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Intestinal Failure in Adults: Recommendations from the ESPEN Expert Groups

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List of abbreviations:

ACS abdominal compartment syndrome; AGI acute gastrointestinal Iinjury; AIF acute intestinal failure; AGIRS autologous gastrointestinal reconstructive surgery; BAPEN British Association of Parenteral and Enteral Nutrition; BSPGHAN British Society of Paediatric Gastroenterology and Nutrition; CIF chronic Intestinal failure (CIF); CRBSI catheter related bloodstream infection; CVC central venous catheter; ESICM European Society of Intensive Care Medicine (ESICM); ESPEN European Society for Clinical Nutrition and Metabolism; GLP glucagon-like peptide; HAN home artificial nutrition; HPN home parenteral nutrition; i3 intestinal ischaemic injury; ICD International Classification of Disease; IF intestinal failure; IFALD intestinal failure associated liver disease; IFU intestinal failure unit; ITx intestinal transplantation; IVS intravenous supplementation; LILT longitudinal intestinal lengthening; MDT multi-disciplinary teams; MODS multiple organ dysfunction syndrome; NST nutrition support team; PYY peptide YY; SBS short bowel syndrome; SCFA short chain fatty acids; SILT spiral intestinal lengthening and tailoring; SIRS systemic inflammatory response syndrome; STEP serial transverse enteroplasty; TNP topical negative pressure; WGAP Working Group on Abdominal Problems

Abstract

Background and aims. 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". Functionally, it may be classified as type I acute intestinal failure (AIF), type II prolonged AIF and type III chronic intestinal failure (CIF) The ESPEN Workshop on IF was held in Bologna, Italy, on 15-16 October 2017 and the aims of this document were to highlight the current state of the art and future directions for research in IF.

Methods. This paper represents the opinion of experts in the field, based on current evidence. It is not a formal review, but encompasses the current evidence, with emphasis on epidemiology, classification, diagnosis and management.

Results. IF is the rarest form of organ failure and can result from a variety of conditions that affect gastrointestinal anatomy and function adversely. Assessment, diagnosis, and short and long-term management involves a multidisciplinary team with diverse expertise in the field that aims to reduce complications, increase life expectancy and improve quality of life in patients.

Conclusions. Both AIF and CIF are relatively rare conditions and most of the published work presents evidence from small, single-centre studies. Much remains to be investigated to improve the diagnosis and management of IF and future studies should rely on multidisciplinary, multicentre and multinational collaborations that gather data from large cohorts of patients. Emphasis should also be placed on partnership with patients, carers and government agencies in order to improve the quality of research that focuses on patient-centred outcomes that will help to improve both outcomes and quality of life in patients with this devastating condition.

Key words: intestinal failure; short bowel syndrome; definitions; management; acute; chronic;

Contents

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 (IVS) is required to maintain health and/or growth"[1]. According to functional criteria it is classified as type I acute intestinal failure (AIF), type II prolonged AIF and type III chronic intestinal failure (CIF)[1]. It may be due to one or more of five major pathophysiological mechanisms that may originate from various gastrointestinal or systemic, congenital or acquired, benign or malignant diseases. A clinical classification of CIF has been devised on the basis of the IVS requirements[1] (BOX 1). The ESPEN Workshop on IF was held in Bologna, Italy, on 15-16 October 2017 focused on IF due to benign disease.

2. Epidemiology

The only available data on the type II-prolonged AIF were provided by a British study in 2006, which estimated an annual incidence of 9 patients per million population[2]. Surgical complications (32%), Crohn's disease (21%), motility disorders (14%), intestinal ischaemia (13%) and malignancy (8%) were the main underlying causes[2].

The epidemiology of CIF is based on the data from home parenteral nutrition (HPN) which often include patients with either benign or malignant diseases. In Europe, the prevalence of HPN for CIF has been estimated to range from 5 to 80 per million population, with the incidence ranging from 7.7 to 15 IF/HPN patients/million inhabitants/year[1, 3-5]. Around 10% of patients were in the paediatric age group[1, 3-5].

The 2015 data collection for the ESPEN "CIF Action Day" database, included 2919 adult patients with benign CIF from 65 HPN centers from 22 countries and gave an updated picture of the mechanisms and the underlying diseases of CIF[6]. Short bowel syndrome (SBS) was the most

frequent pathophysiological mechanism of CIF (64.3%): 36.8% had an end jejunostomy and the remaining had part (19.9%) or all of the colon (5.9%) in continuity. Intestinal dysmotility was present in 17.5% of cases, intestinal fistulae in 7.0%, mechanical obstruction in 4.4% and extensive mucosal disease in 6.8%. The most frequent underlying disease was Crohn's disease (22.4%), followed by mesenteric ischaemia (17.7%), surgical complications (15.8%), primary chronic intestinal pseudo-obstruction (9.7%) and radiation enteritis (7.3%). Furthermore, the data indicated that IVS reflects loss of intestinal function better than energy requirements and allowed formulation of the simplified revision of the formerly proposed 16-category clinical classification of CIF[6]. Strategies to have constantly updated data on incidence and prevalence of AIF and CIF are required to allow adequate allocation of resources from the healthcare systems.

3. Identification of intestinal failure

IF is the rarest type of organ failure. Although publications on “intestinal failure” appear in PubMed from 1980, IF is not yet included in the list of MeSH terms[7]. In 2013, CIF due to benign disease has been included in the ORPHANET list of rare disease (ORPHA:294422)[8]. In addition, CIF is not yet recognized in the International Classification of Disease (ICD) and is not supported uniformly by national health care services[9]. Strategies to identify IF are warranted to allow national healthcare systems to devise appropriate regulations and structures (i.e.: hospital units, multiprofessional teams) for the management of IF.

4. Multidisciplinary management of intestinal failure

The aims of management of patients with IF are to provide IVS, to reduce the severity of IF, to prevent and treat complications, including those related to the underlying disease, IF itself or its treatments, and to achieve good quality of life for patients[10].

Multi-disciplinary teams (MDT) are the key to successful management of IF. This was proposed by Nehme[11] in 1980, after finding that patients requiring IVS who were organised, supported and managed by a nutrition support team (NST) were less likely to develop catheter related bloodstream infection (CRBSI) at 24 months than those managed by a variety of physicians (1.3% versus 26.2%).

The earliest establishment of HPN was as an extension of hospital care provided by the team that cared for the patient whilst in hospital. This was not universal, was frequently driven by a limited number of people and required thorough succession planning to ensure longevity[12].

In the USA, intestinal care centres were established to provide intestinal rehabilitation, but these were mostly focused upon CIF for weaning off HPN, reducing complications and preparing patients for intestinal transplantation (ITx)[13].

The concept of AIF, however, is a more recent one, which has brought with it the idea of a specialised intestinal failure unit (IFU) where specialist care is focused in one particular ward or area[2, 14]. The main aims of these IFUs are to provide consistency of expert care for safe IVS and catheter care to minimise rates of CRBSI, maintain accurate fluid balance, provide stoma and wound care, distal feeding (enteroclysis) and psychological care, all from highly trained and specialised nurses. A full range of specialists should be available at these IFUs, including constant 'expert' medical and surgical care, dieticians, pharmacists, psychologists/psychiatrists and interventional radiologists, with admission of patients for purely IF-related issues. There is evidence that such specialised IFUs, providing a skilled MDT, reduce complication rates and mortality[2, 12].

5. Acute intestinal failure

5.1 Assessment of type II prolonged-acute intestinal failure

The ESPEN classification of AIF is based primarily on duration and does not comprise any severity categorization. As organ dysfunction in critical illness is commonly graded according to severity, the Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM), proposed four grades of Acute Gastrointestinal Injury (AGI), based on motility disorders leading to intolerance of enteral nutrition and progressing to gastrointestinal injury[15]. The ESPEN type I-AIF could be associated with AGI grade I due to impaired gastrointestinal motility, whereas the type II-prolonged AIF could be associated with AGI grades II to IV, due to impaired gastrointestinal motility progressing to gastrointestinal mucosal injury, with clear mucosal injury (e.g. bowel ischaemia and necrosis) seen in AGI Grade IV. Evaluation of gastrointestinal function in AIF is mainly based on bedside clinical assessment, which is largely subjective and not well reproducible, whereas searches for specific marker(s) allowing dynamic evaluation are continuing[16].

5.2 Intestinal ischemic injury as a cause of acute intestinal failure

Aside from these classifications of AIF, the concept of acute intestinal ischemic injury (i3) has been proposed to standardize and organize a management pathway that can be extended to all AIF, whatever the mechanisms[17]. Acute i3, defined as an acute intestinal injury secondary to a vascular insufficiency, can be present in the type I and type II ESPEN functional classification of AIF, as well as in grades I to IV of AGI. The vascular insufficiency can be occlusive (arterial/venous from thrombosis, embolus, dissection, trauma, tumoral invasion) or non-occlusive (low cardiac output, decreased blood pressure, vasoconstriction, venous stasis). The intestinal injury occurs at different degrees of depth (superficial *versus* transmural), and at different stages of progression (early/late, reversible/non reversible, necrotic/non-necrotic). Early and superficial i3 can be reversible whereas late, necrotic and transmural i3 are irreversible[17-20]. The loss of the intestinal barrier function and translocation of luminal contents are the cornerstone of

238 deterioration and lead to a local, regional and then systemic inflammatory response syndrome
239 (SIRS) and multiple organ dysfunction syndrome (MODS).

240 A gut and lifesaving multimodal strategy has been proposed[18], including a wide range of
241 specialists for the management of i3 (**Box 2**). Following the diagnosis of acute i3 a multimodal
242 protocol should be implemented. If the patient is in the early stages of ischaemia then radiological
243 revascularisation is generally recommended, with surgical revascularisation if necessary. In the
244 late and irreversible phases, surgical revascularisation and intestinal resection are the mainstays of
245 management. In a pilot study, patients managed using this multimodal management strategy had
246 a 95% survival at 30 days, with mean lengths of intestinal resection of 30 cm and 207 cm, with or
247 without revascularisation respectively[18]. Recently in the dedicated intestinal stroke center
248 (SURVI) an overall survival of 86% and intestinal resection rates of 27 % have been reported[21].

249

250 *5.3 Nutrition therapy and fluid and electrolyte balance*

251 In the management of AIF, there exist different phases, directed to achievement of
252 different goals (**Figure 1**). Throughout the course, both hypo- and hyper-volaemia should be
253 avoided. In the initial unstable and acute phase of illness capillary leak is observed which leads to
254 hypovolaemia and resultant tissue oedema. There are no clear surrogate markers to quantify the
255 magnitude of the fluid shift, whereas prolonged hypovolaemia is known to aggravate capillary
256 leak. Excessive fluid infusion and hypervolaemia result in bowel oedema, which is more
257 pronounced in injured bowel. This hampers local transport of oxygen and nutrients and impairs
258 anastomotic healing[22-24]. A number of mechanisms influence the occurrence of bowel oedema:
259 capillary leak precipitated by inflammation; increased hydrostatic pressure from hypervolaemia;
260 increased mesenteric venous pressure due to mechanical ventilation, increased intra-abdominal
261 pressure or right heart failure; low oncotic pressure resulting from hypoalbuminaemia; impaired

intestinal lymph flow due to impaired bowel motility, increased intra-abdominal pressure and mechanical ventilation.

Initial fluid administration aims to achieve haemodynamic, tissue perfusion and oxygen delivery goals. Severe hypovolaemia should be avoided as this leads to severe vasoconstriction and activation of the pro-inflammatory cascade. Once hypovolaemia has been corrected, vasodilation commonly occurs and should be treated with vasopressors rather than additional fluids. At the same time, treating severe hypovolaemia with vasopressors is harmful and achieved normal blood pressure does not indicate adequate tissue perfusion. Balanced crystalloids should be used in initial resuscitation. Synthetic colloids may expand the intravascular volume more effectively, but have been associated with renal dysfunction[25]. Replacement of fluids in a later stable phase can usually be guided by measured fluid losses and aim for normal distribution of body water, not only expansion of plasma volume.

In terms of nutritional support, the preferred hierarchy generally ranges from oral intake to gastric then jejunal nutrition to parenteral nutrition. Oral intake is not adequate in most critically ill patients and may carry the risk of aspiration. In the acute phase, early nutrition aiming to meet the patient's full caloric requirements is harmful, but the optimal amount of calories and protein necessary in this early stage is not well established. Parenteral nutrition should be considered if enteral nutrition is not established within one week. Feeding via the enteral route is preferable as it may prevent mucosal atrophy and help preserve the microbiome, but it is difficult to monitor malabsorption in this setting. A combined feeding strategy such as oral and enteral or enteral and parenteral nutrition is, however, known to increase the risk of overfeeding[26]. Contraindications to enteral feeding are summarized elsewhere[27]. In patients with high output fistulae or stoma and achievable distal access, a chyme reinfusion (enteroclysis) should be considered[28].

Electrolyte balance is also crucial in the management of AIF, particularly as low concentrations of potassium, magnesium and phosphate are associated with impaired bowel motility[29] and development of the refeeding syndrome[30]. In case of ileus, high-normal concentrations of these electrolytes could be beneficial, but evidence proving such benefit is lacking. Electrolyte concentrations should be monitored closely, particularly in the setting of insulin administration, which may shift potassium, magnesium and phosphate from the extracellular to the intracellular compartment, and lead to overt refeeding syndrome. Losses are frequently unpredictable in AIF, and an intimate understanding of the site of absorption of fluids, electrolytes and nutrients is the key enable anticipation of the impact of resection or bypassed areas of the gastrointestinal tract.

5.4 Stoma and wound care

High output stomas including enterocutaneous fistulae and complex ostomies as related to type II-prolonged AIF are associated with negative outcomes[31]. Protocols exist for the management of high output stomas, including detection and treatment of the underlying cause, reduction of fluid and electrolyte losses, optimisation with anti-secretory and anti-diarrhoeal medication and ongoing evaluation of efficacy or additional treatment if the high output continues[32-34].

It is particularly important that patients who require monitoring are identified correctly, and that the fluid balance charts are completed accurately, including drain(s) and stoma outputs. Explaining to the patient the reasoning behind fluid restriction has also been shown to improve compliance. Careful observation is recommended, including a measure of size, appearance, function and separation between the stoma and skin surrounding the stoma. A range of appliances is available for expert management of complex stoma and fistulae to maintain skin integrity and minimise leakage.

Laparotomy wounds require an individualised treatment plan describing the surface of the wound, including: length, width, depth, eventual undermining or granulation and surrounding skin. Stomas and wounds must be separated, in order to secure proper healing and reduce infections. As for stomas, a variety of appliances for wound management exist. The stoma and wound care nurse specialist must stock a variety of the necessary products and be familiar with their use. Topical negative pressure (TNP) may be used for large wounds or when undermining is more than 5 cm. It may also be used, when drainage of the wound is desired, and where the wound healing is not progressing. TNP is contraindicated in wounds with necrotic tissue, and in those with visible blood vessels[35].

Fluid restriction carries a risk of oral cavity problems such as mouth sores, xerostomia, thick saliva and fungal infection. Evidence-based oral care, in the form of chlorhexidine mouthwash, glycerol products, crushed ice, and lip care, may reduce the risk of aspiration pneumonia[36].

5.5 Prevention and management of sepsis

Sepsis is the leading cause of death in AIF. Sepsis may originate from the abdominal cavity, be caused by bacterial translocation (e.g. in case of severe bowel distension, subacute bowel ischemia without perforation, etc.), a CRBSI or extraabdominal causes (such as pneumonia or urinary tract infection). Sepsis can present with a wide spectrum of symptoms/signs including impairment of gastrointestinal or hepatic function, fluid retention and oedema, fever, increased metabolic demand and impaired fuel utilisation, insulin resistance and failure to thrive[2]. Abnormal laboratory parameters include elevated C-reactive protein and leucocyte counts, hypoalbuminemia, hyponatraemia and abnormalities in liver function tests. However, clinical signs may be absent in up to 50% of patients, particularly in the severely malnourished[37]. Diagnostic

modalities include CT scanning which has an accuracy exceeding 95% and may provide a therapeutic as well as diagnostic opportunity, ultrasound, MRI, radionucleotide studies and fluoroscopy. These imaging modalities should be supported by cultures from peripheral veins and any indwelling lines, urine and wound swabs, chest imaging, and a thorough search should be made to identify a source of sepsis[2, 14]. In the setting of a proven intra-abdominal collection, a minimally invasive approach is recommended in an expedient manner, in the form of either CT or ultrasound-guided drainage, via percutaneous or alternative routes (e.g. trans-gastric, trans-gluteal, trans-rectal or trans-vaginal. This should be supplemented by antibiotic therapy which should be guided by microbiological review of cultures. Should a minimally invasive route not be an option, surgical drainage is indicated.

Control of sepsis is the primary objective in the management of AIF and some centers use acronyms such as SOWATS (sepsis control, optimisation of nutritional status, wound care, anatomy of the bowel and the fistula, timing of surgery, surgical planning)[37] and SNAP (Sepsis-Nutrition-Anatomy-Plan)[14] which help navigate treatment pathways.

6. Chronic intestinal failure

6.1 Short bowel syndrome: spontaneous and induced intestinal adaptation after resection

Short bowel syndrome is the most frequent pathophysiological mechanism of CIF in adults[6]. A functional small bowel <200 cm affords an accepted anatomical definition of short bowel in adults, but some authors prefer to limit the term to patients with <150 cm[1]. The incidence of SBS is about 2 per million per year and the prevalence about 20 per million[38], however, the exact epidemiology is not known.

SBS is categorized into three types: a) end-jejunostomy (SBS-J); b) jejunocolic anastomosis, where the remnant jejunum is in continuity with part of the colon, most frequently left colon (SBS-

JC); c) jejuno-ileal anastomosis with ileo-caecal valve and the intact colon in continuity (SBS-JIC)[38,39].

Pathophysiologically, SBS can be classified into two subgroups, those with intact colon or part of it in continuity and those without colon in continuity[38-40]. These subgroups differ in three key characteristics: intestinal water and sodium absorption, gastrointestinal hormone secretion and energy absorption from short chain fatty acid (SCFA) produced by the colon microbiota.

Gastrointestinal secretion is about 9 liters/day, with water and electrolyte absorption occurring predominantly in the distal small bowel and colon. Furthermore, in the jejunum, the intracellular tight junctions are relatively weak, and sodium absorption is coupled with the absorption of glucose (solvent drag) and occurs only against a concentration gradient. These mechanisms ensure rapid iso-osmolarity of the jejunal contents: hypertonic fluids cause the passage of water and hypotonic-low sodium fluids determine the secretion of sodium and water into the lumen. SBS-J patients often lose more fluid and sodium than ingested (net secretors), whereas in SBS-J and SBS-JIC there is usually sufficient distal bowel to permit fluid and electrolyte balance (net absorbers). The absorption of sodium and water in the colon are normally around 200 mmol and 2 L/day in healthy adults and can increase up to 800 mmol and 6 L/day in SBS when the colon is in continuity[38-40].

Many gastrointestinal hormones and neuromodulators, which play a key role in the control of gastrointestinal secretions, motility and intestinal growth, are produced by the endocrine L-cells of the small intestinal and colonic mucosa. Peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and GLP-2 are secreted in the distal ileum and the proximal colon after a meal, regulate motility by slowing gastric empting and small bowel transit (ileal brake) and exert a trophic effect on the mucosa by enhancing intestinal villus/crypt cell growth. The secretion of these hormones is

enhanced in SBS-JC and SBS-JIC and is reduced/absent in SBS-J. This translates to less or absent structural and functional adaptation after resection, and in accelerated gastric empting, especially for liquids in SBS-J[38, 41, 42]. The colon can contribute to the absorption of energy, as SCFAs, following the fermentation of non-absorbed carbohydrates by luminal bacteria. This mechanism can yield up to 1000 kcal/day (4 MJ) in patients with SBS and colon in continuity[43].

Spontaneous physiological intestinal adaptation after massive small bowel resection occurs during the following two to three years, and improves intestinal absorption through intestinal mucosa hyperplasia, slowing of gastrointestinal transit, modified gastrointestinal hormonal secretion (GLP-1, GLP-2 and PYY)[38, 41, 43], development of hyperphagia[44] primarily stimulated by an increased secretion of the orexinogenic gut hormone, ghrelin[45], and alteration of the gut microbiota with a higher prevalence of Lactobacillus and a fewer anaerobes (*Clostridium leptum* and *Bacteroides* spp.)[46] and an accumulation of faecal d/l-lactate in some patients[47]. These changes are stimulated by intraluminal nutrients and pancreatico-biliary secretions and are highly variable and unique to each patient.

The ESPEN guidelines additionally describe induced intestinal adaptation based on dietary counseling, oral rehydration solution and drugs to slow gastrointestinal transit and decrease intestinal secretion, as well as antibiotics to treat intestinal bacterial overgrowth, when this occurs[12]. Patients are advised a hypercaloric diet, divided into 5-6 meals. Simple sugars should always be limited, lipids limited when colon is in continuity, and fibre limited when there is an end jejunostomy. Hypo-osmolar low-sodium fluids should be avoided because they increase intestinal losses. The consumption of 500-1000 ml/day of oral rehydration solution according to the World Health Organization formula may favour intestinal absorption of water and electrolytes. Proton pump inhibitors at full dosage can reduce intestinal fluid losses by decreasing gastric secretion. Loperamide and codeine phosphate slow intestinal transit safely. Octreotide decreases

gastrointestinal secretion and slows gastrointestinal motility, and can be useful in individual patients for a short time. This “conventional” therapy for SBS is, however, supported by very few studies[12].

The probability of weaning a patient from HPN with the combination of spontaneous intestinal adaptation, dietary counselling and conventional therapy depends on the length, integrity and anatomy of the residual bowel in continuity. The minimum small bowel length for independence from PN has been reported to be 35 cm in SBS-JIC, 60 cm in SBS-JC and 115 cm in SBS-J[48], provided that the remnant bowel is healthy, but CIF and HPN dependence may occur when longer remnants (e.g. >200 cm) are diseased and sometimes without overt pathology, a condition termed functional SBS[1, 12].

6.2 Short bowel syndrome: enhanced post-resection intestinal adaptation

In the last two decades, gastrointestinal hormonal factors have been investigated and used for intestinal rehabilitation of patients with SBS, with the aim of maximizing absorption in the remnant bowel, decreasing intestinal losses, and reducing the need for intravenous supplements[49]. At present, the only one approved by the FDA and EMA for clinical use is the GLP-2 analogue, teduglutide[50]. Randomized clinical trials have demonstrated its efficacy in reducing intravenous supplements in around two-thirds of patients treated so far, a small number having been able to be weaned off HPN[51, 52]. However, long-term benefits and risks still need to be elucidated and, therefore, regular and expert follow-up is strongly advisable. Furthermore, this treatment is costly, and the cost-efficacy as well as the risk-benefit ratio need to be evaluated.

A few open-label studies investigated the usefulness of GLP-1 analogues, liraglutide[53, 54] and exenatide[55]. Encouraging results have been observed, but have to be validated by controlled trials.

6.3 Outcome on home parenteral nutrition

Patients on HPN for CIF may develop central venous catheter (CVC) or metabolic complications due to factors related to HPN and/or the underlying disease, that may eventually cause death[12, 56]. Patients also suffer commonly from psychological problems and an impaired quality of life as a result of their underlying disease and the burden of HPN[56]. A review of 11 published series demonstrated that 53% of patients with benign CIF requiring HPN died as a result of their underlying disease with only 14% dying because of HPN-related complications; of the latter, 8% occurred as a result of catheter-related bloodstream infection (CRBSI), 4% from intestinal failure associated liver disease (IFALD) and 2% from CVC-related venous thrombosis[57].

6.4 Prevention and treatment of catheter-related bloodstream infection

Older[58, 59], as well as recent[12], international guidelines advise that the diagnosis of CRBSI should be based upon quantitative and qualitative assessment of CVC and peripheral blood cultures. Quantitative blood cultures – counting colony forming units - are the most accurate test for the definitive diagnosis of CRBSI[59]. However, not all IFUs follow such guidance. Indeed, a recent study noted that basing the diagnosis of CRBSI on clinical assessment only, rather than following ESPEN guidance, may lead to over diagnosis of CRBSIs by 46%, which can, in turn, lead to inappropriate antibiotics and increased risk related to repeated CVC re-insertion[58]. Further work is required to address the barriers to units adopting standardised, internationally agreed, protocols to define CRBSIs in patients needing HPN, not least because of the importance placed on CRBSI rate as a quality assurance measure[60]. Furthermore, the role of new diagnostic approaches, such as real-time polymerase chain reaction, aimed at improving diagnostic sensitivity and reducing time to diagnosis, requires further evaluation[14].

Once infected, CVC salvage is paramount to preserving long term venous access[12]. Two recent and large retrospective series from England[61] and the USA[62] demonstrated that successful salvage can be achieved following CRBSI in patients with CIF using standardised protocols involving systemic and local antibiotic therapy. Apparent differences between these studies highlighted that there remain a number of debated issues relating to CVC salvage, including a consensus on salvaging specific microbial isolates, the duration of salvage therapy and the definition of successful salvage. CRBSI rates vary greatly between institutions both nationally and internationally, with reported occurrences between from 0.14 to 1.09 episodes per catheter year[12]. Although ESPEN guidelines are clear on standard approaches to prevention of CRBSI – including education of staff, implementation of handwashing policies, hub disinfection, use of tunneled single lumen catheters – it is clear that there is limited evidence for novel approaches such as antimicrobial lock therapy[12]. There is good evidence that ethanol locks should not be recommended due to the risk of catheter occlusion and damage[12], while a recent multicenter randomised study showed the efficacy of taurolidine lock to reduce the risk of CRBSI significantly in new implanted CVC[63].

6.5 Prevention and treatment of intestinal failure associated liver disease

Liver injury in CIF can occur as a result of nutrient and non-nutrient factors. The former may include calorie overfeeding and/or nutrient deficiencies, including choline, taurine and carnitine. Non-nutrient factors include recurrent episodes of sepsis, bacterial overgrowth, SBS, hepatotoxic medications and underlying parenchymal liver disease[12, 56]. Retrospective series reveal a significant variation in the reported incidence of advanced liver disease from 0-85%[64-67]. Although such variation may have related to the amount of soybean-based lipid administered routinely in clinical practice in the past, it is apparent that a standardised definition of IFALD is

required to allow comparison between individual centres and series. To-date, most studies on IFALD relied on biochemical abnormalities rather than histological information; for example, chronic cholestasis has been defined as the persistent elevation greater than 1.5 times the upper limit of the normal range for more than 6 months of two of the biochemical parameters: alkaline phosphatase, gamma-glutamyl transferase and conjugated bilirubin[64-66]. However, since liver function tests may not correlate with the severity of underlying liver disease, a consensus approach to the diagnosis and categorisation of IFALD is required that synthesises clinical, biochemical, radiological and histological parameters. Indeed, since deterioration of liver disease may not be reflected by changes in standard biochemical parameters, serial liver biopsy is still the gold standard for assessing IFALD[68]; this is, of course, of paramount importance in patients considered for isolated small bowel *vs*. multivisceral transplantation[12]. The role of alternative, non-invasive approaches to liver biopsy, including transient elastography, MR spectroscopy and quantitative ultrasound has been considered[12]. A multicentre study demonstrated that transient elastography values correlated with the serum bilirubin concentration, the severity of histologic cholestasis, the AST to platelet ratio and the FIB-4 score, but not to the histologic fibrosis stage[69]. Further work is required to evaluate the role of these imaging techniques, in tandem with further assessment of the efficacy of specific serological markers of hepatic fibrosis.

Long-established approaches to prevent and/or treat IFALD are agreed: including cycling PN, maintaining oral or enteral intake and preserving small bowel length (wherever possible), avoiding PN overfeeding, limiting the dose of soybean-based lipid to less than 1 g/kg/day and minimising recurrent episodes of sepsis[12]. ESPEN guidelines recommend that the lipid profile of the PN admixture is modified to decrease the omega-6/omega-3 polyunsaturated fatty acid ratio; however, the evidence base for this recommendation is limited[12]. A 4-week randomised controlled, double-blind, multicentre study in 73 patients with CIF[70] demonstrated that

soybean/MCT/olive oil/fish oil emulsion was associated with lower concentrations of bilirubin and transaminases within the normal reference range compared to soybean-based lipid alone[71]. However, more data are required to evaluate the long-term efficacy, tolerance and safety of these and other novel combination lipids. Current evidence does not support the use of choline, taurine or carnitine to treat IFALD in adults, while limited data are available on the usefulness of ursodeoxycholic acid and of oral antibiotics to treat bacterial translocation[12]. A recent ESPEN position paper has focused on the definition and management of IFALD in adults with CIF.

6.6 Non-transplant surgery and intestinal transplantation

Alternative surgical treatments for CIF are ITx and autologous gastrointestinal reconstructive surgery (AGIRS)[72, 73]. The AGIRS may aim to improve intestinal motility in case of a dilated bowel, to slow intestinal transit in the absence of bowel dilatation or to increase mucosal surface area. When AGIRS is indicated, the first option should be restoration of small bowel continuity in case of unused intestinal segments[12]. The most widely accepted timing for restoration of bowel continuity is at 3-6 months after the acute event, even though period as short as 7-10 days could be considered in the “non-hostile” abdomen[12, 73]. The AGIR procedures for SBS are categorized as tapering enteroplasty or plication, reversed intestinal segments (adult patients), colonic interposition (rarely performed nowadays), intussusception valve (in paediatric population to induce bowel dilation) and the lengthening procedures, which are the most frequently performed in patients with SBS[72, 73].

Lengthening procedures are of choice in case of a rapid intestinal transit and bowel dilation (up to 5 cm). In the absence of bowel dilation, reversed segment[74, 75], colonic interposition[76] or neovalve procedures are used[77], the last one to obtain sequential dilatation and then use the lengthening procedures. There are 4 types of lengthening procedures: longitudinal intestinal

lengthening (LILT) or Bianchi's procedure[78], serial transverse enteroplasty (STEP), first described in 2003[79], the Kimura's technique (no more used today)[80] and the spiral intestinal lengthening and tailoring (SILT) procedure, firstly described in 2011[81].

Most of the published data are on pediatric patient cohorts. The LILT procedure is a very complex type of surgery, where the dilated bowel is divided longitudinally. Each half longitudinal portion is tubularised and the two new segments are anastomosed end-to-end[78]. In the STEP surgery, serial transverse surgical stapler is applied on the dilated bowel and the new elongated intestinal channel has a zig-zag appearance[79]. In the SILT procedure, the bowel is incised along spiral lines and stretched to a uniformly longer tube of narrower diameter and the bowel is sutured along the incision line[81]. While no data comparing SILT with the other lengthening procedures are available, LILT and STEP have been compared, with a greater worldwide experience for STEP[72]. Surgical complexity is higher with LILT, that requires significantly more mesenteric handling. The LILT procedure cannot be performed in the duodenum and needs a residual bowel length of at least 20-40 cm. The STEP procedure can be performed with any length of bowel and even in the duodenum and is therefore of choice for ultra-short SB (<20 cm). The STEP can be repeated in the same patient and can also be performed in those who have already undergone LILT (which cannot be repeated). Furthermore, STEP has been demonstrated to be successful in the treatment of intestinal bacterial overgrowth and the associated D-lactic acidosis. Complications such as intestinal bleeding, obstruction and leakage have been described with both the procedures, whereas intestinal necrosis, perforation, fistula and abscess have been reported only after LILT. The results indicate a trend toward a higher percentage of intestinal lengthening with STEP (up to 69%) than with LILT (up to 55%), lower need of ITx after STEP (5-6% compared with 10-26% after LILT), whereas the two procedures showed similar percentages of PN independence (55-60%) and of survival (up to 90%)[73].

549 Intestinal rehabilitation programmes based on medical treatment and AGIRS can improve
550 intestinal function and allow weaning off HPN. Patients with irreversible CIF are destined to life-
551 long HPN or ITx. On the basis of data on safety and efficacy, HPN is considered the primary
552 treatment for CIF, whereas ITx is reserved for those patients at risk of death because of life-
553 threatening complications related to HPN or the underlying gastrointestinal disease[12]. Published
554 cohorts showed mean 5 and 10-year survival rates on HPN of 70% and 55% in adults, and 89% and
555 81% in children[57]. HPN complications were the cause of 14% of deaths in adults and of up to
556 70% of deaths in babies <1 year[57]. The 2013 International Transplant Registry report showed a
557 5-year patient survival rate of 40-60% in adults and 50-70% in children, depending on the type of
558 transplant with the best results after isolated small bowel ITx. Almost all the deaths after ITx were
559 related to the treatment[82].

560 The indications for ITx were firstly developed by expert consensus in 2001 and could be
561 categorized as HPN failure (liver failure due to IFALD; CRBSI, CVC-related vein thrombosis and
562 chronic dehydration), high risk of death due to the underlying disease (invasive intra-abdominal
563 desmoids, congenital mucosal disease, ultra SBS) or very poor quality of life (intestinal failure with
564 high morbidity or low acceptance of parenteral nutrition)[39, 83]. Those indications were
565 challenged by a 5-year prospective survey carried out by the HAN&CIF group ESPEN. The results
566 allowed to define that only intra-abdominal desmoids and IFALD-liver failure were associated with
567 an increased risk of death on HPN[84-86]. Therefore, the ESPEN guidelines recommend that those
568 conditions should be considered indications for straight referral for a life-saving ITx. The early
569 referral of patients with CIF to intestinal rehabilitation centers with expertise in both medical and
570 surgical treatment for CIF is recommended to maximize the opportunity of weaning off HPN, to
571 prevent HPN failure, and to ensure timely assessment of candidacy for ITx[12]. Indeed, the
572 number of transplants performed per year had steadily increased until 2009, after which it

declined steadily, due to improvement in HPN management and to advances in intestinal rehabilitation[82, 87, 88].

6.7 Transition from childhood to adulthood of CIF patients

Transition describes the process by which medical care for adolescents with chronic disorders is handed over from the pediatric to the adult team. Patients deals this process with a mix of emotional feelings that range from anxiety generated by leaving the familiar environment of the pediatric centers to the enthusiastic dreams for a successful or at least as normal as possible life. Furthermore, the process from childhood to adulthood involves a lot of physiological, psychological, cognitive, social and economic changes.

The transition from pediatric to adult CIF/HPN centers represents one of the major clinical challenge of the current era of CIF. The major issues for patients could be taking on the responsibility of administering the PN as well as other medications by themselves and of attending medical appointments and moving from personalized care in a family centred paediatric unit to a large, possibly more impersonal, centre. The paediatric and the adult centres are required to collaborate in order to clarify any confusion around care routines and psychological problems and to educate the young persons about their illness, helping the patient to understand the condition and its management and to realise the serious implications of non-compliance with medical advice. This seems to be a key issue because patient underestimating or psychologically denying the severity of the illness may favor the occurrence of major HPN/underlying disease complications, representing a major risk factor for death during the transition period.

No guidelines have yet been provided about this process. The British Association of Parenteral and Enteral Nutrition (BAPEN) and the British Society of Paediatric Gastroenterology and Nutrition (BSPGHAN) investigated this issue sending a dedicated questionnaire to their

members[89]. The main findings are summarized in **BOX 3**. It was concluded that transition pathway and service standards for adolescents on home PN should be developed, consideration should be given to checklists for practical aspects (e.g. pumps), key worker and psychology input to enhance emotional resilience of the young people and careers.

6.8 The economic and social burden

CIF may result in a lifelong dependence upon HPN, which carries a high complication rate and may impact upon overall patient survival. The provision of HPN is directly related to the national economic status and is particularly controversial in the setting of end-stage malignancy where the HPN-complication rate is higher.

The ESPEN guidelines for CIF[12] recommend that a HPN programme includes the "provision of evidence-based therapy, prevention of HPN-related complications… and ensure quality of life is maximised". A recently published international retrospective study[90] of 472 patients with severe chronic and benign IF who commenced HPN in 2000 demonstrated a survival probability of 88%, 74% and 64% at 1, 3, and 5 years, with survival inversely associated with increasing age, the presence of Crohn's disease or chronic idiopathic pseudo-obstruction. At 5-year follow up, 39% were alive on HPN with a mean age of 55 years, 36% had been weaned from HPN with a mean age of 52 years, 22% had died on HPN with a mean age of 60 years, 2% were alive following intestinal transplant with a mean age of 42 years and 1% had died following intestinal transplant with a mean age of 36 years. The probability of HPN dependency at 5 years is variable depending on the cause of the original HPN requirement, with a significantly increased risk of remaining on HPN at 5 years in those with SBS versus a much lower risk in those with an intestinal fistula. When 1,2, and 5-year survival in patients with CIF is compared between literature from 1999[33] and 2017[90], very little change has been observed (87 *vs*. 88%, 77 *vs*.

621 80%, and 62 *vs*. 64%). The underlying disease process remains responsible for 65% of deaths
622 within this cohort.

623 In the United Kingdom the cost of HPN is estimated at £30,000-40,000 per year if the
624 patient is self-caring, and £55,000-65,000 if they require nursing support, whereas ITx is estimated
625 to cost £80,000 in the first year then £5,000 per year after, thus making this intervention cost-
626 effective after two years[91]. The story is similar in the Netherlands where HPN is estimated at
627 €63,000 per year and ITx at €73,000 per year[92], thus the economic burden of IF is huge.
628 Infectious complications related to HPN also carry a significant economic burden, with CRBSI
629 accounting for 0.4-3 incidences per 1,000 catheter days and 70% of HPN-related hospital
630 admissions. Each CRBSI is estimated to cost around €6,480 per admission[93].

631 The social implications of IF are wide ranging, including disruption from pre-IF social and
632 work life, uncertainty arising from HPN-related problems which frequently occur on an emergency
633 basis and a changed perspective upon life. Depression is estimated at a rate of 65% in this
634 population, and severe fatigue at 63%[94]. A study of 110 Dutch adult HPN patients found that
635 76% had one or more episodes of CRBSI during their treatment[95], and this was strongly
636 associated with psychosocial complaints and decreased quality of life[96]. This emphasised the
637 lack of focus on the early recognition and treatment of psychosocial factors in patients on HPN.

638

639 **7. Conclusions and future view for clinical and research networking**

640 Both AIF and CIF are relatively rare conditions and most of the published work presents
641 evidence from small, single-centre studies. Much remains to be investigated to improve the
642 diagnosis and management of IF and future studies should rely on multidisciplinary, multicentre
643 and multinational collaborations that gather data from large cohorts of patients. Some of the
644 areas of future research are listed in **Box 4**. Emphasis should also be placed on partnership with

patients, carers and government agencies in order to improve the quality of research that focuses on patient-centred outcomes that will help to improve both outcomes and quality of life in patients with this devastating condition.

Box 1 Definition and classification of intestinal failure[1, 6]

Definition

- **Intestinal failure:** the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth.
- **Intestinal insufficiency or deficiency:** the reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency"

Functional classification of intestinal failure

Based on onset, metabolic and expected outcome criteria:

- **Type I - acute**, short-term and usually self-limiting condition; this is a common feature, occurring in the perioperative setting after abdominal surgery and/or in association with critical illnesses; it recedes when those illnesses subside; IVS is required over a period of days or a few weeks
- **Type II - prolonged acute** condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and IVS over periods of weeks or months.
- **Type III - chronic** condition, in metabolically stable patients, requiring IVS over months or years; it represents the chronic intestinal failure (CIF), that may be reversible or irreversible.

Pathophysiological classification

Five major pathophysiological conditions, which may originate from various diseases:

- short bowel
- intestinal fistula
- intestinal dysmotility
- mechanical obstruction
- extensive small bowel mucosal disease

Clinical classification of chronic intestinal failure

On the basis of the requirements for energy and the volume of the IVS, CIF was firstly categorized into 16 subtypes. An international multicenter survey carried out by the CIF Action Day database allowed to simplify it in 8 categories[6]:

Type of the IVS	**Volume of the IVS (mL/day)***			
	≤ 1000	**1001 - 2000**	**2001 - 3000**	**> 3000**
	1	**2**	**3**	**4**
Fluids and electrolytes (FE)	FE 1	FE 2	FE 3	FE 4
Parenteral nutrition (PN)	PN 1	PN 2	PN 3	PN 4

* calculated as daily mean of the total volume infused per week = volume per day of infusion x number of infusions per week / 7

FE = Fluids and Electrolytes alone

PN = Parenteral Nutrition Admixture containing also macronutrients

Box 2: Multimodal management strategy for acute mesenteric ischemia[18]

- Assessment of Intestinal vascular perfusion which consists in a CT scan angiography at the 3 phases (non injected, arterial and portal phase) and the evaluation and control of cardiac and hemodynamic conditions.
- Assessment of intestinal injury, by a combination of clinico-bio-scanographic features. In acute i3 the onset of organ failure and/or elevated blood lactates is highly predictive of intestinal transmural ischemic necrosis[6]. Non-specific clinical and biological manifestations can attest of intestinal injury: oral intolerance and motility disorders, blood losses, abdominal pain, diarrhea, persistent inflammatory syndrome, SIRS, altered liver function tests, anaemia, protein losing enteropathy, inflammation, hypoalbuminaemia. At CT-scan angiography intestinal injury features are mainly dilation, increase or decrease of mucosal enhancement, thickening/thinning, faeces signs, fat stranding mesentery, fluid collections.
- Assessment of length of remnant small bowel, length, site, number of excluded segments, length and integrity of colon/rectum, stoma, drainages, presence/absence of the gallbladder. All these features should be indicated by the surgeon.
- Assessment, identification and treatment of underlying and associated comorbidities at the origin of AIF. In case of acute i3 it can correspond to ischaemic and/or embolic and/or rhythmic and/or valvular cardiopathy. Predisposing thrombophilia should be explored.
- Search for sepsis or fungal/bacterial colonisation or luminal bacterial overload especially in case of persistent inflammatory syndrome, high stoma output, oral intolerance, altered cognitive functions, persistent malnutrition. Physicians should detect and treat infection by repeated sampling of collections, abscesses, urine, lung (if symptoms), blood stream, scars and wall, catheters, swabs.
- Optimisation and equilibration of the following parameters: 1) urine and stoma output with water/electrolytes balance, 2) nutrition (parenteral nutrition, enteral nutrition, distal enteral nutrition) and daily work-up of energy output/expenditure/input, 3) digestive functions with oral intake, treatment of motility disorders, protein losing enteropathy, 4) diabetes, 5) blood pressure and

anticoagulant therapy, 6) control of beverages, 7) wound care, 8) accesses (catheter, stoma), 9) psychology, nursing and social cares

- Consideration at each stage of AIF of the question of the need for surgery: second look, emergency surgery, vascular rehabilitation, digestive rehabilitation. The criteria for surgery should always be discussed and planned *a priori*.
- Evaluation and determination of the timing for each step of the strategy: closure of stoma, rehabilitation after nutritional recovery, cholecystectomy, surgical technics that promote intestinal adaptation (STEPS, segmental reversal of the small bowel), wound cares, home return and home parenteral nutrition.
- Anticipation and prevention of complications of AIF: recurrence or complication of underlying disease, refeeding syndrome, hypernutrition, liver disease, respiratory complications, lines infections, stroke, anticoagulants.

Box 3. Results of the BAPEN/BSPGHAN survey on transition of care from paediatric age group to adulthood[89]

1) Transition can take as long as two years and is greatly facilitated by the appointment of an identified key worker for the young person.
2) Psychological issues need to be addressed prior to transition.
3) Written information can ensure clarity about all aspects of care.
4) Communication between the paediatric and adult centre is facilitated with at least one patient consultation where a professional from each centre is present.
5) Aim to keep the same infusion pump after transition.

Box 4. Areas for future investigation

Identification, epidemiology and management of intestinal failure

- Strategies to make AIF and CIF recognized at institutional, clinical and research levels
- Studies to update incidence and prevalence of AIF type I and type II and CIF
- Studies to demonstrate the positive cost-benefit ratio of the MDT in AIF and CIF management.
- Strategies to increase the awareness of medical professionals on AIF type II and CIF
- Acknowledgement of the role of nursing experts in IF with HOS and CO
- Strategies to minimise the socioeconomic burden of CIF and HPN and to improve the patients' quality of life
- Strategies to homogenize HPN management (i.e., such as dialysis for chronic renal failure) in order to allow patient to receive the same high level of care, independently of the HPN center
- Structured protocols for a successful transition from childhood to adulthood of patients with CIF

Acute intestinal failure

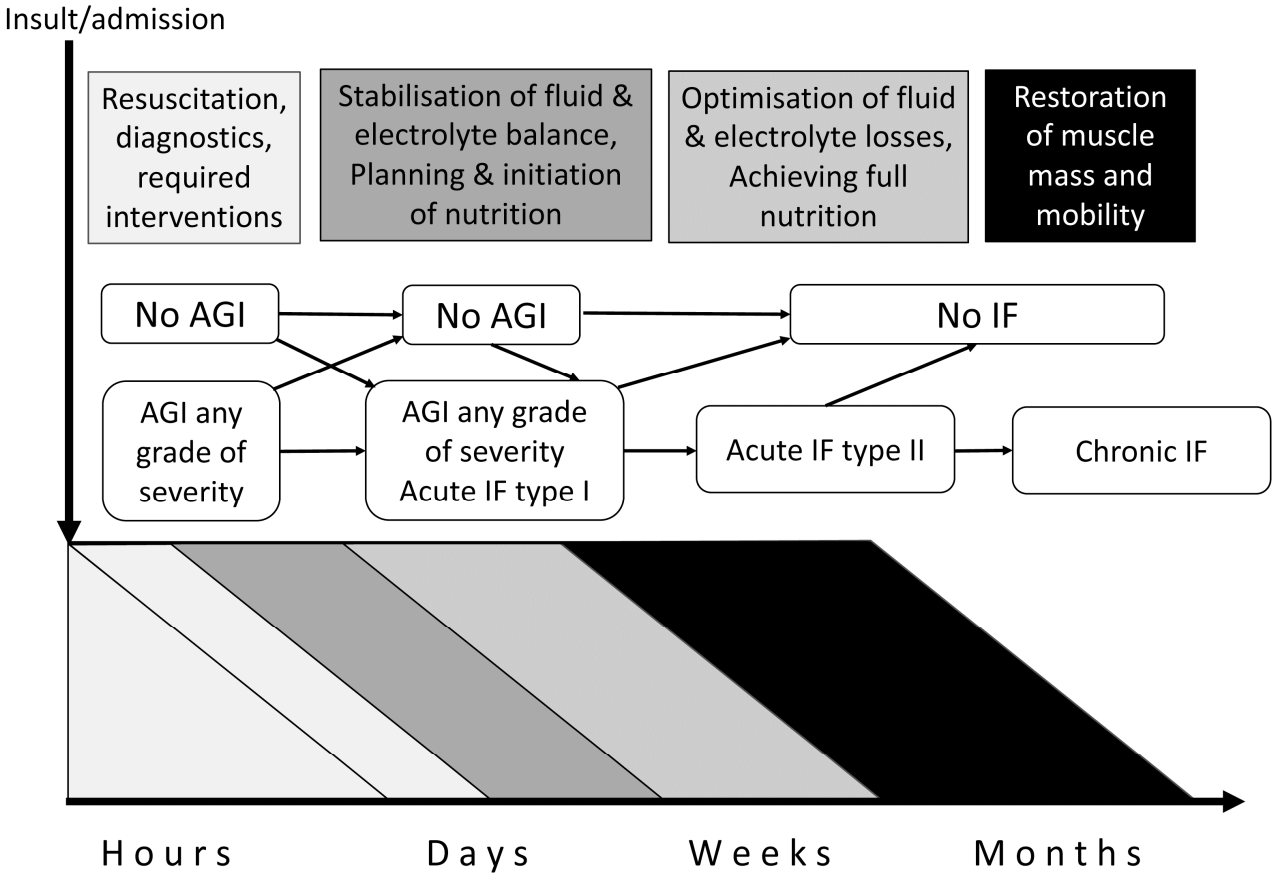
- Risk factors and outcome of AIF type I and II
- Recognition, diagnosis and management of acute intestinal ischaemic injury (i3)
- Biomarkers of acute intestinal ischaemic injury (i3), intestinal viability, mucosal perfusion and mucosal barrier integrity
- Impact of type 1-2 IF on the onset and course of type 3
- Markers of nutritional status and of hydration status in ICU patients
- Medications to foster intestinal adaptation
- Early prokinetics and laxatives in patients at risk for AIF type II
- Early postpyloric EN vs. early PN in AIF type I patients with gastroparesis
- Trophic EN vs PN in patients with AIF type I and at risk of AIF type II
- Early liberal vs. conservative fluid strategy in abdominal surgical patients at risk for AIF type II
- Electrolyte balance and GI motility in AIF type I and II
- Early mobilization in AIF type II
- Strategies to avoid post-operative fistula formation or encourage healing
- Surgical and radiological techniques (including plugs and implants) to promote fistula closure
- Impact of chyme reinfusion in ECF;
- PPIs and fistula output
- Role of bile salt signaling on the onset of liver test abnormalities in AIF type I and II

Chronic intestinal failure

- Short bowel syndrome
  - Safety and efficacy of intestinal growth factors in the very long term
  - Criteria to predict efficacy or failure of treatment with intestinal growth factors
  - Development of new intestinal growth factors
  - Safety and efficacy of high doses and prolonged use of opioids
  - Safety and efficacy of high doses and prolonged use of PPIs
  - Alternatives to WHO oral rehydration solution mixtures and the polysaccharide mixes which might be predicted to be better tolerated and more effective
  - Role of microbiota in post-surgical adaptation and metabolic complications
  - Intestinal stem cells transplantation to treat patients with intestinal failure
  - Parenteral nutrition admixture:
    - Lipids, role of emulsions containing fish oils

785 - Sugars, alternative to glucose
786 - Amino acid profiles, better parallels with physiological and pathophysiological needs
787 – Safety and efficacy of new oral anticoagulants
788
789 • Catheter related bloodstream infection (CRBSI)
790 – Evaluating and addressing the barriers to adopting a standardised approach for diagnosing
791 CRBSI between IF centres
792 – Role of future technologies (e.g. real time PCR) in diagnosing CRBSI
793 – Clinical & cost effectiveness of CVC salvage vs. replacement in risk-stratified CRBSI cases
794 – Consensus on CVC salvage methodology
795 – Role of antimicrobial locks in primary prophylaxis of CRBSI
796
797 • Intestinal failure associated liver disease
798 – Novel methods for diagnosis and monitoring (e.g. MR spectroscopy, serum markers).
799 – Evidence for current preventative strategies (e.g. long-term efficacy & safety of second/third
800 generation lipids)
801 – Novel therapeutic targets
802
803 • Non-transplant surgery
804 – Studies to clarify, compare, and standardize the timing and type of lengthening procedure
805

806 **Figure 1**. Phases of intestinal failure evolution
807



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Authorship contributions

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