

1 **Intestinal Failure in Adults: Recommendations from the ESPEN Expert Groups**

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69 **List of abbreviations:**

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

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90 **Abstract**

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92 **Background and aims.** Intestinal failure (IF) is defined as “the reduction of gut function below the  
93 minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that  
94 intravenous supplementation is required to maintain health and/or growth”. Functionally, it may  
95 be classified as type I acute intestinal failure (AIF), type II prolonged AIF and type III chronic  
96 intestinal failure (CIF) The ESPEN Workshop on IF was held in Bologna, Italy, on 15-16 October  
97 2017 and the aims of this document were to highlight the current state of the art and future  
98 directions for research in IF.

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

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

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

113

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

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142 **1. Introduction**

143 Intestinal failure (IF) is defined as “the reduction of gut function below the minimum  
144 necessary for the absorption of macronutrients and/or water and electrolytes, such that  
145 intravenous supplementation (IVS) is required to maintain health and/or growth”[1]. According to  
146 functional criteria it is classified as type I acute intestinal failure (AIF), type II prolonged AIF and  
147 type III chronic intestinal failure (CIF)[1]. It may be due to one or more of five major  
148 pathophysiological mechanisms that may originate from various gastrointestinal or systemic,  
149 congenital or acquired, benign or malignant diseases. A clinical classification of CIF has been  
150 devised on the basis of the IVS requirements[1] (BOX 1). The ESPEN Workshop on IF was held in  
151 Bologna, Italy, on 15-16 October 2017 focused on IF due to benign disease.

152

153 **2. Epidemiology**

154 The only available data on the type II-prolonged AIF were provided by a British study in  
155 2006, which estimated an annual incidence of 9 patients per million population[2]. Surgical  
156 complications (32%), Crohn's disease (21%), motility disorders (14%), intestinal ischaemia (13%)  
157 and malignancy (8%) were the main underlying causes[2].

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

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

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

176

### 177 **3. Identification of intestinal failure**

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

185

### 186 **4. Multidisciplinary management of intestinal failure**

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

190 Multi-disciplinary teams (MDT) are the key to successful management of IF. This was  
191 proposed by Nehme[11] in 1980, after finding that patients requiring IVS who were organised,  
192 supported and managed by a nutrition support team (NST) were less likely to develop catheter  
193 related bloodstream infection (CRBSI) at 24 months than those managed by a variety of physicians  
194 (1.3% versus 26.2%).

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

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

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

211

## 212 **5. Acute intestinal failure**

### 213 *5.1 Assessment of type II prolonged-acute intestinal failure*

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

#### 226 *5.2 Intestinal ischemic injury as a cause of acute intestinal failure*

227 Aside from these classifications of AIF, the concept of acute intestinal ischemic injury (i3)  
228 has been proposed to standardize and organize a management pathway that can be extended to  
229 all AIF, whatever the mechanisms[17]. Acute i3, defined as an acute intestinal injury secondary to  
230 a vascular insufficiency, can be present in the type I and type II ESPEN functional classification of  
231 AIF, as well as in grades I to IV of AGI. The vascular insufficiency can be occlusive (arterial/venous  
232 from thrombosis, embolus, dissection, trauma, tumoral invasion) or non-occlusive (low cardiac  
233 output, decreased blood pressure, vasoconstriction, venous stasis). The intestinal injury occurs at  
234 different degrees of depth (superficial *versus* transmural), and at different stages of progression  
235 (early/late, reversible/non reversible, necrotic/non-necrotic). Early and superficial i3 can be  
236 reversible whereas late, necrotic and transmural i3 are irreversible[17-20]. The loss of the  
237 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

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

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

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

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

#### 295 *5.4 Stoma and wound care*

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

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

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

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

322

### 323 *5.5 Prevention and management of sepsis*

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

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

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

347

## 348 **6. Chronic intestinal failure**

### 349 *6.1 Short bowel syndrome: spontaneous and induced intestinal adaptation after resection*

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

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

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

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

364 Gastrointestinal secretion is about 9 liters/day, with water and electrolyte absorption  
365 occurring predominantly in the distal small bowel and colon. Furthermore, in the jejunum, the  
366 intracellular tight junctions are relatively weak, and sodium absorption is coupled with the  
367 absorption of glucose (solvent drag) and occurs only against a concentration gradient. These  
368 mechanisms ensure rapid iso-osmolarity of the jejunal contents: hypertonic fluids cause the  
369 passage of water and hypotonic-low sodium fluids determine the secretion of sodium and water  
370 into the lumen. SBS-J patients often lose more fluid and sodium than ingested (net secretors),  
371 whereas in SBS-J and SBS-JIC there is usually sufficient distal bowel to permit fluid and electrolyte  
372 balance (net absorbers). The absorption of sodium and water in the colon are normally around  
373 200 mmol and 2 L/day in healthy adults and can increase up to 800 mmol and 6 L/day in SBS when  
374 the colon is in continuity[38-40].

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

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

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

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

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

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

415

#### 416 *6.2 Short bowel syndrome: enhanced post-resection intestinal adaptation*

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

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



429

### 430 *6.3 Outcome on home parenteral nutrition*

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

439

### 440 *6.4 Prevention and treatment of catheter-related bloodstream infection*

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

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

#### 468

#### 469 *6.5 Prevention and treatment of intestinal failure associated liver disease*

470           Liver injury in CIF can occur as a result of nutrient and non-nutrient factors. The former  
471 may include calorie overfeeding and/or nutrient deficiencies, including choline, taurine and  
472 carnitine. Non-nutrient factors include recurrent episodes of sepsis, bacterial overgrowth, SBS,  
473 hepatotoxic medications and underlying parenchymal liver disease[12, 56]. Retrospective series  
474 reveal a significant variation in the reported incidence of advanced liver disease from 0-85%[64-  
475 67]. Although such variation may have related to the amount of soybean-based lipid administered  
476 routinely in clinical practice in the past, it is apparent that a standardised definition of IFALD is

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

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

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

508

#### 509 *6.6 Non-transplant surgery and intestinal transplantation*

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

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

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

528         Most of the published data are on pediatric patient cohorts. The LILT procedure is a very  
529 complex type of surgery, where the dilated bowel is divided longitudinally. Each half longitudinal  
530 portion is tubularised and the two new segments are anastomosed end-to-end[78]. In the STEP  
531 surgery, serial transverse surgical stapler is applied on the dilated bowel and the new elongated  
532 intestinal channel has a zig-zag appearance[79]. In the SILT procedure, the bowel is incised along  
533 spiral lines and stretched to a uniformly longer tube of narrower diameter and the bowel is  
534 sutured along the incision line[81]. While no data comparing SILT with the other lengthening  
535 procedures are available, LILT and STEP have been compared, with a greater worldwide  
536 experience for STEP[72]. Surgical complexity is higher with LILT, that requires significantly more  
537 mesenteric handling. The LILT procedure cannot be performed in the duodenum and needs a  
538 residual bowel length of at least 20-40 cm. The STEP procedure can be performed with any length  
539 of bowel and even in the duodenum and is therefore of choice for ultra-short SB (<20 cm). The  
540 STEP can be repeated in the same patient and can also be performed in those who have already  
541 undergone LILT (which cannot be repeated). Furthermore, STEP has been demonstrated to be  
542 successful in the treatment of intestinal bacterial overgrowth and the associated D-lactic acidosis.  
543 Complications such as intestinal bleeding, obstruction and leakage have been described with both  
544 the procedures, whereas intestinal necrosis, perforation, fistula and abscess have been reported  
545 only after LILT. The results indicate a trend toward a higher percentage of intestinal lengthening  
546 with STEP (up to 69%) than with LILT (up to 55%), lower need of ITx after STEP (5-6% compared  
547 with 10-26% after LILT), whereas the two procedures showed similar percentages of PN  
548 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

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

575

#### 576 *6.7 Transition from childhood to adulthood of CIF patients*

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

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

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

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

601

## 602 *6.8 The economic and social burden*

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

607 The ESPEN guidelines for CIF[12] recommend that a HPN programme includes the  
608 “provision of evidence-based therapy, prevention of HPN-related complications... and ensure  
609 quality of life is maximised”. A recently published international retrospective study[90] of 472  
610 patients with severe chronic and benign IF who commenced HPN in 2000 demonstrated a survival  
611 probability of 88%, 74% and 64% at 1, 3, and 5 years, with survival inversely associated with  
612 increasing age, the presence of Crohn’s disease or chronic idiopathic pseudo-obstruction. At 5-  
613 year follow up, 39% were alive on HPN with a mean age of 55 years, 36% had been weaned from  
614 HPN with a mean age of 52 years, 22% had died on HPN with a mean age of 60 years, 2% were  
615 alive following intestinal transplant with a mean age of 42 years and 1% had died following  
616 intestinal transplant with a mean age of 36 years. The probability of HPN dependency at 5 years is  
617 variable depending on the cause of the original HPN requirement, with a significantly increased  
618 risk of remaining on HPN at 5 years in those with SBS versus a much lower risk in those with an  
619 intestinal fistula. When 1,2, and 5-year survival in patients with CIF is compared between  
620 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

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

648

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

650 *Definition*

651 ▪ **Intestinal failure:** the reduction of gut function below the minimum necessary for the absorption of  
652 macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to  
653 maintain health and/or growth.

654 ▪ **Intestinal insufficiency or deficiency:** the reduction of gut absorptive function that doesn't require  
655 intravenous supplementation to maintain health and/or growth, can be considered as “intestinal  
656 insufficiency”

657

658 *Functional classification of intestinal failure*

659 Based on onset, metabolic and expected outcome criteria:

660 ▪ **Type I - acute**, short-term and usually self-limiting condition; this is a common feature, occurring in the  
661 perioperative setting after abdominal surgery and/or in association with critical illnesses; it recedes when  
662 those illnesses subside; IVS is required over a period of days or a few weeks

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

665 ▪ **Type III - chronic** condition, in metabolically stable patients, requiring IVS over months or years; it  
666 represents the chronic intestinal failure (CIF), that may be reversible or irreversible.

667

668 *Pathophysiological classification*

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

- 670 ▪ short bowel
- 671 ▪ intestinal fistula
- 672 ▪ intestinal dysmotility
- 673 ▪ mechanical obstruction
- 674 ▪ extensive small bowel mucosal disease

675

676 *Clinical classification of chronic intestinal failure*

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

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

680

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

683 FE = Fluids and Electrolytes alone

684 PN = Parenteral Nutrition Admixture containing also macronutrients

685

686

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

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

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

715 • Consideration at each stage of AIF of the question of the need for surgery: second look, emergency  
716 surgery, vascular rehabilitation, digestive rehabilitation. The criteria for surgery should always be  
717 discussed and planned *a priori*.

718 • Evaluation and determination of the timing for each step of the strategy: closure of stoma,  
719 rehabilitation after nutritional recovery, cholecystectomy, surgical technics that promote intestinal  
720 adaptation (STEPS, segmental reversal of the small bowel), wound cares, home return and home  
721 parenteral nutrition.

722 • Anticipation and prevention of complications of AIF: recurrence or complication of underlying disease,  
723 refeeding syndrome, hypernutrition, liver disease, respiratory complications, lines infections, stroke,  
724 anticoagulants.

725

726

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

729

730 1) Transition can take as long as two years and is greatly facilitated by the appointment of an  
731 identified key worker for the young person.

732 2) Psychological issues need to be addressed prior to transition.

733 3) Written information can ensure clarity about all aspects of care.

734 4) Communication between the paediatric and adult centre is facilitated with at least one patient  
735 consultation where a professional from each centre is present.

736 5) Aim to keep the same infusion pump after transition.

737

738

739 **Box 4. Areas for future investigation**

740 **Identification, epidemiology and management of intestinal failure**

- 741 • Strategies to make AIF and CIF recognized at institutional, clinical and research levels
- 742 • Studies to update incidence and prevalence of AIF type I and type II and CIF
- 743 • Studies to demonstrate the positive cost-benefit ratio of the MDT in AIF and CIF management.
- 744 • Strategies to increase the awareness of medical professionals on AIF type II and CIF
- 745 • Acknowledgement of the role of nursing experts in IF with HOS and CO
- 746 • Strategies to minimise the socioeconomic burden of CIF and HPN and to improve the patients' quality of life
- 747
- 748 • 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
- 749
- 750 • Structured protocols for a successful transition from childhood to adulthood of patients with CIF

751

752 **Acute intestinal failure**

- 753 • Risk factors and outcome of AIF type I and II
- 754 • Recognition, diagnosis and management of acute intestinal ischaemic injury (i3)
- 755 • Biomarkers of acute intestinal ischaemic injury (i3), intestinal viability, mucosal perfusion and mucosal barrier integrity
- 756
- 757 • Impact of type 1-2 IF on the onset and course of type 3
- 758 • Markers of nutritional status and of hydration status in ICU patients
- 759 • Medications to foster intestinal adaptation
- 760 • Early prokinetics and laxatives in patients at risk for AIF type II
- 761 • Early postpyloric EN vs. early PN in AIF type I patients with gastroparesis
- 762 • Trophic EN vs PN in patients with AIF type I and at risk of AIF type II
- 763 • Early liberal vs. conservative fluid strategy in abdominal surgical patients at risk for AIF type II
- 764 • Electrolyte balance and GI motility in AIF type I and II
- 765 • Early mobilization in AIF type II
- 766 • Strategies to avoid post-operative fistula formation or encourage healing
- 767 • Surgical and radiological techniques (including plugs and implants) to promote fistula closure
- 768 • Impact of chyme reinfusion in ECF;
- 769 • PPIs and fistula output
- 770 • Role of bile salt signaling on the onset of liver test abnormalities in AIF type I and II

771

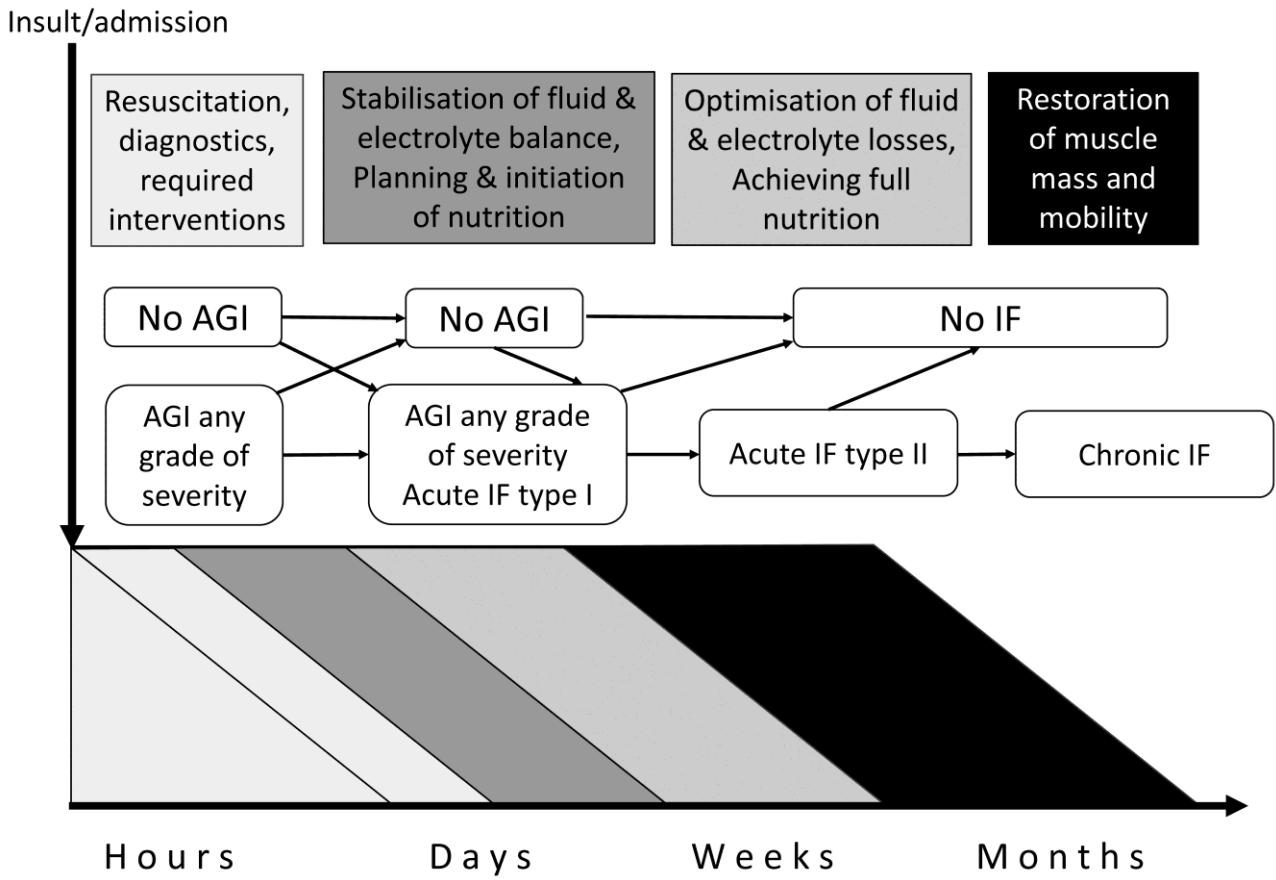
772 **Chronic intestinal failure**

- 773 • Short bowel syndrome
  - 774 – Safety and efficacy of intestinal growth factors in the very long term
  - 775 – Criteria to predict efficacy or failure of treatment with intestinal growth factors
  - 776 – Development of new intestinal growth factors
  - 777 – Safety and efficacy of high doses and prolonged use of opioids
  - 778 – Safety and efficacy of high doses and prolonged use of PPIs
  - 779 – Alternatives to WHO oral rehydration solution mixtures and the polysaccharide mixes which might be predicted to be better tolerated and more effective
  - 780
  - 781 – Role of microbiota in post-surgical adaptation and metabolic complications
  - 782 – Intestinal stem cells transplantation to treat patients with intestinal failure
  - 783 – Parenteral nutrition admixture:
    - 784 ○ 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



808  
809

810 **Authorship contributions**

811 All the authors were speakers of the 5th ESPEN Workshop on Intestinal Failure in Adults, held in  
812 Bologna, Italy, 15-16 October 2017, contributed in the manuscript writing, revised and approved  
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814

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835 **References**  
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