italy
[f] Rigshospitalet, Department of Intestinal Failure and Liver Diseases Gastroenterology, Copenhagen, Denmark
[g] Centre for Intestinal Failure, Department of Gastroenterology and Nutritional Support, Hôpital Beaujon, Clichy, France
[h] Intestinal Failure Unit, Salford Royal Foundation Trust, Salford, UK
[i] General and Oncology Surgery Unit, Stanley Dudrick's Memorial Hospital, Skawina, Poland
[j] Medico-Surgical Department of Gastroenterology, Hôpital Erasme, Free University of Brussels, Belgium
[k] Intestinal Failure Unit, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
[l] Gastroenterology and Clinical Nutrition, CHU of Nice, University of Nice Sophia Antipolis, Nice, France
[m] Department of Nutritional Medicine and Prevention, University of Hohenheim, Stuttgart, Germany
[n] Emeritus of Auckland City Hospital, Auckland, New Zealand
[o] Emeritus of Mayo Graduate School of Medicine, Rochester, Minnesota

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SUMMARY

Background: This practical guideline is based on the ESPEN Guidelines on Chronic Intestinal Failure in Adults.
Methodology: ESPEN guidelines have been shortened and transformed into flow charts for easier use in clinical practice. The practical guideline is dedicated to all professionals including physicians, dieticians, nutritionists, and nurses working with patients with chronic intestinal failure.
Results: This practical guideline consists of 112 recommendations with short commentaries for the management and treatment of benign chronic intestinal failure, including home parenteral nutrition and its complications, intestinal rehabilitation, and intestinal transplantation.
Conclusion: This practical guideline gives guidance to health care providers involved in the management of patients with chronic intestinal failure.

1. Introduction

Intestinal failure (IF) 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 the gut's absorptive function that does not require any intravenous supplementation to maintain health and/or growth, can be considered as intestinal insufficiency.

IF can be classified according to different criteria:

* Corresponding author. Nutrition Unit, Hospital General Universitario Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain.
E-mail address: cuerda.cristina@gmail.com (C. Cuerda).
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[2] C.C. and L.P. share co-first authorship.

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Abbreviations

CIPO	chronic intestinal pseudo-obstruction
CRBSI	catheter-related bloodstream infection
CRI	catheter-related infection
CRVT	catheter-related venous thrombosis
CVC	central venous catheter
DXA	dual-energy X-ray absorptiometry
EFA	essential fatty acids
EN	enteral nutrition
GLP-2	glucagon-like peptide-2
HEN	home enteral nutrition
HPN	home parenteral nutrition
IF	intestinal failure
IFALD	intestinal failure associated liver disease
ITx	intestinal transplantation
LILT	longitudinal intestinal lengthening and tailoring
MCT	medium-chain triglycerides
NST	nutrition support team
ONS	oral nutritional supplements
PICC	peripherally Inserted Central Venous Catheter
PN	parenteral nutrition
PUFA	poly-unsaturated fatty acids
QoL	quality of life
RCT	randomized controlled trial
SBS	short bowel syndrome
SRSB	segmental reversal of the small bowel
STEP	serial transverse enteroplasty

- Functional classification (type I or an acute, short-term condition, type II or a prolonged acute condition, and type III a potentially chronic condition).
- Pathophysiological classification (short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction, and extensive small bowel mucosal disease).
- Clinical classification (on the basis of the energy and the volume of the required intravenous supplementation)

The clinical condition associated with the remaining small bowel in continuity of less than 200 cm is defined as short bowel syndrome (SBS). Depending on the anatomy of the remnant bowel, three categories of SBS are identified: end-jejunostomy, jejunocolic anastomosis, and jejunoileal anastomosis with both the ileo-cecal valve and the entire colon in continuity.

Chronic intestinal failure (CIF) may be the consequence of severe gastrointestinal or systemic benign diseases, or the end stage of intra-abdominal or pelvic cancer. The present guideline is limited to CIF due to benign disease in adults, where the term benign means the absence of end-stage malignant disease.

2. Methodology

This practical guideline consists of 112 recommendations and is based on the ESPEN Guidelines on Chronic Intestinal Failure in Adults [1]. The original guideline was shortened by restricting the commentaries to the gathered evidence and literature on which the recommendations are based on. The recommendations were not changed (except "artificial nutrition" was replaced by "medical nutrition" and language adaptions to American English), but the presentation of the content was transformed into a graphical presentation consisting of decision-making flow charts wherever possible. The original guideline was developed according to the ESPEN methodology [2]. The experts followed the GRADE method, which is based on determinations of grade of evidence and strength of recommendation. Grading from High to Very Low was used to rate the quality of the underlying evidence and the level of certainty for effect. In brackets, the original recommendation numbers (R1, R2, …) and the grading is indicated. The strength of recommendation (strong-weak resulting in "we recommend/do not recommend …" or in "we suggest/do not suggest …") was based on a consensus discussion, which included expression and deliberation of expert opinions, risk-benefit ratio of recommendation, costs, and a review of supportive evidence, followed by Delphi rounds and votes until agreement was reached. The working group included gastroenterologists, surgeons, endocrinologists, anesthesiologists, and dietitians with long-term expertise in IF and home parenteral nutrition (HPN). The guideline process was funded exclusively by the ESPEN society. The shortened guideline and dissemination were funded in part by the UEG society, and also by the ESPEN society.

3. Results

Management and Treatment of benign Chronic Intestinal Failure covers 112 recommendations structured in 4 main chapters and diverse subchapters (Fig. 1).

3.1. Home parenteral nutrition (HPN)

3.1.1. Management of HPN (Fig. 2)

The management of HPN is summarized in Fig. 2.

3.1.1.1. General recommendations (aims of HPN, audits, selection of patients, discharge from hospital). **1) We recommend that the aims of an HPN program include provision of evidence-based therapy, prevention of HPN–related complications such as catheter-related infections (CRI) and metabolic complications and ensure quality of life (QoL) is maximized.**

(R1, Grade of evidence: very low)

Commentary

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

2) We recommend regular audit of therapy and outcomes against standards to ensure safety and efficacy of an HPN program.

(R2, Grade of evidence: very low)

Commentary

To measure and provide evidence of the safety and efficacy of the HPN service, there should be regular audits of outcomes and scrutiny of results concerning HPN-related major complications, including re-admission rates. Furthermore, a recognized instrument for measuring QoL should be used regularly to monitor HPN patients. Accreditation programs for HPN providers must also ensure regular audit against these quality measures.

3) We recommend that patients selected for an HPN program have confirmed CIF that despite maximal medical therapy would lead to deterioration of nutrition and/or fluid status.

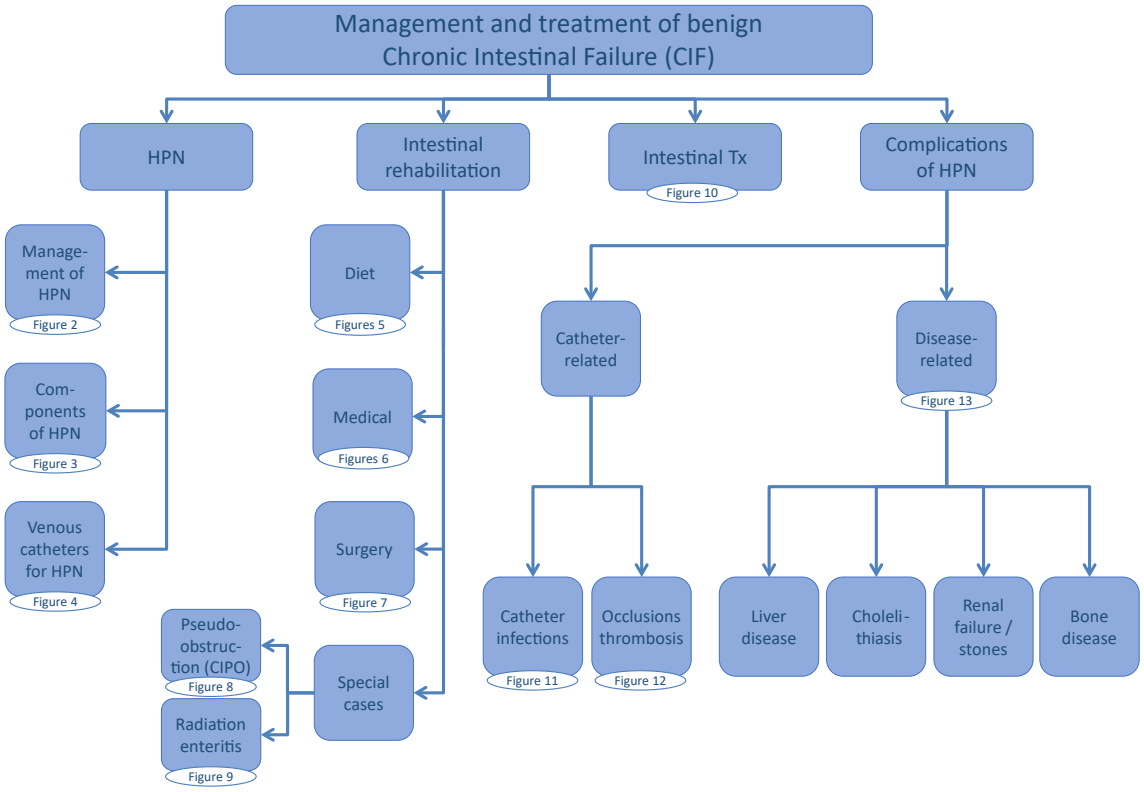

Fig. 1. Structure of the ESPEN practical guideline "Clinical nutrition in chronic intestinal failure" (CIF, chronic intestinal failure, CIPO, chronic intestinal pseudo-obstruction; HPN, home parenteral nutrition; Tx, transplantation).

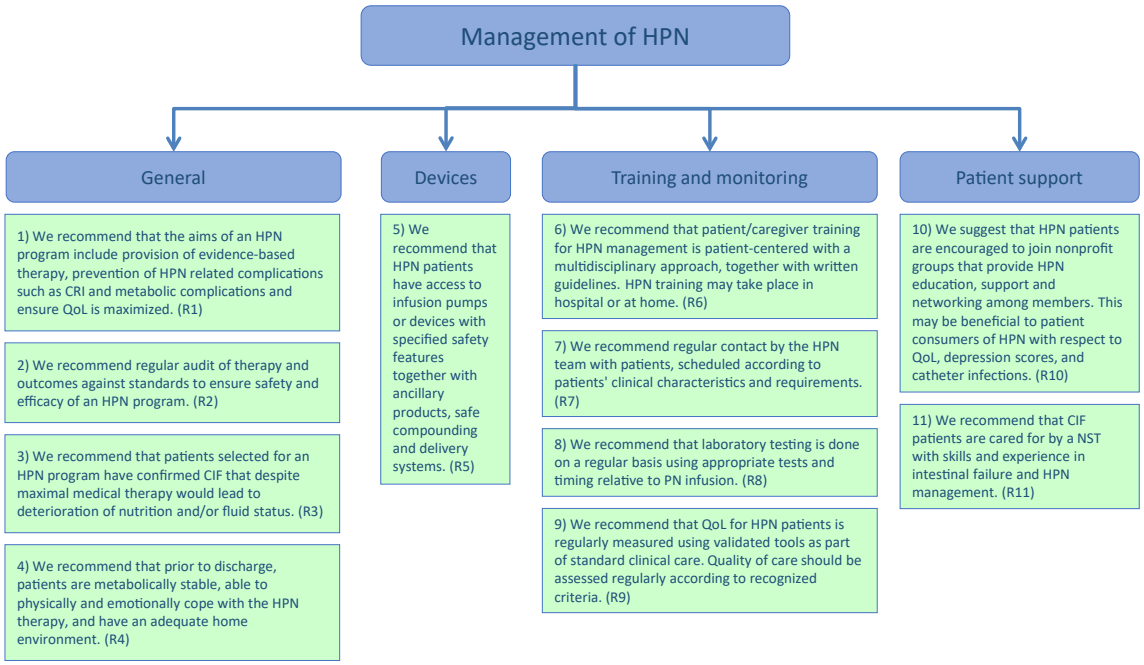

Fig. 2. Management of home parenteral nutrition. For details see text. Abreviations: CIF, chronic intestinal failure; CRI, catherter-related infection; HPN, home parenteral nutrition; NST, nutrition support team.

(R3, Grade of evidence: very low)

Commentary

All patients who are considered for entry into an HPN program should have documented prolonged CIF which, if untreated, would lead to deteriorating nutritional and/or fluid status and should have undergone an adequate trial of enteral nutrition (EN), if feasible (except, for example, in the case of extreme short bowel). They should be managed by a clinician and multidisciplinary nutrition

support team (NST) that have an interest and experience in CIF. To optimize safety and efficacy, evidence-based procedures and protocols should be used to educate patients and carers (including hospital and home care provider staff) on catheter care and for monitoring the nutritional, metabolic, and clinical status of the patient.

4) We recommend that prior to discharge, patients are metabolically stable, able to physically and emotionally cope with the HPN therapy, and have an adequate home environment.

(R4, Grade of evidence: very low)

Commentary

The patient and/or carers must be physically and emotionally able to undertake HPN training and demonstrate self-care competency prior to discharge. The home situation must be stable and have adequate facilities for safe administration of HPN.

3.1.1.2. Devices. **5) We recommend that HPN patients have access to infusion pumps or devices with specified safety features together with ancillary products, safe compounding and delivery systems.**

(R5, Grade of evidence: very low)

Commentary

Electronic pumps with appropriate delivery sets should be used where possible to manage and monitor the delivery of HPN. An ambulatory pump further enables these individuals to achieve desired independence. The range of other sterile consumable products or accessories required for use by the patient at home will vary, depending on the pump in use and individual patient requirements.

Parenteral nutrient admixtures can be compounded in single bags, two chamber bags or three chamber bags. Vitamins and trace elements can be added prior to infusion in the home setting. Two and three chamber bags have advantages for HPN patients as they have a longer shelf life. Some three chamber bags do not require refrigeration which provides advantages for HPN patients while travelling. Stability is also markedly prolonged by refrigeration. This requires a dedicated refrigerator for HPN solution storage. HPN admixtures should be visually inspected for lipid emulsion coalescence as well as calcium phosphate precipitates prior to use.

Delivery of HPN admixtures to patients should be in strong containers under known temperature/time conditions to ensure safe storage requirements are not exceeded in transit. The ambient temperature of the HPN solution must be kept at 4–8 C° and air excluded from a three-chamber bag.

3.1.1.3. Training and monitoring. **6) We recommend that patient/caregiver training for HPN management is patient-centered with a multidisciplinary approach, together with written guidelines. HPN training may take place in hospital or at home.**

(R6, Grade of evidence: very low)

Commentary

HPN patients should be trained by a NST (medical, nursing, dietetic, and pharmacy clinicians with experience in an HPN program) as an inpatient in preparation for the home environment. The patient will need to be stable on the HPN regimen before being discharged.

Initiation of HPN at home is of interest to patients, health care providers, and third-party payers. The training process may take from several days to weeks depending on the patients' ability to learn the techniques to ensure safe practice in the home. In a few instances, care in a residential care facility may be an option.

Before discharge the patient/carer(s) should be able to:

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

7) We recommend regular contact by the HPN team with patients, scheduled according to patients' clinical characteristics and requirements.

(R7, Grade of evidence: very low)

Commentary

After hospital discharge it is critical that the HPN team contacts the patients 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 parenteral nutrition (PN) infusion, and general health. Monitoring of hydration status is particularly important to prevent hospitalization with dehydration by early provision of extra intravenous fluid. If insulin is required, capillary blood sugars should be performed frequently and also recorded by the HPN team clinicians.

8) We recommend that laboratory testing is done on a regular basis using appropriate tests and timing relative to PN infusion.

(R8, Grade of evidence: very low)

Commentary

Electrolytes, including Na^{+}, K^{+}, Cl^{-}, HCO^{3-}, plus studies of renal function (creatinine and blood urea nitrogen) should be measured frequently until stable, then at regular intervals. Assays of liver enzymes, bilirubin, albumin, and complete blood counts should also be monitored on a regular basis. Vitamin levels and trace element levels are typically done less frequently, often once or twice annually. Bone mineral densitometry should be done when HPN is initiated and at intervals thereafter.

9) We recommend that QoL for HPN patients is regularly measured using validated tools as part of standard clinical care. Quality of care should be assessed regularly according to recognized criteria.

(R9, Grade of evidence: very low)

Commentary

QoL should be patient-based rather than the clinician's perspective. Studies acknowledge the difficulty of trying to identify the effects of the underlying illness, resulting in the need for HPN, and the HPN itself. The use of different QoL instruments, scales, and lifestyle domains limit comparison among studies. The HPN-QoL® is a treatment specific questionnaire for patients with benign underlying disease [3]. It is a 48-item questionnaire that focuses on physical, emotional, and symptomatic issues.

The quality of care can be reflected by measuring several factors in practice such as the number of CRI, the incidence of hospital readmission for the patient, the QoL, weight change, or the incidence of dehydration.

3.1.1.4. Patient support. **10) We suggest that HPN patients are encouraged to join non-profit groups that provide HPN education, support and networking among members. This may be beneficial to patient consumers of HPN with respect to QoL, depression scores, and catheter infections.**

(R10, Grade of evidence: very low)

Commentary

The first known organization for persons on 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.

A case–control study (matched for age, gender, duration of HPN, and diagnosis) showed that the 49 HPN patients affiliated with the Oley Foundation had significantly fewer episodes of CRI, less depression, and better QoL life than the control group (n = 50) [4]. HPN peer-support groups primarily designed for mutual support and networking, are active in several European countries and in Australia–New Zealand. The UK organization PINNT (Patients on Intravenous and Nasogastric Nutrition Treatment) has collaborated in some projects with the National Health Service of the UK and the National Institute for Health and Care Excellence (NICE). Other non-profit groups that support individuals on HPN exist around the world. The International Alliance of Patient Organisations for Chronic Intestinal Failure and Home Artificial Nutrition (PACIFHAN) is an international non-profit organization to promote international sharing of information and resources, to improve the QoL of patients on medical nutrition at home, and to increase global awareness of CIF and medical nutrition at home.

11) We recommend that CIF patients are cared for by a NST with skills and experience in CIF and HPN management.

(R11, Grade of evidence: very low)

Commentary

The core members of a NST are defined as surgical and gastroenterological specialists, nurse specialists, dietitians, and pharmacists. Additional disciplines may be required, for example, psychologists and social workers. An experienced NST improves safety, increases bowel rehabilitation, and decreases complications of long-term CIF. Specialist nurses as part of the NST have been repeatedly shown to favorably influence rates of central line-associated blood stream infections.

3.1.2. Components of HPN (Fig. 3)

Parenteral nutrition admixtures are composed of macronutrients, micronutrients, fluids and electrolytes (Fig. 3).

3.1.2.1. Macronutrients

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

(R12, Grade of evidence: very low)

Commentary

Protein requirements must be assessed as individual requirements based on a formal nutritional assessment which includes disease-specific needs, medical condition, nutritional status, age, sex, and organ function. In healthy individuals, national and international guidelines have recommended that protein requirements are 0.8–1 g/kg/day [5,6]. Administration of mixed essential and non-essential amino acids in HPN prescriptions must be based on the needs of the individual and be infused over time. Many stable patients on HPN are satisfactorily maintained on prescriptions that provide 0.8–1.4 g of protein (0.13–0.24 g of nitrogen)/kg/day [6,7].

Energy sources for HPN prescriptions can be derived either from a combined carbohydrate and fat emulsion administered together or from separate glucose and fat emulsion HPN prescriptions delivered on different days. Determining energy requirements 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. HPN patients often have significant oral intake which may be at least partly absorbed and contribute to energy intake. The colon has been shown to be an energy salvaging organ. Many stable patients on HPN are satisfactorily maintained on 20–35 kcals total energy per kg per day [6,7]. 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.

3.1.2.1.2. Carbohydrates. **13) We recommend that HPN patients have optimal blood glucose control, based on blood glucose below 180 mg/dl (10.0 mmol/L) during HPN infusion and normal HbA1c levels (if diabetic), through regular monitoring.**

(R13, Grade of evidence: very low)

Commentary

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. 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 on-going review of treatment to prevent hypoglycemia. 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) [8–11].

14) We cannot make a recommendation at this time on addition of insulin to HPN admixtures due to lack of evidence-based data regarding insulin prescription for HPN patients who have hyperglycemia.

(R14, Grade of evidence: very low)

Commentary

There is limited data on strategies for managing hyperglycemia in patients receiving HPN. 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. Short-acting insulin may be cautiously added to HPN prescriptions after dosage requirements have been established.

3.1.2.1.3. Lipids. **15) We suggest, in patients totally dependent on HPN, a minimal supply of 1 g/kg/week of intravenous lipid emulsion containing essential fatty acids (EFA), to prevent EFA deficiency.**

(R15, Grade of evidence: very low)

Commentary

Patients on long-term PN are in the group at high risk to develop EFA deficiency if not given an external source of EFA. The clinical signs of EFA deficiency may develop within two to six months of fat-free PN. In long-term PN, the necessary minimum of lipid emulsion that should be administered to prevent EFA deficiency is 1 g/kg/week [12]. If patients take some oral diet in the form of fat, EFA deficiency is rarely a specific problem.

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

(R16, Grade of evidence: very low)

Commentary

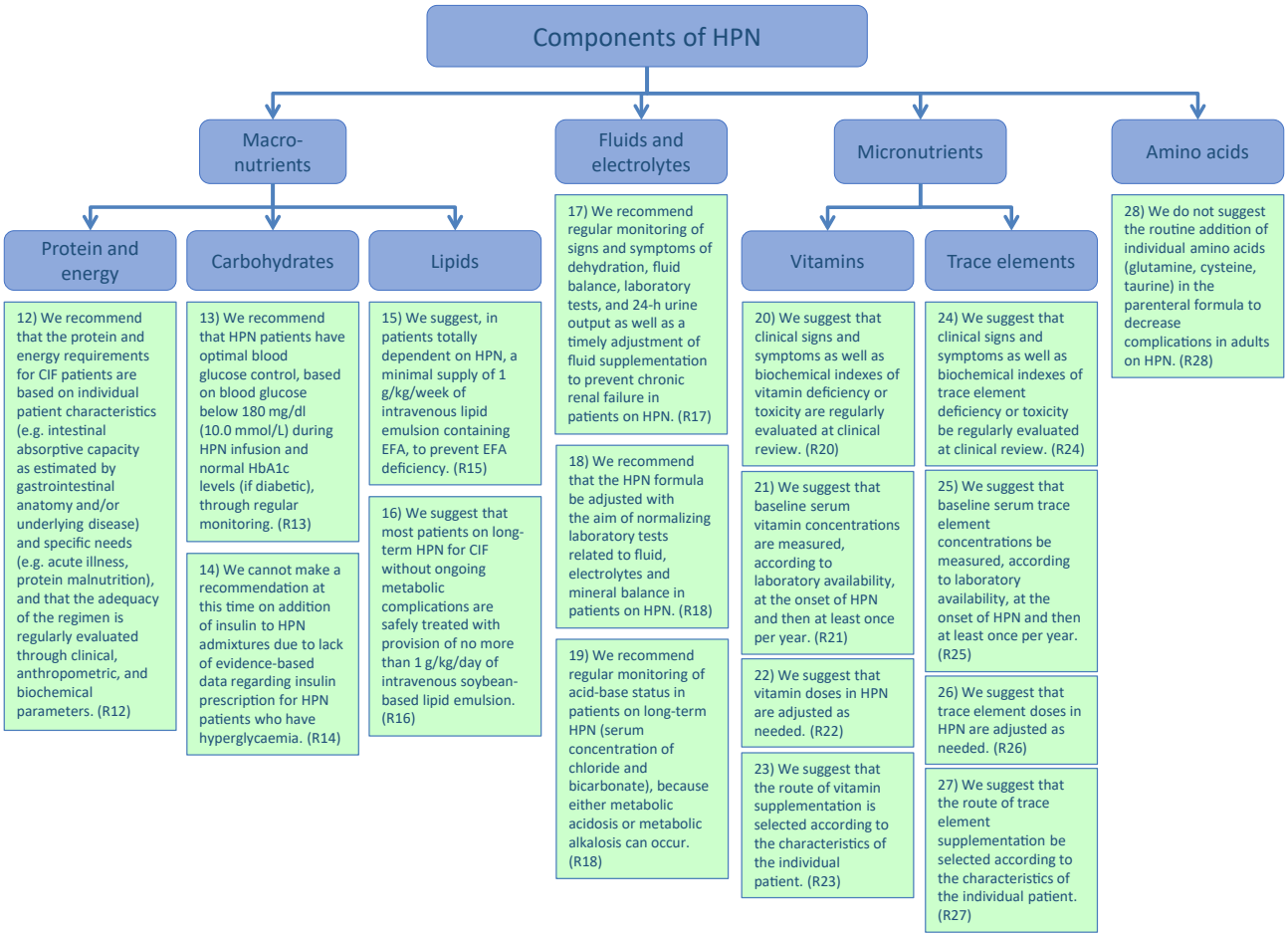

Fig. 3. Components of home parenteral nutrition. For details see text. Abreviations: CIF, chronic intestinal failure; EFA, essential fatty acids; HPN, home parenteral nutrition.

Lipid emulsions serve as a source of EFA and non-protein energy. The optimal amount of lipids for patients on HPN is not precisely established. For long-term HPN treatment (more than six months), the amount of intravenous soybean oil lipid emulsion should not exceed 1 g/kg per day. Administration of soybean oil lipid emulsion in higher doses was associated with significantly increased risk of development of intestinal failure associated liver disease (IFALD) [13,14]. Infusion of parenteral lipid emulsions at rates of 0.8–1.5 g/kg body weight per day is safe, but should not exceed 2.6 g/kg per day (0.11 g/kg/h) [15].

3.1.2.2. Fluids and electrolytes. **17) We recommend regular monitoring of signs and symptoms of dehydration, fluid balance, laboratory tests, and 24-h urine output as well as a timely adjustment of fluid supplementation to prevent chronic renal failure in patients on HPN.**

(R17, Grade of evidence: very low)

Commentary

Patients on HPN, particularly those with SBS, are at risk for fluid and electrolyte imbalance, which can lead to acute and chronic renal failure. The daily parenteral water requirement varies from 25 to 35 mL/kg (approximately 2.0–2.5 L) for the well-hydrated individual [7]. For patients on HPN who have normal renal function and are not on diuretics, the urine output should be at least 0.8–1 L per day. 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. Parenteral nutrition fluid and electrolyte dosing recommendations are based on clinical experience, as there are no randomized studies available (Table 1).

18) We recommend that the HPN formula be adjusted with the aim of normalizing laboratory tests related to fluid, electrolytes and mineral balance in patients on HPN.

(R18, Grade of evidence: very low)

Commentary

The adequacy of the HPN volume may be assessed by measuring 24-h urine output. Serum sodium concentrations are more commonly related to hydration rather than to amount of sodium in the PN formula. 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. Hypophosphatemia occurs

Table 1
Fluid and electrolyte recommendations for parenteral nutrition.

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

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

during refeeding with either parenteral or enteral formulas, and it can have potentially life-threatening outcomes. Magnesium deficiency is a common finding in SBS and inflammatory bowel disease involving the distal small bowel. While serum magnesium levels are measurable, it has been found that low urinary magnesium excretion is a more accurate reflection of total body magnesium depletion. It is recommended that the calcium, magnesium, and phosphate content of the HPN should maintain normal serum concentrations and 24-h urinary excretion.

19) We recommend regular monitoring of acid-base status in patients on long-term HPN (serum concentration of chloride and bicarbonate), because either metabolic acidosis or metabolic alkalosis can occur.

(R19, Grade of evidence: very low)

Commentary

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. 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 SBS with a colon in continuity.

3.1.2.3. Micronutrients

3.1.2.3.1. Vitamins. **20) We suggest that clinical signs and symptoms as well as biochemical indexes of vitamin deficiency or toxicity are regularly evaluated at clinical review.**

(R20, Grade of evidence: very low)

Commentary

An early report of laboratory analyses consisting of 63 individuals on HPN 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 [16]. Subsequently, similar results were reported from France where 27 patients on HPN were studied [17]. Because of parenteral multivitamin shortages in the United States, attention has turned to the length of time a patient on HPN could be maintained with only oral vitamins in the face of restricted parenteral products. 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.

21) We suggest that baseline serum vitamin concentrations are measured, according to laboratory availability, at the onset of HPN and then at least once per year.

(R21, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 20.

22) We suggest that vitamin doses in HPN are adjusted as needed.

(R22, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 20.

23) We suggest that the route of vitamin supplementation be selected according to the characteristics of the individual patient.

(R23, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 20.

3.1.2.3.2. Trace elements. **24) We suggest that clinical signs and symptoms as well as biochemical indexes of trace element deficiency or toxicity be regularly evaluated at clinical review.**

(R24, Grade of evidence: very low)

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 affects the metabolism of micronutrients or the effects of differences in mode of delivery, bioavailability, and absorption as a result of medical nutrition. In addition, good markers of overall status are available only for a limited number of trace elements and few clinical laboratories are equipped to measure them, with the attendant difficulties in identifying deficits and monitoring supplementation. The nine known essential trace elements are chromium, copper, fluorine, iodine, iron, manganese, molybdenum, selenium and zinc. ASPEN developed a position statement for each micronutrient to address evidence-based data on its use and to provide recommendations for changes in the products available on the market [18] (Table 2). The choices of trace element products vary from country to country, but in many countries only multitrace element preparations with fixed combinations are licensed, and individual trace element products may not be routinely available.

25) We suggest that baseline serum trace element concentrations be measured, according to laboratory availability, at the onset of HPN and then at least once per year.

(R25, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 24.

26) We suggest that trace element doses in HPN are adjusted as needed.

(R26, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 24.

27) We suggest that the route of trace element supplementation be selected according to the characteristics of the individual patient.

(R27, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 24.

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

(R28, Grade of evidence: low)

Commentary

Very little information is available on the efficacy of glutamine supplemented PN in home patients. In a randomized controlled trial (RCT) in 22 HPN patients receiving PN containing glycylglutamine during the first or second 6-month study period (0.14–0.15 g/kg/day dipeptide, 10 g Gln), no differences were observed in infectious complications, nutritional status, intestinal permeability, plasma glutamine concentrations, or QoL [19].

Table 2
Recommended daily doses of trace elements for parenteral nutrition [18].

Trace elements	Dose (g)	Dose (mol)
Zinc	2.5–4 mg	38–61 μmol
Copper	0.3–0.5 mg	4.7–7.9 μmol
Manganese	60–100 μg	1.1–1.8 μmol[a]
Chromium	10–15 μg[b]	0.2–0.3 μmol
Selenium	60–100 μg	0.8–1.3 μmol
Iodine	70–150 μg	0.5–1.2 μmol
Iron	1 mg	17.9 μmol

[a] Less than 1 μmol/day [18].
[b] 0.14–0.87 μg/day [18].

Cysteine is commonly believed to be a conditionally essential amino acid in preterm neonates However, in adults there are no published studies on the clinical effects of cysteine added to PN.

Taurine is believed to be conditionally essential in premature neonates. In a pilot study of adults on HPN for SBS, taurine supplemented HPN at a dose of 6 mg/kg provided no benefit [20].

3.1.3. Venous catheters for HPN (Fig. 4)

29) We recommend that the choice of central venous catheter (CVC) type and location of exit site is made by a multidisciplinary HPN team, along with an experienced specialist as well as the patient.

(R78, Grade of evidence: low)

Commentary

The process of choosing a CVC for an adult to be started on HPN must include a multidisciplinary HPN team, an experienced interventional radiologist or surgeon, and most importantly, the patient. For those needing long-term HPN, tunneled CVCs (such as Hickman, Broviac or Groshong) or totally implantable devices (port) are the usual choices.

It is important that the exit site of the catheter can be easily seen by the patient who does self-care. Consideration must be given to proximity to wounds, prior exit sites, tracheotomies, stomas or fistulae.

The choice of single lumen versus multiple lumen catheter must also be made. Placement of the tip of lines using internal jugular and subclavian approaches should be near the junction of the superior vena cava and right atrium to decrease the risk of thrombosis.

30) We recommend that access to the upper vena cava is the first choice for CVC placement, via internal jugular vein or subclavian vein.

(R79, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 29.

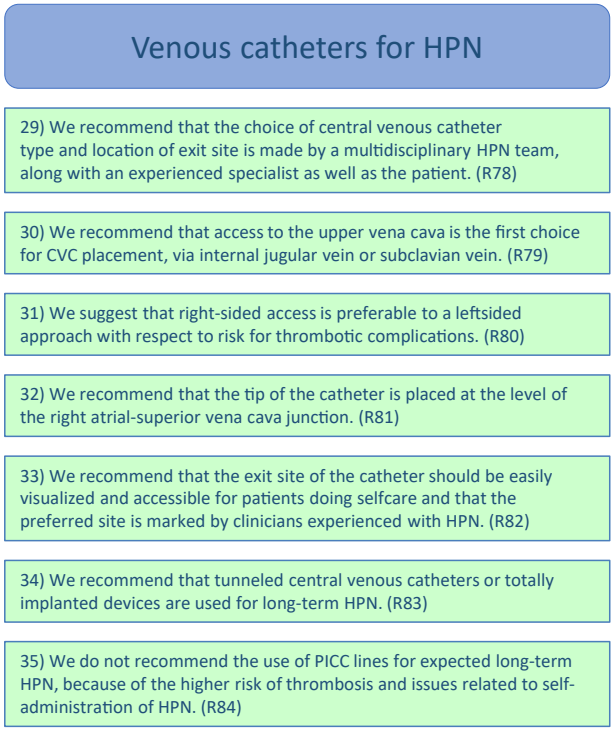

Fig. 4. Venous catheters for home parenteral nutrition. For details see text. Abreviations: CVC, central venous catheter; HPN, home parenteral nutrition.

31) We suggest that right-sided access is preferable to a left-sided approach with respect to risk for thrombotic complications.

(R80, Grade of evidence: low)

Commentary: see Commentary to Recommendation 29.

32) We recommend that the tip of the catheter is placed at the level of the right atrial-superior vena cava junction.

(R81, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 29.

33) We recommend that the exit site of the catheter should be easily visualized and accessible for patients doing self-care and that the preferred site is marked by clinicians experienced with HPN.

(R82, Grade of evidence: low)

Commentary: see Commentary to Recommendation 29.

34) We recommend that tunneled CVCs or totally implanted devices are used for long-term HPN.

(R83, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 29.

35) We do not recommend the use of peripherally inserted central venous catheters (PICCs) lines for expected long-term HPN, because of the higher risk of thrombosis and issues related to self-administration of HPN.

(R84, Grade of evidence: low)

Commentary

PICCs are occasionally used but are generally preferred only for those who will be on HPN for the short-term (<3 months). Most PICCs are easily dislodged and are difficult for the patient to use independently because arm movement is restricted. An RCT of PICC vs. non-tunneled subclavian catheters in 102 hospitalized patients documented a higher complication rate with PICCs, but this was primarily the result of central venous thrombosis rather than catheter infections [21].

When the superior vena cava tract is obstructed, an alternate approach must be considered. Although the femoral vein is often used, it is associated with greater risks of catheter-related bloodstream infection (CRBSI) and thrombosis. However, a Cochrane systemic review [22] found that there were no significant differences between femoral and internal jugular central venous access routes in catheter colonization, CRBSI, and thrombotic complications, but fewer mechanical complications occurred in the femoral access route. However, this review was based on patients in an intensive care unit.

3.2. Intestinal rehabilitation

3.2.1. Diet (Fig. 5)

36) We recommend that SBS patients are advised to consume regular whole food diets, and are encouraged to compensate for malabsorption by hyperphagia.

(R29, Grade of evidence: low)

Commentary

In general, SBS patients should consume regular whole food diets, and they are to be encouraged to compensate for malabsorption by hyperphagia. Oral sip feeds between meals may help to increase overall energy intake.

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.

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. The rare condition of D-lactic acidosis may be seen in SBS patients with a preserved colon in relation to

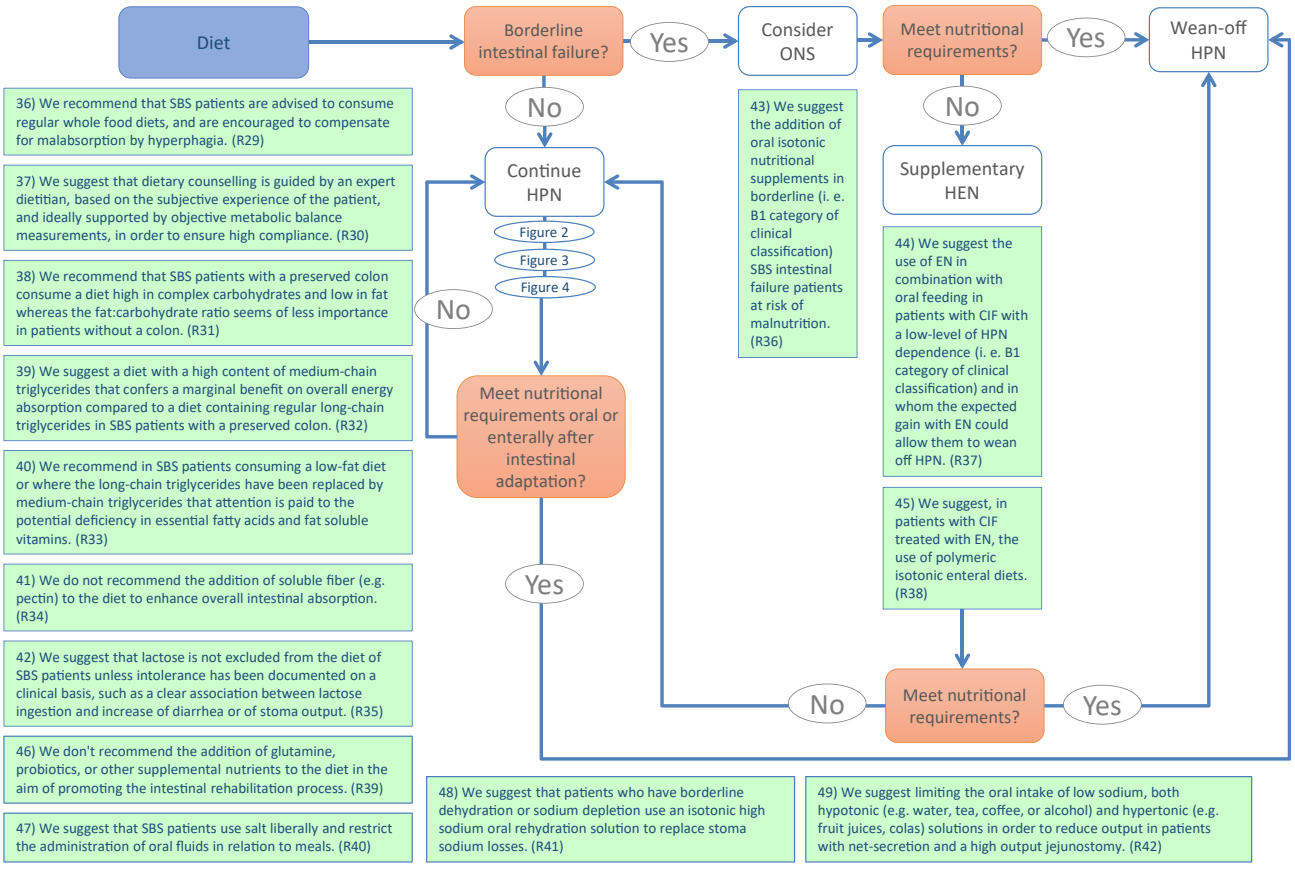

Fig. 5. Intestinal rehabilitation – Diet. For details see text. Abreviations: HEN, home enteral nutrition; HPN, home parenteral nutrition; ONS, oral nutritional supplements; SBS, short bowel syndrome.

the intake of easy fermentable carbohydrates. In patients with jejuno- or ileostomies, significantly higher fat intakes are possible but at the expense of an increased loss of divalent cations: calcium, magnesium, zinc, and copper.

37) We suggest that dietary counselling is 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.

(R30, Grade of evidence: low)

Commentary: see Commentary to Recommendation 36.

38) We recommend that SBS patients with a preserved colon consume a diet high in complex carbohydrates and low in fat whereas the fat:carbohydrate ratio seems of less importance in patients without a colon. (R31, Grade of evidence: low)

Commentary: see Commentary to Recommendation 36.

39) We suggest a diet with a high content of medium-chain triglycerides (MCT) that confers a marginal benefit on overall energy absorption compared to a diet containing regular long-chain triglycerides in SBS patients with a preserved colon.

(R32, Grade of evidence: low)

Commentary

Replacement of 50% of normal long-chain triglycerides in a 60% fat-rich diet by MCT resulted in an improvement in energy-absorption of approximately 1.5 MJ/day in SBS-patients with a preserved colon [23].

40) We recommend in SBS patients consuming a low-fat diet or where the long-chain triglycerides have been replaced by MCT that attention is paid to the potential deficiency in EFA and fat-soluble vitamins.

(R33, Grade of evidence: low)

Commentary: see Commentary to Recommendation 39.

41) We do not recommend the addition of soluble fiber (e.g. pectin) to the diet to enhance overall intestinal absorption.

(R34, Grade of evidence: low)

42) We suggest that lactose is not 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.

(R35, Grade of evidence: low)

Commentary

In general, a diet containing 20 g/day of lactose was well tolerated in patients with SBS but should be carefully titrated in case of previous intolerance [24].

43) We suggest the addition of oral isotonic nutritional supplements in borderline (i.e. B1 category of clinical classification) CIF patients at risk of malnutrition.

(R36, Grade of evidence: low)

Commentary

Following intestinal resection, SBS patients are typically advanced from complete parenteral support to enteral or oral feeding as tolerated. The aim 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.

44) We suggest the use of EN in combination with oral feeding in patients with CIF with a low-level of HPN dependence

(i.e. B1 category of clinical classification) and in whom the expected gain with EN could allow them to wean off HPN.

(R37, Grade of evidence: low)

Commentary: see Commentary to Recommendation 43.

45) We suggest, in patients with CIF treated with EN, the use of polymeric isotonic enteral diets.

(R38, Grade of evidence: low)

Commentary

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. Polymeric diets are less costly and less hyperosmotic than elemental diets and are generally well tolerated.

A study in 15 adults with SBS (3–130 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 [25]. An energy gain of approximately 400 kcal/day was achieved by increasing the oral energy intake by approximately 4.2 MJ/day (1003 kcal). Thus, this treatment could be recommended in patients on the borderline with a low-level of HPN (HPN, i.e. parenteral nutrition and/or intravenous fluids and electrolytes) dependence and in whom the expected gain with EN could allow them to wean off HPN.

46) We do not recommend the addition of glutamine, probiotics, or other supplemental nutrients to the diet in the aim of promoting the intestinal rehabilitation process.

(R39, Grade of evidence: low)

Commentary

In an 8-week, randomized, placebo-controlled, cross-over study in eight SBS patients, no effects were found with glutamine supplementation on bowel morphology, transit, D-xylose absorption, or stool losses [26]. 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 [27].

47) We suggest that SBS patients use salt liberally and restrict the administration of oral fluids in relation to meals.

(R40, Grade of evidence: low)

Commentary: see Commentary to Recommendation 49.

48) We suggest that patients who have borderline dehydration or sodium depletion use an isotonic high sodium oral rehydration solution to replace stoma sodium losses.

(R41, Grade of evidence: low)

Commentary: see Commentary to Recommendation 49.

49) We suggest limiting the oral intake of low sodium, both hypotonic (e.g. water, tea, coffee, or alcohol) and hypertonic (e.g. fruit juices, colas) solutions in order to reduce output in patients with net-secretion and a high output jejunostomy.

(R42, Grade of evidence: low)

Commentary

The aim of providing SBS patients with oral rehydration solutions 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. Most SBS patients tend to prefer the liberal use of table salt in relation to meals and on snacks, whereas others tolerate sodium chloride capsules (up to 7 g/24 h).

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.

Maximal sodium absorption occurred with a mixture of 120 mmol/L (2160 mg) of sodium chloride and 30 mmol/L (540 mg) of glucose. Oral rehydration solutions are rarely indicated in SBS patients with a preserved colon. 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.

3.2.2. Medical (Fig. 6)

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

(R56, Grade of evidence: very low)

Commentary

Pharmacotherapy in SBS patients remains a difficult clinical problem, as drug absorption from the gastrointestinal tract may be considerably impaired in such patients. 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.

3.2.2.1. Antisecretory drugs

3.2.2.1.1. H2-receptor antagonists and PPI. **51) We recommend the use of H_2-receptor antagonists or proton pump inhibitors in reducing 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/day.**

(R43, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 52.

52) We suggest that in the individual patient, H_2-receptor antagonists or proton pump inhibitors are also effective in reducing fecal wet weight and sodium excretion in the long-term.

(R44, Grade of evidence: very low)

Commentary

Enterectomy is associated with gastric hypergastrinemia and hypersecretion. The 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, which may further aggravate conditions for absorption. The main treatments for gastric hypersecretion are H_2-receptor antagonists and proton pump inhibitors, in case of lack of effect of tablets and capsules, soluble forms or intravenous administration should be considered. Double-blind placebo-controlled studies [28,29] 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%.

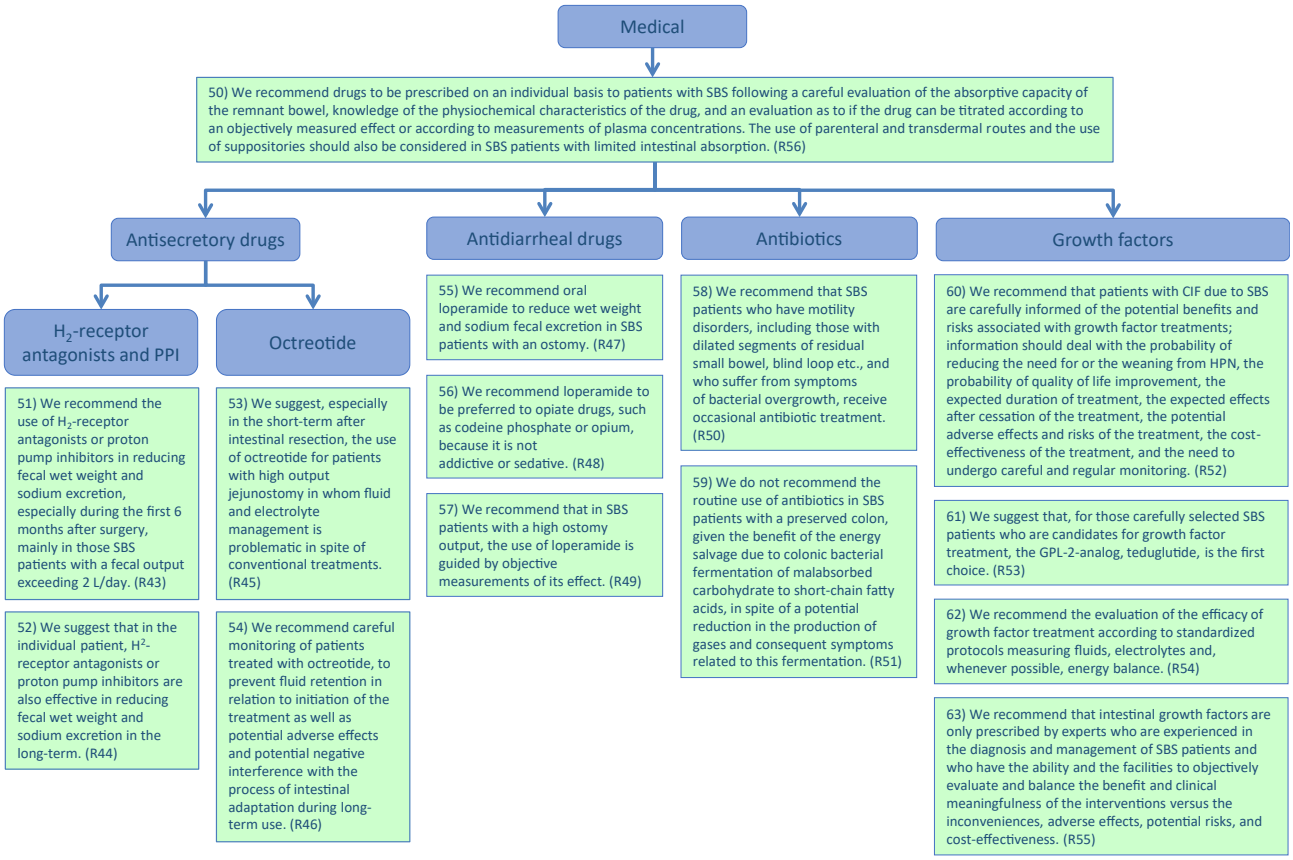

Fig. 6. Intestinal rehabilitation – medical. For details see text. Abreviations: CIF, chronic intestinal failure; GLP-2, glucagon-like peptide-2; PPI, proton pump inhibitor; SBS, short bowel syndrome.

3.2.2.1.2. Octreotide. **53) We suggest, especially in the short-term after intestinal resection, the use of octreotide for patients with high output jejunostomy in whom fluid and electrolyte management is problematic in spite of conventional treatments.**

(R45, Grade of evidence: low)

Commentary: see Commentary to Recommendation 54.

54) We recommend careful monitoring of patients treated with octreotide, to prevent fluid retention in relation to initiation of the treatment as well as potential adverse effects and potential negative interference with the process of intestinal adaptation during long-term use.

(R46, Grade of evidence: low)

Commentary

Somatostatin decreases gastric, biliary, and pancreatic secretions. It may inhibit secretagogue-induced water and electrolyte secretion in the jejunum and the colon, stimulates sodium and chloride absorption in the ileum, decreases intestinal motility, and inhibit the release of hormones that may contribute to diarrhea (e.g. VIP, GIP, gastrin). Although it has beneficial effects on intestinal absorption potential detrimental effects have also been suggested interfering with the physiological process of adaptation to intestinal resection.

Somatostatin and the somatostatin analog octreotide have been shown to reduce ileostomy diarrhea and large volume jejunostomy output in a single placebo-controlled trial [30]. 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.

3.2.2.2. Anti-diarrheal drugs. **55) We recommend using oral loperamide to reduce wet weight and sodium fecal excretion in SBS patients with an ostomy.**

(R47, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 57.

56) We recommend loperamide to be preferred to opiate drugs, such as codeine phosphate or opium, because it is not addictive or sedative.

(R48, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 57.

57) We recommend that in SBS patients with a high ostomy output, the use of loperamide is guided by objective measurements of its effect.

(R49, Grade of evidence: moderate)

Commentary

The use of anti-diarrheal medication aims to reduce the losses of water and electrolytes and to minimize the symptoms and consequences of diarrhea. 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. Opiates increase duodenal muscle tone and inhibit propulsive motor activity, 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.

Loperamide is chemically related to, but more potent, lacks central opiate effects, is more gut-specific, and has longer duration

of action than diphenoxylate. 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 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 RCTs of loperamide have been performed but mainly in patients with an ileostomy or ileocecal resection [31,32]. The treatment reduced fecal wet weight output by 15–30%.

3.2.2.3. Antibiotics. **58) We recommend that SBS patients who have motility disorders, including those with dilated segments of residual small bowel, blind loop etc., and who suffer from symptoms of bacterial overgrowth, receive occasional antibiotic treatment.**

(R50, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 59.

59) We do not recommend the routine use of antibiotics in SBS patients with a preserved colon, given the benefit of the energy salvage due to colonic bacterial fermentation of malabsorbed carbohydrate to short-chain fatty acids, in spite of a potential reduction in the production of gases and consequent symptoms related to this fermentation.

(R51, Grade of evidence: very low)

Commentary

Very little is known about the presence of small bowel bacterial overgrowth in patients with SBS. 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.

3.2.2.4. Growth factors (GH, GLP2-analog, teduglutide). **60) We recommend that patients with CIF due to SBS are carefully informed of the potential benefits and risks associated with growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of 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.**

(R52, Grade of evidence: low)

61) We suggest that, for those carefully selected SBS patients who are candidates for growth factor treatment, the GPL2-analogue, teduglutide, is the first choice.

(R53, Grade of evidence: moderate)

Commentary: see Commentary to Recommendation 63.

62) We recommend the evaluation of the efficacy of growth factor treatment according to standardized protocols measuring fluids, electrolytes and, whenever possible, energy balance.

(R54, Grade of evidence: low)

Commentary: see Commentary to Recommendation 63.

63) We recommend that intestinal growth factors are only prescribed by experts who are experienced in the diagnosis and management of SBS patients and who have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks, and cost-effectiveness.

(R55, Grade of evidence: low)

Commentary

The aim of intestinal rehabilitation of SBS patients, is to maximize absorption in the remnant bowel, decreasing intestinal losses, and reducing the need for intravenous supplementation.

At this time, only two molecules have been approved for SBS patients, the growth hormone somatotropin (only in US) and the glucagon-like peptide-2 (GLP-2) analogue, teduglutide (in US and Europe).

However, since the number of patients treated with these agents is still low, it is advised that these treatments should only be used under the guidance of a physician experienced in the management of SBS. Since potential long-term complications are unknown, careful long-term monitoring is required. For patients and healthcare providers, the issue of costs may also need to be addressed. High-dose growth hormone treatment in SBS patients may have a positive effect on intestinal wet-weight absorption, but its use is often associated with significant side effects [33,34]. Low-dose growth hormone has been demonstrated to have a beneficial effect on intestinal energy absorption in a single study, but this effect may be partly due to a stimulatory effect on oral energy intake [35]. Side effects seem to be lower with the lower dose. The positive effects of growth hormone have mainly been described in SBS patients with a colon in continuity.

GLP-2 and the degradation-resistant analogue, teduglutide, mainly increases intestinal wet weight absorption and decreases the need for parenteral fluid support in SBS patients with IF [36–38]. 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.

With both growth factors, the effects on intestinal functions quickly decrease and vanish after stopping the treatment. Therefore, life-long treatment is required. Adverse events are mainly localized to the gastrointestinal tract with teduglutide and are mainly systemic and appear to be more frequent with growth hormones. Careful patient surveillance for the risk of cancer must be performed. Overall, these data would be in favor of teduglutide as the current drug of choice for intestinal rehabilitation of SBS patients. However, both treatments are costly, and the cost-efficacy as well as the risk-benefit ratio need to be considered when the decision to treat a patient is considered.

3.2.3. Non-transplant surgery (Fig. 7)

The recommendations of non-tranplant surgery in patietns with SBS are summarized in Fig. 7.

3.2.3.1. General. **64) We recommend that, in patients with SBS, during intestinal resection, bowel length is conserved to the fullest extent possible to avoid dependence on HPN.**

(R66, Grade of evidence: low)

3.2.3.2. Restoration of intestinal continuity. **65) We recommend that, in patients with SBS, restoration of intestinal continuity, is realized whenever possible, to decrease HPN dependency.**

(R 67, Grade of evidence: moderate)

Commentary

Once the patient is stabilized, ostomy reversal and recruitment of distal unused bowel should be prioritized whenever feasible.

3.2.3.3. Surgical options. **66) We recommend that, in patients with SBS, management is performed through a multidisciplinary approach to optimize intestinal rehabilitation and overall patient outcome.**

(R69, Grade of evidence: low)

Commentary: see Commentary to Recommendation 67.

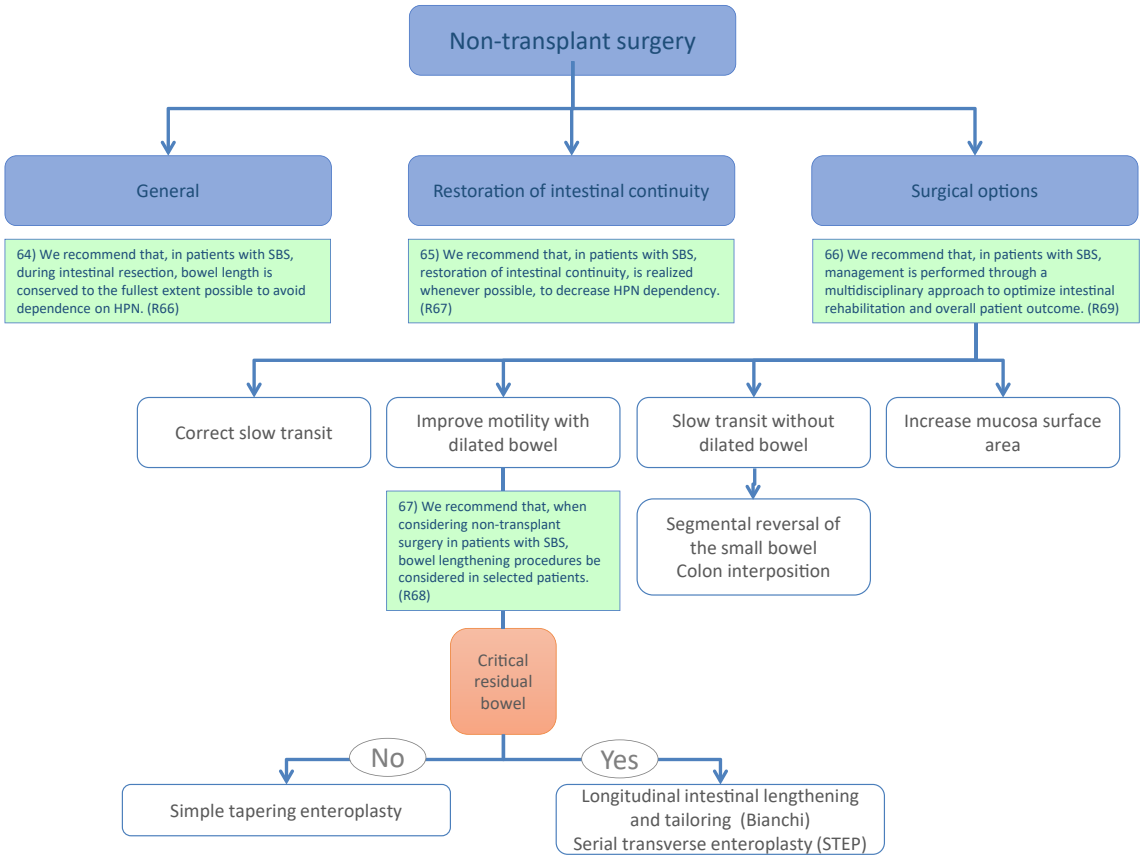

Fig. 7. Intestinal rehabilitation – non-translplant surgery. For details see text. Abreviations: SBS, short bowel syndrome, STEP, serial transverse enteroplasty.

67) We recommend that, when considering non-transplant surgery in patients with SBS, bowel lengthening procedures be considered in selected patients.

(R 68, Grade of evidence: very low)

Commentary

Surgical options in patients with CIF fall into four main categories: operations to correct slow transit, operations to improve intestinal motility in cases of dilated bowel, operations to slow intestinal transit in the absence of bowel dilatation, and operations to increase mucosal surface area.

Segmental bowel dilatation with poor peristalsis often results in clinical features of small bowel bacterial overgrowth. Excessive intestinal dilatation is most easily managed by a simple tapering enteroplasty, 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 accomplishes intestinal tapering without loss of surface area. LILT creates a loop of bowel that is twice the length of the original and half the original diameter.

Tapering without loss of surface area is accomplished effectively and relatively simply by the serial transverse enteroplasty (STEP) procedure described by Kim et al., 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.

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.

Of procedures designed to slow transit in the absence of bowel dilatation, segmental reversal of the small bowel (SRSB) shows the greatest promise. SRSB creates an antiperistaltic segment of bowel approximately 10–12 cm in length, located ~10 cm proximal to an end-stoma or small bowel-colon anastomosis.

3.2.4. Special cases

3.2.4.1. Chronic intestinal pseudo-obstruction (CIPO) (Fig. 8). The management of patients with CIPO is shown in Fig. 8.

3.2.4.1.1. Nutritional therapy. **68) We recommend that no specific diet is prescribed but that patients with CIPO are encouraged to eat according to individual tolerance.**

(R57, Grade of evidence: very low)

Commentary

The main goals of CIPO management are to reduce the major symptoms by improving intestinal propulsion and maintaining adequate nutritional status.

Oral intake should be fractionated and 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. Associated multivitamin and micronutrient 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.

69) We suggest trying EN as a first step in patients with chronic gastrointestinal motility dysfunctions who are not able to meet their energy needs with oral nutrition alone and continue to lose weight, before using HPN.

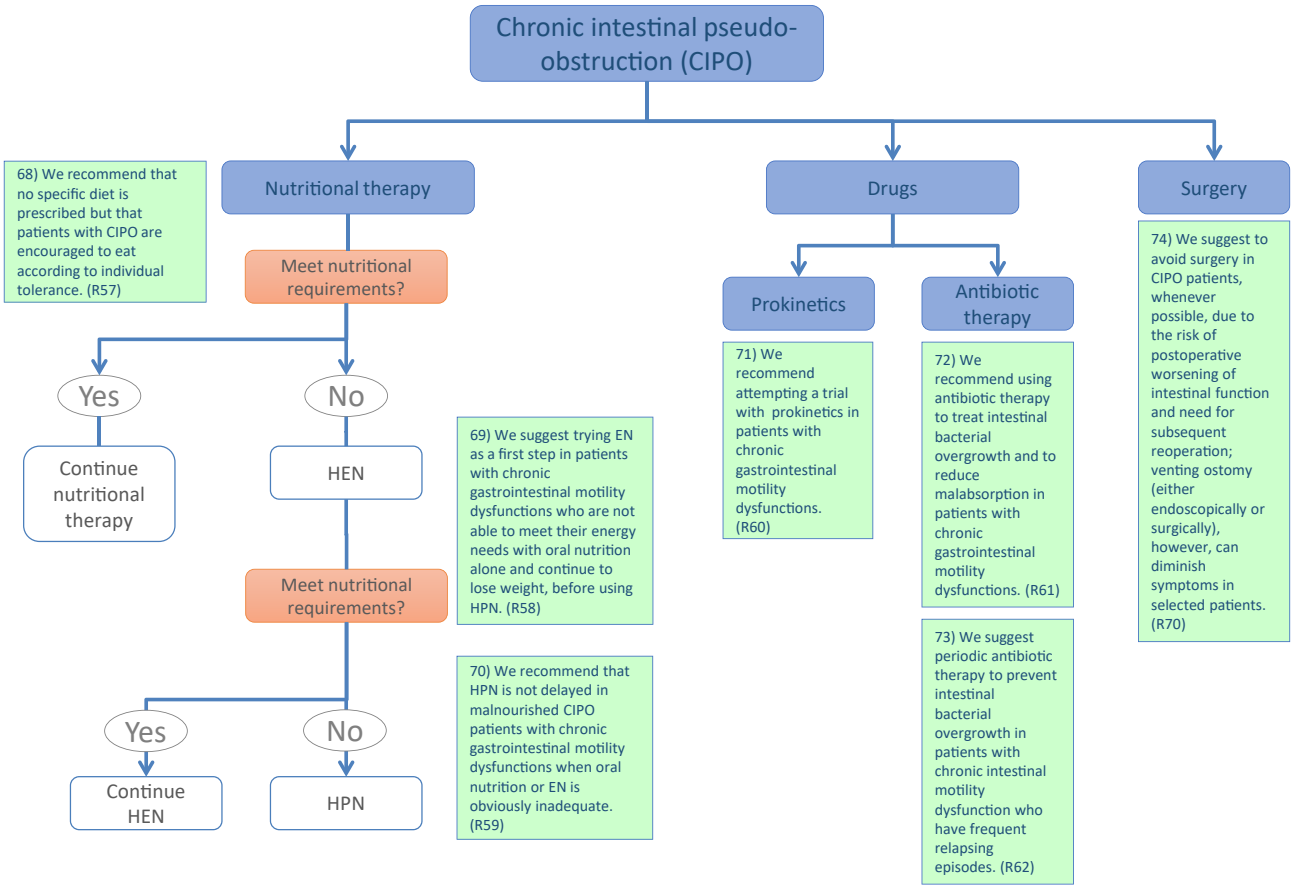

Fig. 8. Intestinal rehabilitation – special cases – chronic intestinal pseudo-obstruction. For details see text. Abreviations: CIPO, chronic intestinal pseudo-obstruction; HEN, home enteral nutrition; HPN, home parenteral nutrition.

(R 58, Grade of evidence: very low)

Commentary

EN is an option for patients whose motility disorder is mainly localized. It presents fewer complications than PN, but clinical experience suggests that EN is rarely tolerated by patients. Percutaneous endoscopic gastrostomy can be performed in patients who do not have significant gastroparesis. Temporary or permanent small bowel access can be achieved by endoscopic, surgical, and radiological placement. In cases of severe gastroparesis, a venting gastrostomy can be added to the jejunostomy.

70) We recommend that HPN is not delayed in malnourished CIPO patients with chronic gastrointestinal motility dysfunctions when oral nutrition or EN is obviously inadequate.

(R59, Grade of evidence: very low)

Commentary

In most severe cases, when small bowel function is diffusely affected, PN is necessary to satisfy nutritional requirements.

3.2.4.1.2. Drugs. Prokinetics and antibiotic therapy are used in the management of patients with CIPO.

3.2.4.1.3. Prokinetics. **71) We recommend attempting a trial with prokinetics in patients with chronic gastrointestinal motility dysfunctions.**

(R60, Grade of evidence: very low)

Commentary

There are no motility agents on the market able to restore normal gastrointestinal motor function, particularly in those patients with a generalized motility disorder. However, even if drugs stimulating intestinal contractions are helpful only in a minority of patients, a trial with prokinetics should always be attempted. The main drugs used are metoclopramide, domperidone, erythromycin, octreotide, and neostigmine. Octreotide has been shown to benefit adults with scleroderma associated CIPO. The prokinetic effect occurs at a subcutaneous dose of 50–100 μg/day. The latest drug assessed was prucalopride, a highly specific serotonin receptor agonist with enterokinetic effects [39–41].

3.2.4.1.4. Antibiotic therapy. **72) We recommend using antibiotic therapy to treat intestinal bacterial overgrowth and to reduce malabsorption in patients with chronic gastrointestinal motility dysfunctions.**

(R61, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 73.

73) We suggest periodic antibiotic therapy to prevent intestinal bacterial overgrowth in patients with chronic intestinal motility dysfunction who have frequent relapsing episodes.

(R62, Grade of evidence: very low)

Commentary

Sequential antibiotic therapy is very effective in treating intestinal bacterial overgrowth and reducing malabsorption. It has also been shown to improve nutritional status and sometimes bloating. Bacterial overgrowth may lead to life-threatening bacterial translocation. Poorly absorbable antibiotics such as aminoglycosides and rifaximine are preferred, but alternating cycles with metronidazole and tetracycline may be necessary to limit resistance. In clinical practice, the most commonly used antibiotics are metronidazole, amoxicillin-clavulanate, doxycycline, and norfloxacine.

3.2.4.1.5. Surgery. **74) We suggest to avoid surgery in CIPO patients, whenever possible, due to the risk of postoperative worsening of intestinal function and need for subsequent**

reoperation; venting ostomy (either endoscopically or surgically), however, can diminish symptoms in selected patients.

(R70, Grade of evidence: very low)

Commentary

Surgery plays a limited role in the management of CIPO patients and should be avoided due to the risk of postoperative worsening and need for subsequent reoperation. Nevertheless, a surgery is often performed before and/or during CIPO management with an average of three procedures per patient. Main procedures used include intestinal resection, explorative laparotomy, and creation of venting or feeding ostomy.

3.2.4.2. Radiation enteritis (Fig. 9). The nutritional management of patients with radiation enteritis is summarized in Fig. 9.

3.2.4.2.1. Nutritional therapy. **75) We recommend that the nutritional regime in chronic radiation enteritis patients follows the same criteria adopted for the HPN of patients with other causes of CIF.**

(R63, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 77.

76) We suggest trying EN in patients with radiation enteritis if oral nutrition including use of oral nutritional supplements is inadequate.

(R64, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 77.

77) We recommend HPN is not delayed in malnourished radiation enteritis patients, if oral nutrition/EN is obviously inadequate.

(R65, Grade of evidence: very low)

Commentary

Radiation enteritis still occurs in up to one-fifth of all patients undergoing pelvic radiotherapy.

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

In an early RCT comparing PN with elemental diets, Loiudice and Lang [42] reported improvements in nutritional assessment data,

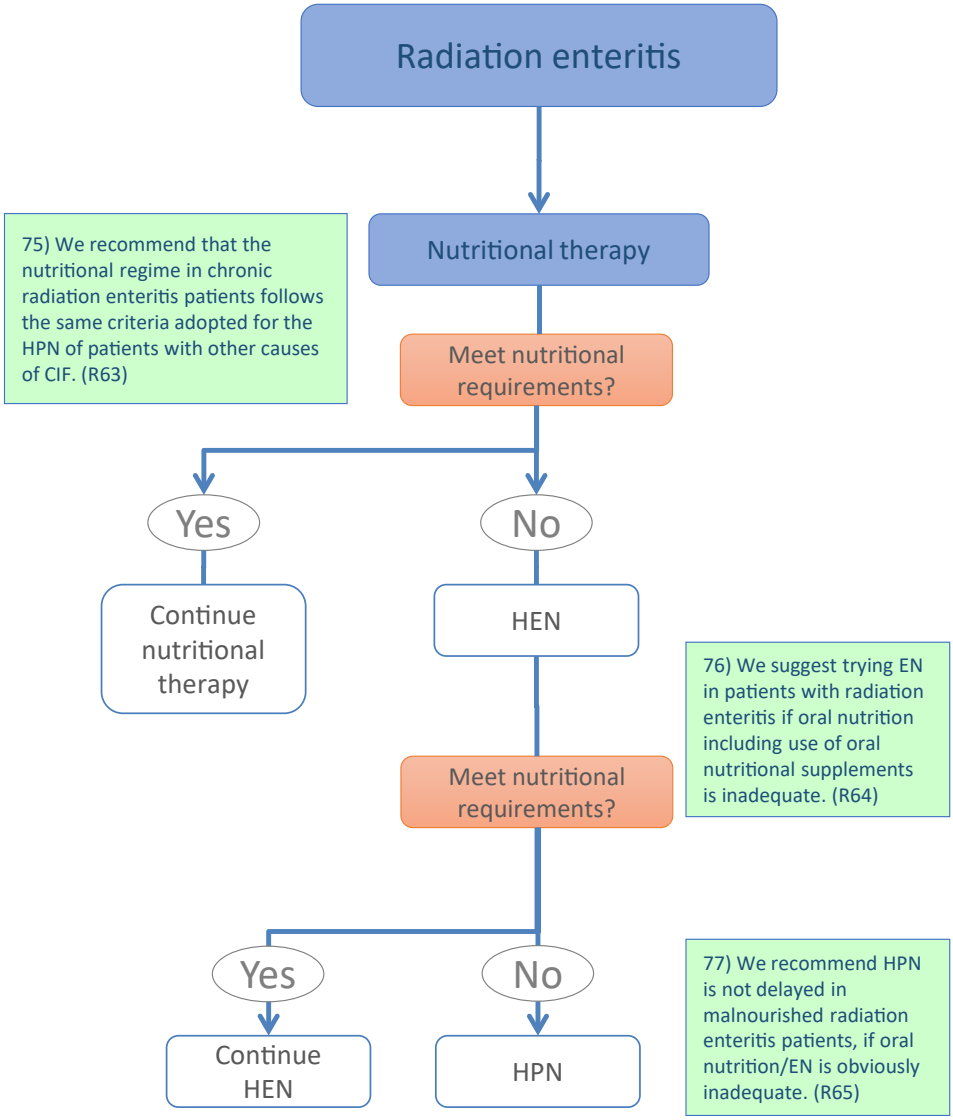

Fig. 9. Intestinal rehabilitation – special cases – radiation enteritis. For details see text. Abreviations: CIF, chronic intestinal failure; EN, enteral nutrition; HEN, home enteral nutrition; HPN, home parenteral nutrition.

nitrogen balance, radiographic, and clinical parameters after therapy in patients on intravenous supplementation. 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.

3.3. Intestinal transplantation (ITx) (Fig. 10)

The recommendations for ITx are shown in Fig. 10.

3.3.1. General

78) We recommend HPN as the primary treatment for patients with CIF and the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, to maximize the opportunity of weaning off HPN, to prevent HPN failure, and to ensure timely assessment of candidacy for ITx.

(R71, Grade of evidence: very low)

Commentary

The data on safety and efficacy indicate HPN as the primary treatment for CIF and ITx as the treatment for patients with a high risk of mortality on HPN. The progress in intestinal rehabilitation therapy has modified the strategy of treatment of CIF, moving from a straight referral for ITx of any patients with a potential risk of death on HPN to the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, in order to maximize the opportunity of weaning off HPN, to prevent HPN-failure, and to ensure timely ITx when this is needed.

3.3.2. Indications for ITx

79) We recommend assessment for candidacy for ITx, when one of the following indications exists:

1. **Failure of HPN:**
   - **Impending (total bilirubin above 3–6 mg/dl (54–108 μmol/L), progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of IFALD.**
   - **CVC related thrombosis of two or more central veins (internal jugular, subclavian or femoral).**
   - **Frequent central line sepsis: two or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock and/or acute respiratory distress syndrome.**
   - **Frequent episodes of severe dehydration despite intravenous fluid in addition to HPN.**
2. **High risk of death attributable to the underlying disease**
   - **Invasive intra-abdominal desmoid tumors**

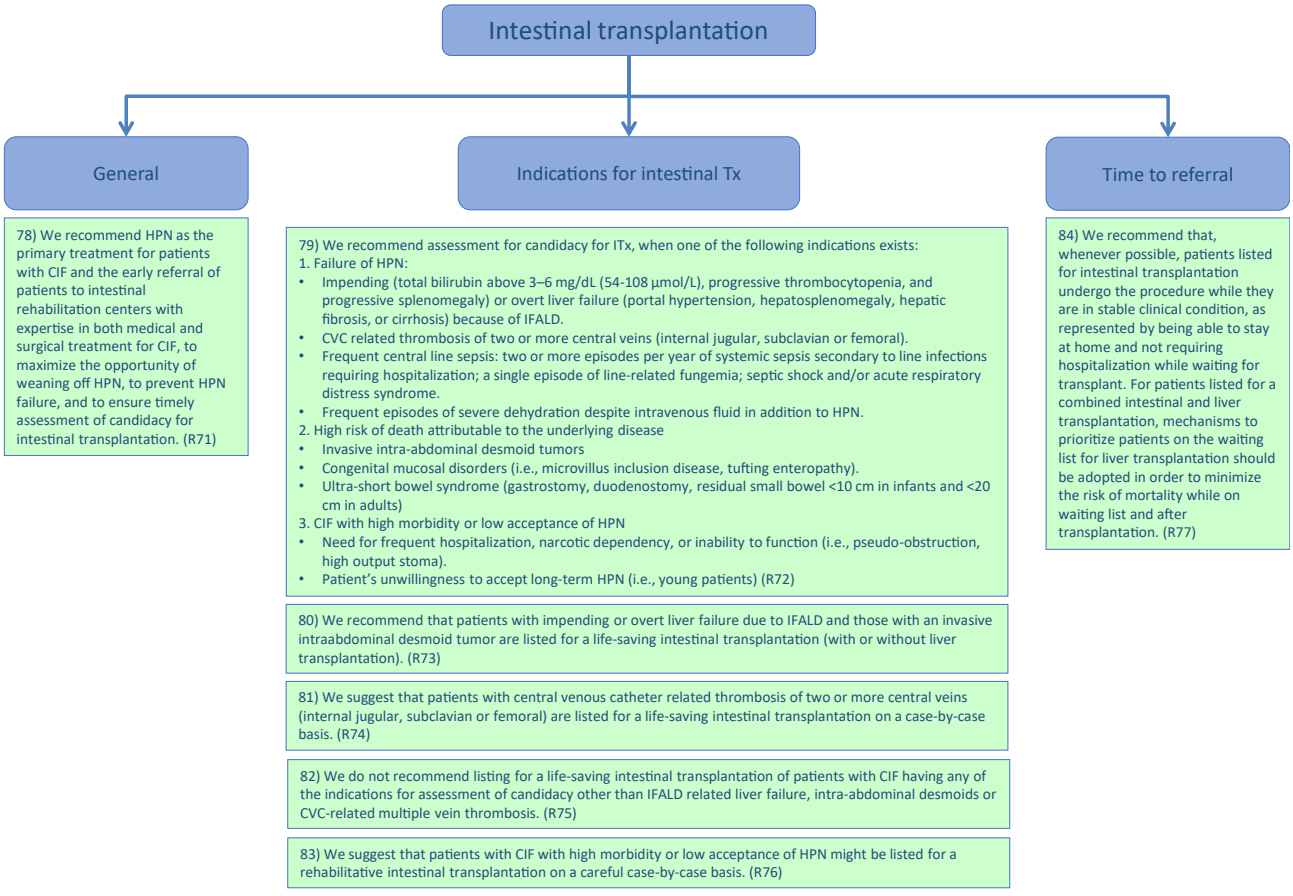

Fig. 10. Intestinal transplantation. For details see text. Abreviations: CIF, chronic intestinal failure; CVC, central venous catheter; HPN, home parenteral nutrition; IFALD, intestinal failure associated liver disease; Tx, transplantation.

- **Congenital mucosal disorders (i.e., microvillus inclusion disease, tufting enteropathy).**
- **Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel < 10 cm in infants and < 20 cm in adults)**

3. **CIF with high morbidity or low acceptance of HPN**
   - **Need for frequent hospitalization, narcotic dependency, or inability to function (i.e., pseudo-obstruction, high output stoma).**
   - **Patient's unwillingness to accept long-term HPN (i.e., young patients)**

(R72, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 81.

80) We recommend that patients with impending or overt liver failure due to IFALD and those with an invasive intra-abdominal desmoid tumor are listed for a life-saving ITx (with or without liver transplantation).

(R73, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 81.

81) We suggest that patients with CVC related thrombosis of two or more central veins (internal jugular, subclavian or femoral) are listed for a life-saving ITx on a case-by-case basis.

(R74, Grade of evidence: very low)

Commentary

The indications for ITx were initially developed by expert consensus in 2001 and were categorized as HPN failure, high risk of death due to the underlying disease, or CIF with high morbidity or low acceptance of HPN [43,44].

In 2004, the Home Artificial Nutrition and Chronic Intestinal Failure working group (HAN&CIF group) of ESPEN carried out a prospective comparative study to evaluate the appropriateness of the 2001 indications for ITx [45]. Two cohorts of patients on HPN for CIF were compared, one of candidates for ITx and a control group of patients with no indication for ITx. The 5-year survival rate on HPN was 87% in non-candidates. The 5-year survival rate for ITx candidates however was 74% in candidates with HPN-failure, 84% in those with high-risk underlying disease, 100% in those with high morbidity CIF/low acceptance of HPN, and 54% in ITx recipients. These data compare well with those of the International ITx Registry that shows a 1-year conditional survival for patients transplanted since 2000, actuarial 5-year patient and graft survival of 58% and 50%, respectively [46].

82) We do not recommend listing for a life-saving ITx of patients with CIF having any of the indications for assessment of candidacy other than IFALD-related liver failure, intra-abdominal desmoids or CVC-related multiple vein thrombosis.

(R75, Grade of evidence: very low)

Commentary: see Commentary to Recommendation 83.

83) We suggest that patients with CIF with high morbidity or low acceptance of HPN might be listed for a rehabilitative ITx on a careful case-by-case basis.

(R76, Grade of evidence: very low)

Commentary

The analysis of the risk of death and the causes of death on HPN associated with each indication showed that only patients with liver failure due to IFALD (RR 3.2) or with invasive intra-abdominal desmoids (RR 7.1) had an actual statistically significant increased risk of death on HPN. A non-statistically significant increase of the risk of death on HPN was observed also for candidates because of multiple CVC-related deep vein thrombosis (RR 2.1, P = 0.058). None of the other indications for ITx showed an increased risk of death on HPN. These data indicate that only liver failure due to IFALD and invasive intra-abdominal desmoids can be considered indications for a straight referral for a lifesaving ITx. CVC-related thrombosis of ≥2 central veins can be also considered for a life-saving ITx, in appropriately selected patients. For patients having none of the above indications, ITx has no life-saving role, but it might have a potential rehabilitative role on a case-by-case basis for adequately informed patients [45].

3.3.3. Time to referral

84) We recommend that, whenever possible, patients listed for ITx undergo the procedure while they are in stable clinical condition, as represented by being able to stay at home and not requiring hospitalization while waiting for transplant. For patients listed for a combined intestinal and liver transplantation, mechanisms to prioritize patients on the waiting list for liver transplantation should be adopted in order to minimize the risk of mortality while on waiting list and after transplantation.

(R 77, Grade of evidence: very low)

Commentary

The data from the International ITx Registry revealed that transplantation while the recipient is waiting at home prior to transplant versus at hospital (that would indicate a better clinical status), younger recipient age, maintenance on rapamycin, and the presence of a liver component were the factors significantly associated with improved graft survival [46].

3.4. Complications of HPN

3.4.1. Catheter related complications

3.4.1.1. Catheter-related infections (Fig. 11). The management of catheter-related infections is summarized in Fig. 11.

3.4.1.1.1. Diagnosis. **85) We recommend that CVC-related infections are diagnosed according to current guidelines on CRI.**

(R85, Grade of evidence: very low)

Commentary

CRI in the setting of HPN should be defined as local, including infections of the catheter exit site, port pocket, or subcutaneous catheter tunnel, or systemic, in the form of CRBSI.

Infections can be bacterial or fungal in origin, but most problems are caused by skin-derived flora. The catheter hub is regarded as a common cause of endo-luminal CRI, whereas infections originating from the exit site or tunnel tract are considered extra-luminal in nature.

CRBSI rates in experienced referral centers can be expected to range from 0.14 to 1.09 episodes per catheter year [47–61].

CVC-related sepsis rates can be regarded as a surrogate measure of overall quality of catheter care.

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

(R86, Grade of evidence: moderate)

Commentary

In general, HPN patients require a conservative approach with systemic and local (locks) use of antibiotics for simple infections due to *S. aureus*, coagulase-negative staphylococci, and Gram-negative bacilli, before removing the catheter.

Catheter removal is inevitable in case of tunnel infections, port abscesses, in patients with septic shock, or in case of complicated infections, including endocarditis, metastatic infections, septic thrombosis, and when paired blood cultures are positive for fungi

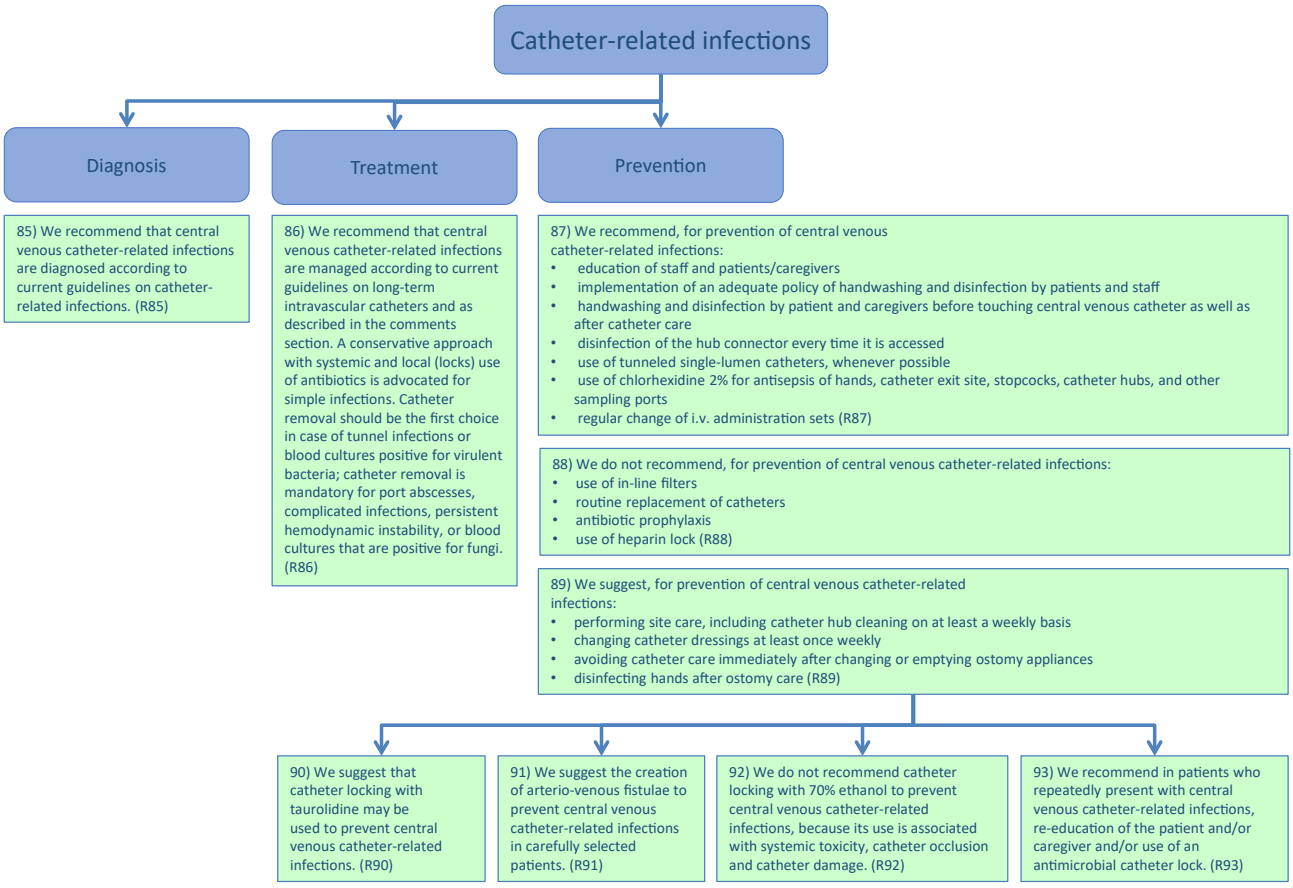

Fig. 11. Complications of home parenteral nutrition – catheter-related infections. For details see text.

or virulent bacteria. For salvage of devices 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. Reinsertion of long-term devices should be postponed until after appropriate systemic antimicrobial therapy is begun, based on susceptibilities of the bloodstream isolate, and after repeat cultures of blood samples yield negative results. If time permits, insertion of a new device in a stable patient ideally should be done after a systemic antibiotic course of therapy is completed, and repeat blood samples drawn five to ten days later yield negative results. Successful salvage of infected implanted ports by antibiotic treatment is rare and most of these devices have to be removed.

3.4.1.1.3. Prevention. **87) We recommend, for prevention of CRI:**

- **education of staff and patients/caregivers**
- **implementation of an adequate policy of handwashing and disinfection by patients and staff**
- **handwashing and disinfection by patient and caregivers before touching CVCs as well as after catheter care**
- **disinfection of the hub connector every time it is accessed**
- **use of tunneled single-lumen catheters, whenever possible**
- **use of chlorhexidine 2% for antisepsis of hands, catheter exit site, stopcocks, catheter hubs, and other sampling ports**
- **regular change of i.v. administration sets**

(R87, Grade of evidence: high)
Commentary: see Commentary to Recommendation 89.
88) We do not recommend, for prevention of CRI:

- **use of in-line filters**
- **routine replacement of catheters**
- **antibiotic prophylaxis**
- **use of heparin lock**

(R88, Grade of evidence: low)
Commentary: see Commentary to Recommendation 89.
89) We suggest, for prevention of CRI:

- **performing site care, including catheter hub cleaning on at least a weekly basis**
- **changing catheter dressings at least once weekly**
- **avoiding catheter care immediately after changing or emptying ostomy appliances**
- **disinfecting hands after ostomy care**

(R89, Grade of evidence: very low)
Commentary

Implementation of an adequate written policy and education of healthcare personnel and patients is necessary for the prevention of complications. Center for Disease Control and Prevention Guidelines emphasize the importance of decontaminating the hands before and after caring for CVCs [62]. They recommend the use of soap and water or waterless alcohol-based gels or foams.

The length of time for optimal hand washing is not defined in the literature. For patients with ostomies or fistulae, it is important that care of ostomy and fistula appliances should be temporally separated from catheter care.

Site care should be done on a regularly prescribed schedule, at least once weekly, as well as every time the dressing becomes wet or contaminated. The use of chlorhexidine 2% for skin antisepsis of the hands, catheter exit site, and of the skin before catheter insertion is recommended. Stopcocks, catheter hubs, and other sampling ports should always be disinfected, preferably using chlorhexidine 2% in 70% isopropyl alcohol. Intravenous administration sets should be changed every 24 h. There is no definitive proof that the use of needle-free connectors reduces CRBSI risk in HPN patients.

A randomized trial has provided evidence that interactive video-based education of both staff and patients reduces CRI in HPN patients and improves problem-solving capacities and QoL [63].

Strategies that have been proven to be ineffective for prevention of CRI include the use of in-line filters, routine replacement of catheters, antibiotic prophylaxis, and the use of heparin.

90) We suggest that catheter locking with taurolidine may be used to prevent CRI.

(R90, Grade of evidence: low)

Commentary

Taurolidine prevents microbial adhesion to catheter surfaces and biofilm formation by an irreversible reaction of its metabolites with bacterial cell walls and has a broad spectrum of activity against bacterial and fungal pathogens. In 2013, Liu and co-workers [64] 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). No association was observed with taurolidine locks and catheter-associated thrombosis. Overall, the use of taurolidine reduced CRBSIs without obvious adverse effects or bacterial resistance [64].

91) We suggest the creation of arterio-venous fistula to prevent CRI in carefully selected patients.

(R91, Grade of evidence: very low)

Commentary

In 127 consecutive patients receiving HPN between 2000 and 2006, comprising 344 access years of tunneled catheters/ports and 194 access years of arterio-venous fistula, the rate of bloodstream infections per year was 0.03/year for arterio-venous fistula and 1.37/year for ports and tunneled catheters, with occlusion rates of 0.60 and 0.35 per year, respectively, showing that although occlusions were somewhat more frequent for arterio-venous fistula than for tunneled catheters, the incidence of bloodstream infections was much lower [65].

92) We do not recommend catheter locking with 70% ethanol to prevent CRI, because its use is associated with systemic toxicity, catheter occlusion and catheter damage.

(R92, Grade of evidence: high)

Commentary

70% ethanol has not only been used to dissolve debris and unclog PN catheters, but ethanol locking therapy has also been shown to be a promising therapy for the prevention of CRBSI in small studies in adult and pediatric HPN patients. However, a recent systematic review on the adverse effects associated with ethanol locking therapy 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 [66]. These data do not allow us to recommend ethanol lock for the prevention of CRBSI in patients on long-term HPN.

93) We recommend in patients who repeatedly present with CRI, re-education of the patient and/or caregiver and/or use of an antimicrobial catheter lock. (R93, Grade of evidence: low)

3.4.1.2. Occlusions/thrombosis (Fig. 12). The management of catheter occlusions and thrombosis is shown in Fig. 12.

3.4.1.2.1. CVC-related venous thrombosis. **94) We recommend**

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

(R94, Grade of evidence: low)

Commentary

Catheter-related venous thrombosis (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. CRVT may be clinically manifest or subclinical and can develop soon after catheter insertion or be delayed in patients with long-term catheterization. Retrospective series with large patient cohorts reported a rate of clinically manifest thrombosis around 0.02–0.09 cases/catheter/year or 0.12/1000 catheter-days [51,56,67–69]. In a recent prospective study in 62 patients on HPN, the incidence of CRVT with serial Color Doppler Duplex Sonography (CDDS) evaluations for twelve months after catheter insertion was 0.045/catheter/year [70]. See also Info Box "Treatment of CVC-related venous thrombosis".

Info Box "Treatment of CVC-related venous thrombosis"

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.

CRVT is usually treated with anticoagulation. Initial anticoagulation treatment usually involves low molecular weight heparin, followed by vitamin K antagonists, except in patients with cancer and patients with poor oral absorption, for whom low molecular weight heparin is preferred. The length of time a patient should be anticoagulated will depend on individual case characteristics (risk factors, extent and characteristics of the thrombus, catheter removal) but generally is 3-6 months and in some cases forever.

The decision to remove or maintain the catheter will be based on each individual situation. 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.

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

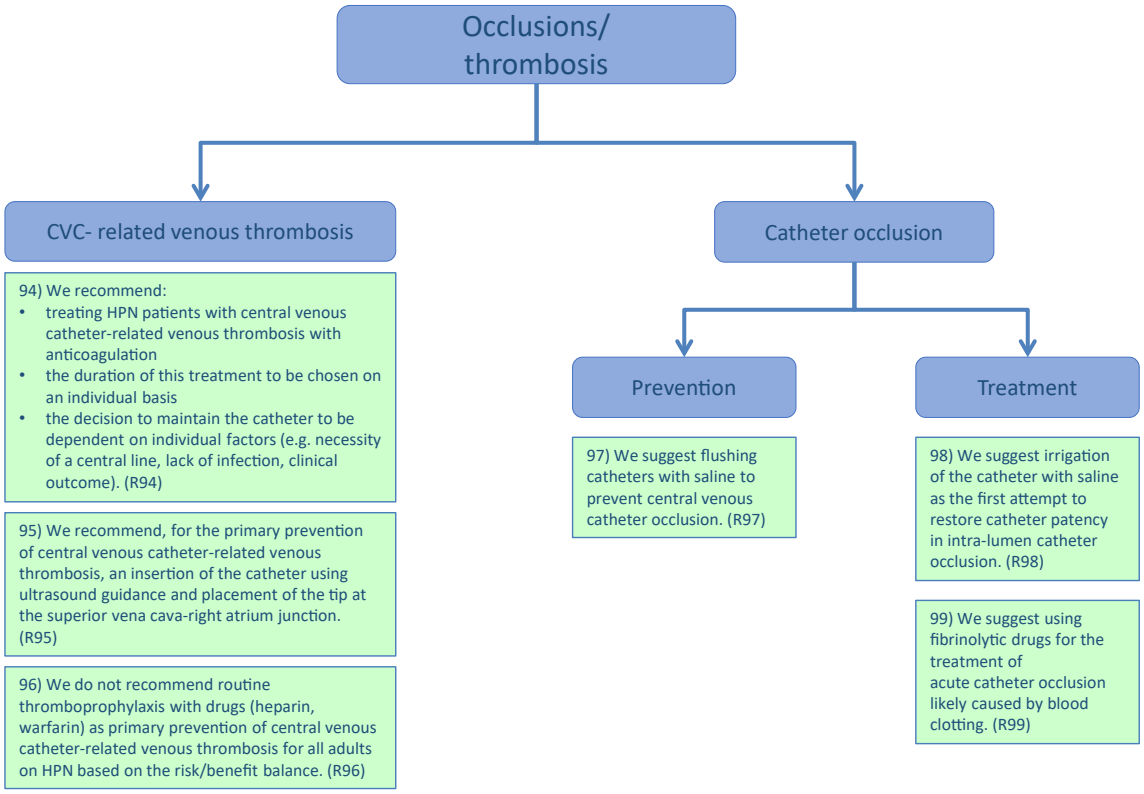

Fig. 12. Complications of home parenteral nutrition – occlusions/thrombosis. For details see text. Abreviations: HPN, home parenteral nutrition.

indicated only in those patients with persistent symptoms and signs and failure of anticoagulation or thrombolysis.

95) We recommend for the primary prevention of CRVT, an insertion of the catheter using ultrasound guidance and placement of the tip at the superior cavoatrial junction -right atrium junction.

(R95, Grade of evidence: low)

Commentary

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. CVCs composed of silicon or polyurethane are less often associated with local thrombosis than those made of polyethylene. The role of the puncture site of CVC insertion is still much debated, the right jugular vein is the preferred one due to its direct route to the right atrium. Left-sided catheters also have been associated with a higher thrombosis risk. In a systematic review, PICCs and insertion of CVCs at femoral sites increases CRVT when compared with other catheter types or insertion sites, respectively [71].

96) We do not recommend routine thromboprophylaxis with drugs (heparin, warfarin) as primary prevention of CVC-related venous thrombosis for all adults on HPN based on the risk/benefit balance.

(R96, Grade of evidence: low)

Commentary

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 towards fewer thrombotic events in the venogram [72–76]. 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.

Three studies evaluated warfarin prophylaxis in HPN adults. In a prospective non-randomized trial of 2 mg of warfarin given to 23 HPN patients, the incidence of venous thrombosis was one in 1617 catheter days compared with one in 251 days prior to the study [77]. 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/day warfarin compared with a rate of 0.09 thromboses per patient per month in 38 patients on no prophylaxis [78]. 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) [79].

Based on this evidence, the decision to use anticoagulation therapy to prevent venous thrombosis requires an assessment of the risk of thrombosis, bleeding risk with anticoagulation therapy, and patient compliance.

3.4.1.2.2. Catheter occlusion

3.4.1.2.2.1. Prevention

97) We suggest flushing catheters with saline to prevent CVC occlusion.

(R97, Grade of evidence: low)

Commentary

The incidence of catheter occlusion in HPN patients is about 0.07 episodes/catheter/year (0.059–0.083) [80]. 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.

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. 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. A systematic review

in adults with CVCs (excluding ports) comparing the effectiveness of different means of maintaining catheter patency concluded that there is weak evidence that heparin flushing reduces occlusion of catheters, but no evidence that it reduces CRBSI rate [81].

3.4.1.2.2.2. Treatment

98) We suggest irrigation of the catheter with saline as the first attempt to restore catheter patency in intra-lumen catheter occlusion.

(R98, Grade of evidence: low)

Commentary

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. 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 0.1 N hydrochloric acid (HCl), drug precipitates are treated according to their pH, acidic drugs can be cleared with 0.1 N HCl, basic medications can be cleared with sodium bicarbonate or 0.1 N sodium hydroxide (NaOH).

99) We suggest using fibrinolytic drugs for the treatment of acute catheter occlusion likely caused by blood clotting.

(R99, Grade of evidence: low)

Commentary

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. New thrombolytic drugs with potentially higher efficacy and shorter dwell times than alteplase are being investigated: reteplase, recombinant urokinase, alfimeprase.

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, the authors concluded that there is some low quality evidence from a meta-analysis of two studies investigating urokinase and some very weak evidence from two single studies investigating alteplase 2 mg/2 mL that suggest that these two drug interventions may be effective in treating withdrawal or total occlusion of CVC lumens caused by thrombosis [82].

In 2014, the first report of the safe and effective use of endoluminal brushing to manage occluded CVCs in patients requiring long-term HPN has been published [83]. 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 [83].

3.4.2. Disease-related complications of HPN (Fig. 13)

Disease-related complications of HPN include: liver disease, gall-bladder sludge and stones, renal failure and stones, and bone disease.

3.4.2.1. Liver disease. **100) We recommend for the prevention of IFALD that**

- **sepsis is prevented and/or managed, if present**
- **attempts are made to preserve small intestinal length and retain the colon in continuity with small bowel;**
- **oral/enteral intake is maintained;**
- **PN is cycled;**
- **PN overfeeding is avoided;**
- **the dose of soybean-oil based lipid is limited to less than 1 g/kg/day**

(R100, Grade of evidence: low)

Commentary

The term IFALD refers to liver injury as a result of several factors relating to CIF, including, but not limited to PN. 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. The decision to perform a liver biopsy should be made on a case-by-case basis.

Unlike infants, adults are more likely to demonstrate steatosis and are less susceptible to hepatocellular injury or cholestasis. Furthermore, the rate of progression of liver dysfunction in adults varies and does not always correlate with biochemical markers.

Studies report the prevalence of abnormal liver tests and/or cholestasis with rates ranging from 19% to 95%. Moreover, the incidence of clinically advanced liver disease also varies in published studies from 0% to 50%. Furthermore, mortality in patients with IFALD has been reported to range from 0 to 22% in various studies [13,14,53,84–86].

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

Soybean-based lipid emulsions in excess of 1 g/kg/day have been shown to be detrimental to liver function, with associated morbidity and mortality [13]. A recent 4-week randomized controlled, double-blind study in adults demonstrated that a combination lipid emulsion (soybean/MCT/olive/fish oil) yielded lower levels of transaminases and bilirubin within the normal reference range compared to soybean-based lipid [87]; however, longer term studies are required before the routine use of this or other novel (e.g. MCT/LCT mixtures and monounsaturated fatty acids) combination lipids can be recommended to reduce the risk of IFALD in adults with CIF.

101) We suggest for the treatment of IFALD

- **to re-consider all the measures to prevent IFALD**
- **to revise the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω6/ω3 poly-unsaturated fatty acid (PUFA) ratio**
- **to revise any potential inflammatory/infective foci**

(R101, Grade of evidence: low)

Commentary

Energy requirements should be tailored to the individual, with optimization of oral nutrition/EN, wherever possible. A prospective, non-randomized study evaluating adults with hyperbilirubinemia receiving PN demonstrated an improvement in liver function following cycling of the infusion [88].

Observational data in adults support the rationale that soybean-based lipid should be limited to less than 1 g/kg/day [13]. 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

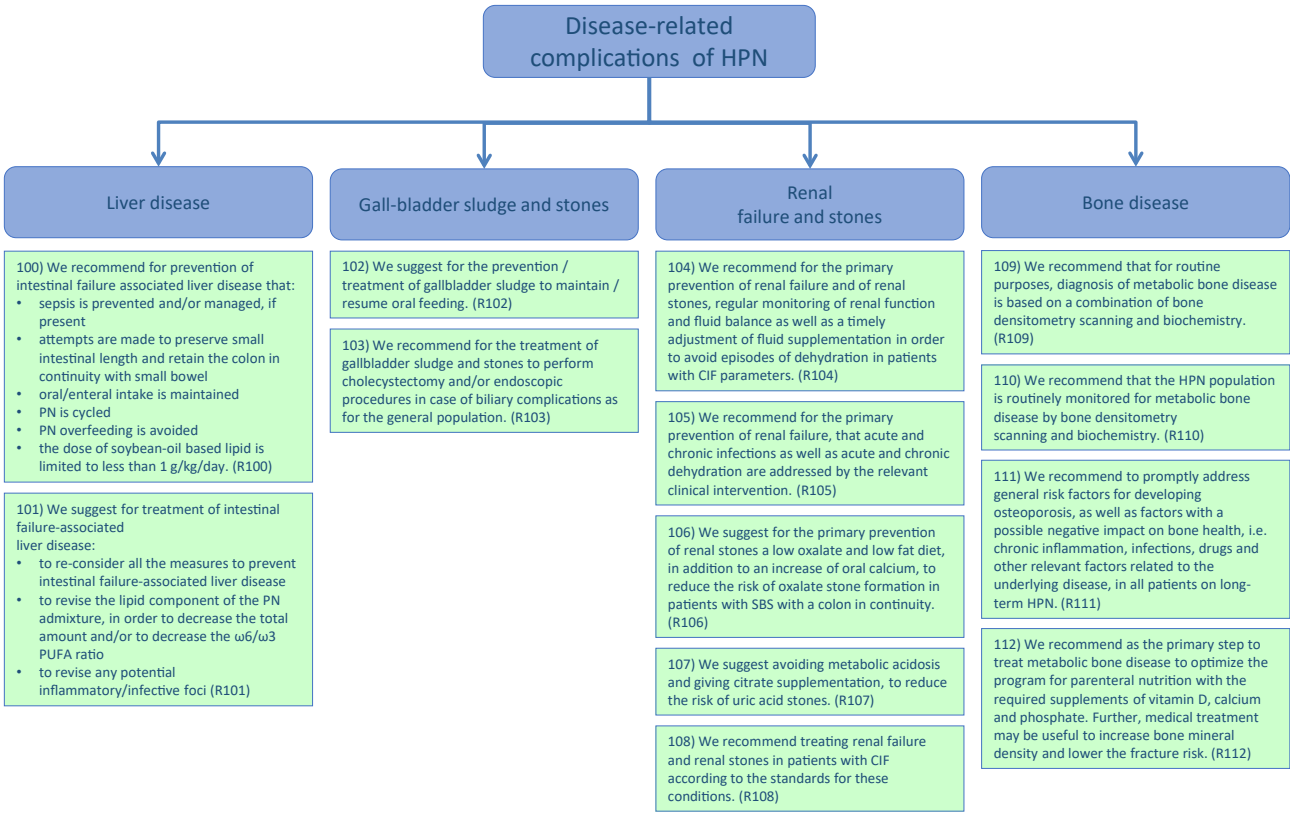

Fig. 13. Disease-related complications of home parenteral nutrition. For details see text. Abreviations: HPN, home parenteral nutrition; PN, parenteral nutrition; PUFA, poly-unsaturated fatty acids.

to normalization of bilirubin levels [89]. There are currently no data to support the role of lipid-free regimens to treat IFALD. Equally, while there are case reports [90,91] case series [92], and reviews [93,94] to support the role of pure fish oil emulsion or newer combination lipid emulsions (e.g. MCT/LCT mixtures, olive oil, and fish oils) in improving liver function in children and adults with IFALD, more data are required before their routine use can be recommended to treat IFALD. The evidence base for the use of ursodeoxycholic acid to treat IFALD is limited. The use of choline, taurine, or carnitine cannot currently be recommended to treat IFALD in adults with CIF. Impending or overt liver failure is an indication for small intestinal/multivisceral transplantation.

3.4.2.2. Gall-bladder sludge and stones. **102) We suggest for the prevention/treatment of gallbladder sludge to maintain/resume oral nutrition.**

(R102, Grade of evidence: very low)

Commentary

Patients on PN have been recognized as at risk of developing biliary sludge or cholelithiasis. Several risk factors for developing sludge or stones have been identified including an intestinal remnant length less than 180 cm, an absent ileocecal junction, the duration of PN, and Crohn's disease but risk is mostly attributable to nil or negligible ingesta. In practice, the major recommendation for preventing biliary sludge or stone formation is to encourage oral nutrition and/or EN as fast as possible. The use of narcotics or anticholinergics should be limited as much as possible.

103) We recommend for the treatment of gallbladder sludge and stones to perform cholecystectomy and/or endoscopic procedures in case of biliary complications as for the general population.

(R103, Grade of evidence: low)

3.4.2.3. Renal failure and stones. **104) We recommend for the primary prevention of renal failure and of renal stones, regular monitoring of renal function and fluid balance as well as a timely adjustment of fluid supplementation in order to avoid episodes of dehydration in patients with CIF.**

(R104, Grade of evidence: low)

Commentary: see Commentary to Recommendation 107.

105) We recommend for the primary prevention of renal failure, that acute and chronic infections as well as acute and chronic dehydration are addressed by the relevant clinical intervention.

(R105, Grade of evidence: low)

Commentary: see Commentary to Recommendation 107.

106) We suggest for the primary prevention of renal stones a low oxalate and low-fat diet, in addition to an increase of oral calcium, to reduce the risk of oxalate stone formation in patients with SBS with a colon in continuity.

(R106, Grade of evidence: low)

Commentary: see Commentary to Recommendation 107.

107) We suggest avoiding metabolic acidosis and giving citrate supplementation, to reduce the risk of uric acid stones.

(R107, Grade of evidence: very low)

Commentary

Renal complications, reduced kidney function, and renal stones are among the metabolic complications that patients on long-term HPN are up against. Expert opinions in reviews state that CIF is associated with renal failure due to chronic dehydration caused by stomal losses. Also, a suggested mechanism for renal damage is repeated CRBSI but this has not definitely been demonstrated by

the data. The use of nephrotoxic medications and existing renal disease may also play a role. Speculations have been put forward that PN might induce renal damage, but this is not supported by evidence.

Renal stones and nephrocalcinosis are linked to increased absorption of oxalate and hypovolemia and dehydration. Hypomagnesemia and metabolic acidosis may also increase the risk of renal precipitations including uric acid stones. 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. In prevention, one should focus on sufficient parenteral supply with good hydration and high urinary flow. Preventive measures with reduced intake of oxalate and the use of cholestyramine have been reported but are not always successful. A low-fat diet or replacing with MCT and oral calcium supplementation at mealtime have also to be considered. Correction of metabolic acidosis and supplementation with citrate and magnesium supplementation may prevent stone formation.

108) We recommend treating renal failure and renal stones in patients with CIF according to the standards for these conditions.

(R108, Grade of evidence: very low)

3.4.2.4. Bone disease. **109) We recommend that for routine purposes, diagnosis of metabolic bone disease is based on a combination of bone densitometry scanning and biochemistry.**

(R109, Grade of evidence: low)

Commentary

The gold standard for diagnosing metabolic bone disease currently is dual-energy X-ray absorptiometry (DXA). Measurement of bone density cannot distinguish between osteomalacia and osteoporosis. For a more specific diagnosis, bone histology may be needed, but the invasive character of this diagnostic approach is a barrier. The pathogenesis of metabolic bone disease is most likely related to the underlying disease, malabsorption, chronic inflammation, or the use of medications, in particular corticosteroids. Possible PN-related factors include toxicity from aluminum contamination of the nutrition formula, increased sensitivity to vitamin D suppressing PTH secretion, and hypercalciuria induced by the intravenous infusion of nutrients. HPN related metabolic bone disease might also be caused by deficiencies or toxic effects of other micronutrients known to interfere with bone metabolism. Vitamin K, vitamin C, copper, fluoride, boron, and silicon deficiency, and for vitamin A, cadmium, strontium, and vanadium toxicity.

An ESPEN multicenter cross-sectional survey [95]of 165 patients evaluated the prevalence of metabolic bone disease by DXA. By the WHO criteria, 41% of the patients presented with osteoporosis, with a T-score below 2.5.

The calcium, magnesium, and phosphate content of the PN must aim at maintaining serum concentrations and 24-h urinary excretions within the normal range. The recommended intravenous dose of vitamin D is 200 IU/day.

110) We recommend that the HPN population is routinely monitored for metabolic bone disease by bone densitometry scanning and biochemistry.

(R110, Grade of evidence: low)

Commentary

For monitoring purposes, we recommend repeated DXA measurements at yearly intervals. The biochemical assessment of metabolic bone disease 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 bone mineral density T-scores.

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

(R111, Grade of evidence: very low)

Commentary

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.

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

(R112, Grade of evidence: low)

Commentary

In a single RCT of bisphosphonate treatment in patients on HPN [96], intravenous clodronate decreased the urinary excretion of markers of bone resorption. Bone mineral density of the lumbar spine was maintained in patients on HPN after twelve months, but a significant increase in bone mineral density was not observed.

Conflicts of interest

The authors declare no conflict of interest.

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