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ESPEN endorsed recommendation

ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults

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SUMMARY

Background & aims: Intestinal failure (IF) is not included in the list of PubMed Mesh terms, as failure is the term describing a state of non functioning of other organs, and as such is not well recognized. No scientific society has yet devised a formal definition and classification of IF. The European Society for Clinical Nutrition and Metabolism guideline committee endorsed its "home artificial nutrition and chronic IF" and "acute IF" special interest groups to write recommendations on these issues.
Methods: After a Medline Search, in December 2013, for "intestinal failure" and "review"[Publication Type], the project was developed using the Delphi round methodology. The final consensus was reached on March 2014, after 5 Delphi rounds and two live meetings.
Results: The recommendations comprise the definition of IF, a functional and a pathophysiological classification for both acute and chronic IF and a clinical classification of chronic IF. IF was defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or

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water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth".

Conclusions: This formal definition and classification of IF, will facilitate communication and cooperation among professionals in clinical practice, organization and management, and research.

Abbreviations

AIF	acute intestinal failure
CIF	chronic intestinal failure
CIPO	chronic idiopathic pseudo-obstruction
EC	enterocutaneous
ESPEN	European Society for Clinical Nutrition and Metabolism
IF	intestinal failure
ITx	intestinal transplantation
HAN&CIF	home artificial nutrition and chronic intestinal failure
HPN	home parenteral nutrition
SBS	short bowel syndrome

1. Introduction

Intestinal failure (IF) was first defined in 1981 by Fleming and Remington as "a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food" [1]. IF may be due to acquired or congenital, gastrointestinal or systemic, benign or malignant diseases, which may affect all age categories [2,3]. It may have an abrupt onset, or may be the slow, progressive evolution of a chronic illness, and may be a self-limiting short-term or a long-lasting condition (chronic intestinal failure, CIF). Treatment of CIF relies on intestinal rehabilitation programs that aim to restore bowel function through nutrition, pharmacological and/or surgical therapy [4]. Patients with irreversible CIF are destined to need life-long home parenteral nutrition (HPN) or to undergo intestinal transplantation (ITx) [5].

The definition of IF by Fleming and Remington has been revised by other experts [2–6], but no scientific society has yet devised a formal definition and classification of IF. Indeed, IF is not included in the list of PubMed Mesh terms, as failure is the term describing a state of non functioning of organs. A PubMed search on March 15th 2014, using "intestinal failure" as general term, nonetheless generated a total of 981 items, and showed that the number of publications has rapidly grown in the past decades, indicating an increased awareness of this condition (Table 1).

The European Society for Clinical Nutrition and Metabolism (ESPEN) has two "special interest groups" devoted to IF, "the home artificial nutrition and chronic intestinal failure group (HAN&CIF)" established in 1992 and the "acute intestinal failure group (AIF)" established in 2010 [7]. The Guideline Committee of ESPEN committed the two groups to develop the ESPEN guidelines on IF [8] and endorsed them to support the Guidelines with recommendations on the definition and classification of IF.

2. Material and methods

The project of writing "recommendations on definition and classification of IF in adults" was agreed on March 14th 2013, with a member of the ESPEN Guideline committee to assist the development of the guidelines on IF, and was formally approved by the AIF and the HAN&CIF special interest groups at their meetings held at the ESPEN Congress in Leipzig, September 2013. All the members of the two groups were invited to be part of the expert panel.

The work was carried out between December 2013 and February 2014, using Delphi round methodology [9]. The results of the Delphi rounds were also discussed during the face-to-face winter meetings of the two groups.

Each Delphi round consisted of a proposal, to which each expert replied as "agree", "agree, with suggested minor changes", or "disagree, with suggested major changes". The first proposal was based on a MedLine Search, performed on 10/12/2013, for "intestinal failure" AND "review"[Publication Type], which resulted in a total of 298 articles. Only publications in English specifically dedicated to the definition and classification of IF were selected. Any pertinent publications retrieved from the references of the selected papers were also considered. In order to avoid duplicates, only those articles with an "original" definition and classification were chosen. These initially selected papers, used as starting point for the first round are reported in Table 2. The subsequent proposals were based on the collected comments as well as on any further publications found non systematically but suggested by the experts. All the proposals were prepared and circulated by LP. The final consensus was reached on March 1st 2014, after 5 Delphi rounds (on 16/12/14, 27/12/14, 19/01/14, 25/02/14 and 01/03/14) and two live meetings (AIF 11/01/14, HAN&CIF 22/02/14). For the purpose of the paper, the following terms were used: "oral feeding", to indicate the ingestion of food, "oral supplementation"

Table 1
PubMed search on March 15th, 2014.

	1946–1959	1960–1969	1970–1979	1980–1989	1990–1999	2000–2009	2010–2014 March	Total
Intestinal failure [general term]	0	0	0	20	118	450	399	981
Kidney failure [MeSH Term]	393	4226	13012	18086	24268	39768	21790	120939
Heart failure [MeSH Term]	2184	5141	7372	9420	13218	30803	16811	84385
Liver failure [MeSH Term]	153	833	1572	1594	3719	6627	3382	17788
Respiratory failure [MeSH Term]	4	3942	9154	7892	10633	13216	5805	50433

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Table 2
Main original definitions and classifications of Intestinal Failure reported in the literature prior to March 15th 2014, in order of publication date. Bold characters indicate the original contribution of each paper.

Author, date (ref)	Definition and classification of intestinal failure
Fleming CR and Remington M. 1981 [1]	**A reduction in the functioning gut mass below the minimum amount necessary for adequate digestion and absorption of food**
Irving M. 1995 [10]	The **spectrum of intestinal failure** covers a wide range of diseases but essentially they can be placed in **four major categories:** short bowel syndrome, motility disorders of the bowel (chronic pseudoobstruction), small bowel parenchymal disease, intestinal fistula
Irving M. 2000 [11]	Intestinal failure can be **complete or partial**, the former typically following total small bowel enterectomy, whilst the latter is seen following partial resection. The condition can be **acute and temporary**, as seen with recoverable motility disorders such as ileus and obstruction, or chronic and permanent. Although a wide spectrum of conditions can be associated with IF, four **major underlying causes** can be identified. These are: (i) the short bowel syndrome; (ii) total parenchymal bowel disease (e.g. Crohn's disease); (iii) motility disorders, such as visceral myopathy and chronic intestinal obstruction; and (iv) small bowel fistulation causing premature loss of enteric content. **The principal resulting nutritional disorders are starvation and dehydration**, but loss of body mass is frequently made worse by catabolism from associated sepsis. **Treatment** is complicated, but has at its core the provision of **nutritional support, principally through the intravenous route**. **Resolution of IF can occur spontaneously** by the process of intestinal adaptation.
Jeppesen PB and Mortensen PB. 2000 [12]	**Intestinal failure** may be defined by the **minimum energy and wet weight absorption required to avoid home parenteral nutrition** Patients with **intestinal insufficiency** who maintained intestinal autonomy and did not depend on parenteral supplements Involuntary ingestion below the minimal amount necessary to maintain nutrient and fluid balance, frequently termed **oral failure**, is seen in patients with pseudoobstruction and dysmotility syndromes.
Nightingale J. 2001 [13]	Intestinal failure occurs 'when there is **reduced intestinal absorption so that macronutrient and/or water and electrolyte supplements** are needed to maintain health and/or growth'.
Shaffer J. 2002 [14]	**A novel classification of intestinal failure** was recently devised to reflect this: **Type I** intestinal failure is classified as self-limiting intestinal failure as occurs following abdominal surgery; **Type II** is intestinal failure in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery; **Type III** is chronic intestinal failure requiring long-term nutritional support.
Buchman AL et al., 2003 [15]	It has been suggested that intestinal failure is better defined in terms of fecal energy loss rather than residual bowel length. However, fecal energy loss is a function of both energy intake and energy absorption. **Patients who are unable to increase their oral intake sufficiently or are unable to absorb sufficient energy despite significantly increased intake,** are defined as patients with intestinal failure and require parenteral nutrition support.
Ding LA and Li jS. 2004 [16]	**Staging** of intestinal failure: Acute intestinal failure, Chronic intestinal failure **Grading** of intestinal failure: severe, moderate, mild
Goulet O et al., 2004 [17]	Intestinal failure can be defined as the reduction of functional gut mass below the minimum needed for **digestion** and absorption of nutrient and fluids required for maintenance in adults or growth in children. It has been suggested that IF is better defined in terms of fecal energy loss rather than residual bowel length in patients with short bowel syndrome. Another approach is **to define the degree of IF according to the amount of PN required** for maintenance in adults and growth in children
Kocoshis SA, 2004 [18]	Although intestinal failure can be defined by excessive fecal energy loss, a more widely accepted definition is "**the inability of the gastrointestinal tract to sustain life autonomously**".
Jeejeebhoy KN. 2005 [19]	Gastrointestinal function is inadequate to maintain the nutrition and hydration of the individual without supplements given **orally** or intravenously
O'Keefe SJD. 2006 [3]	Intestinal failure '**results from obstruction, dysmotility, surgical resection, congenital defect or disease–associated loss of absorption and is characterized by the inability** to maintain protein-energy, fluid, electrolyte **or micronutrient balance**'
Lal S. (2006) [20]	Causes of intestinal failure are varied, with self-limiting or '**Type 1**' intestinal failure occurring relatively commonly following abdominal surgery, necessitating short-term fluid or nutritional support. The rarer, '**Type 2**' intestinal failure, is associated with septic, metabolic and complex nutritional complications, usually following surgical resection in patients with Crohn's or mesenteric vascular disease. In broad terms, intestinal failure **can result** from **intestinal resection, inflammation or fistulization, from mechanical or functional intestinal obstruction, or indirectly from the effects of sepsis on the gastrointestinal tract**
Messing B and Joly F [21]	The recognized definition of **chronic intestinal failure** is a nonfunctioning small bowel either removed after severe disease leading to very short bowel syndrome, or present but **impossible to use by enteral support** even accessed through jejunostomy (eg, chronic intestinal pseudo-obstruction or extensive villous atrophy diseases).
Nightingale J and Woodward JM (2006) [22]	IF may be defined and quantified by balance study techniques; however, only few centres have the facilities for these difficult metabolic studies, and therefore **nutrient/fluid requirements determine whether IF** is termed **severe, moderate, or mild. Severe is when parenteral, moderate when enteral, and mild when oral nutritional fluid supplements are needed**.
Beath S et al., 2008 [23]	Intestinal failure is defined as the **inability of the alimentary tract** to digest and absorb sufficient nutrients to maintain normal fluid balance, growth and health.
Gillanders L. et al., 2008 [24]	Intestinal failure occurs when there is reduced intestinal absorption **so that intravenous** nutrients and/or water and electrolyte supplements are needed to maintain health and/or growth. IF can be **short (<1 y) or long term**.
NHS National Commissioning Group for Highly Specialised Services. 2008 [6]	Intestinal Failure comprises a group of disorders with many different **causes**, all of which are characterised by an inability to maintain adequate nutrition via the intestines. **It results from obstruction, abnormal motility, major surgical resection, congenital defect or disease–associated**

(*continued on next page*)

Table 2 (*continued*)

Author, date (ref)	Definition and classification of intestinal failure
	loss of absorption. It is characterised not only by the inability to maintain protein-energy, but also often in difficulties in maintaining water, electrolyte or micronutrient balance, particularly when there has been a major loss of length of the small bowel. **If it persists for more than a few days it demands treatment with the intravenous delivery of nutrients and water–parenteral nutrition**. **Type I** – this type of Intestinal Failure is short-term, self limiting and often peri-operative in nature. Type I Intestinal Failure is common and these patients are managed successfully in a multitude of healthcare settings, especially surgical wards, including all units which perform major, particularly abdominal surgery. Some patients on high dependency units (HDU) and intensive care units (ICU) will also fall into this category Care location: Wards, (HDU, ITU) **Type II** – Type II IF occurs in metabolically unstable patients in hospital and requires prolonged parenteral nutrition over periods of weeks or months. It is often associated with sepsis, and may be associated with renal impairment. These patients often need the facilities of an Intensive Care or High Dependency Unit for some or much of their stay in hospital. This type of IF is rarer and needs to be managed by a multi-professional specialist intestinal failure team. Effective management of Type II IF can reduce the likelihood of the development of Type III Intestinal Failure. Care location: HDU, ITU (Wards) **Type III** – Type III is a chronic condition requiring long term parenteral feeding. The patient is characteristically metabolically stable but cannot maintain his or her nutrition adequately by absorbing food or nutrients via the intestinal tract. These are, in the main, the group of patients for which Home Parenteral Nutrition (HPN) is indicated. Care location: Wards to home
Fishbein TM. 2009 [25]	Intestinal failure refers to a**ctual or impending loss of nutritional autonomy due to gut dysfunction.** The condition **is initially managed by parenteral delivery of nutrition**.
Staun M et al., 2009 [26]	Intestinal failure is defined as a condition with reduced intestinal absorption to the extent that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth. Intestinal failure is **severe when parenteral nutrition and or additional parenteral electrolytes and water are required**. The condition may be **transient** if gut function can be restored, but HPN is indicated for patients with **chronic** intestinal failure.
Rudolph A and Squires R. 2010 [27]	Intestinal failure, defined as an inability of a child to achieve adequate weight and growth without intravenous nutritional support, **has two principal components: the intestine is too short as a consequence of surgical resection and the intestine is dysfunctional despite adequate length.**
Gardiner KR. 2011 [28]	The term intestinal failure was introduced by Fleming and Remington(1) and defined as a 'reduction in functioning gut mass below the minimum necessary for adequate digestion and absorption of nutrients'. Initially, this definition was used interchangeably with the need for parenteral nutrition. Since that time the definition has been broadened and is now recognised to occur when 'gastrointestinal function is inadequate to maintain the nutrition and hydration of the individual **without supplements given orally or intravenously**. IF has been sub-classified into three types on the basis of duration and irreversibility.
Krawinkel MB. 2012 [29]	The term "**chronic intestinal failure**" (CIF) refers to the **body's inability** to meet its energy and nutritional needs through the gastrointestinal tract
Murray JS and Mahoney JM. 2012 [30]	IF is defined as the **inability of the gastrointestinal system** to properly function for the adequate digestion and absorption of necessary nutrients and fluids for growth and development Other experts describe this illness as a state in which **gastrointestinal function** is not adequate to support sufficient growth and physiological balance in children
Pironi L. et al., 2012 [5]	Intestinal failure results from reduction in the functioning gut mass characterized by the inability to maintain protein-energy, fluid, electrolyte **and/or micronutrient** balance.
Squires RH et al., 2012 [31]	Intestinal failure in infants and children is a **devastating condition** that can be broadly defined as the inability of the gastrointestinal tract to **sustain life** without supplemental parenteral nutrition

to indicate the ingestion of nutritional supplements, "enteral nutrition" to indicate enteral tube feeding and "parenteral nutrition" to indicate the intravenous infusion of nutritional admixtures or of water and electrolyte solutions.

The definitive recommendations consist in the "definition of IF", a "functional classification of IF", a "pathophysiological classification of IF" and a "clinical classification of chronic IF".

As there were no published data available to serve as a starting point for a "clinical classification", this was developed on the basis of the common experience of the panel experts. The applicability of the devised "clinical classification" was verified on two samples of randomly selected patients, currently on HPN for CIF due to either benign or active malignant disease. This consisted in a cross-sectional investigation of the energy content and volume of the parenteral nutrition admixture of 114 patients cared for at the Center for Benign Chronic Intestinal Failure of the S. Orsola-Malpighi University Hospital, Bologna (Italy) and of 50 patients with active cancer cared for at the Tumor Biology Center, Albert-Ludwigs-University, Freiburg (Germany).

3. Results

The definition and classification of IF are reported and discussed below and are summarized in Table 3. Table 4 summarizes the pathophysiological mechanisms of IF. The diseases that may determine an IF are listed in Table 5.

3.1. Definition of intestinal failure

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

The reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning).

The panel identified IF as a "state of non-functioning", where the gut function referred to was the "absorption of proteins, lipids, carbohydrates, water and electrolytes" [12,13,15,24,29,30], and the "threshold for loss of function" was the "need for intravenous supplementation" to maintain health and/or growth [6,12–14,21,24,31]. For this purpose, the original definition by Fleming and Remington was modified by deleting the term "mass", identifying "absorption" as the key gut function, replacing the term "food" with "macronutrients and/or water and electrolytes", and by specifying the "need for intravenous supplementation to maintain

Table 3
ESPEN recommendations: definition and classification of intestinal failure.

Definition
Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.
The reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency" (or "intestinal deficiency" for those languages where "insufficiency" and "failure" have the same meaning).
Functional classification
On the basis of onset, metabolic and expected outcome criteria, intestinal failure is classified as:
- Type I – acute, short-term and usually self limiting condition
- Type II – prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
- Type III – chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible.

Pathophysiological classification
Intestinal failure can be classified into five major pathophysiological conditions, which may originate from various gastrointestinal or systemic diseases:
- short bowel
- intestinal fistula
- intestinal dysmotility
- mechanical obstruction
- extensive small bowel mucosal disease

Clinical classification of chronic intestinal failure
On the basis of the requirements for energy and the volume of the intravenous supplementation (IV), chronic intestinal failure is categorized into 16 subtypes

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

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

health and growth". The panel was aware that balance study techniques, comparing nutrient requirement with nutrient absorption, would be the optimal way to identify and quantify IF in the individual patient [12]. However, considering that very few centres have the facilities for these difficult metabolic studies, the requirement of intravenous nutrient/fluid supplementation was used as a "surrogate diagnostic criterion". The exclusive need for intravenous supplementation was the most debated issue, because some previous definitions of IF included also oral supplementation and enteral nutrition [2,5,6,11,18,19,22,23,25,26,28]. Micronutrients were not mentioned in the definition in order to avoid any misunderstanding about impaired gut absorption resulting in micronutrient deficiency alone, as this would not be considered as IF [2,5,6].

The proposed definition indicates that for the diagnosis of IF two criteria must be simultaneously present: a "decreased absorption of macronutrients and/or water and electrolytes due to a loss of gut function" and the "need for intravenous supplementation". This facilitates an understanding of which conditions cannot be considered IF because only one criterion is present: patients with reduced food intake but normal gut function, like those with disease-related hypophagia, or with anorexia nervosa or any other psychiatric disorders; patients with altered gut function but conserved intestinal absorption, like neurological or cancer patients with impaired swallowing or dysphagia; patients, especially children, with active Crohn's disease treated by enteral nutrition; patients treated by parenteral nutrition because of refusal of otherwise effective enteral nutrition; patients with a reduction of gut function impairing intestinal absorption but in whom health and growth can be maintained by oral supplementation, enteral nutrition, re-feeding enteroclysis (reinfusion of chyme to the distal limb of a high output small bowel fistula), or those who require only vitamins and trace element supplementation. For these last conditions, the panel proposes that the term "intestinal insufficiency or intestinal deficiency" could be considered [12]. The alternative between "insufficiency" and "deficiency" has been included to allow an appropriate translation in those languages where "insufficiency" and "failure" have the same meaning, such as in French, Italian and other Latin languages.

3.2. Functional classification

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

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

This classification, termed "functional", was also used in the UK project "A Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for Adults in England" [6], and was first described in 2002 [14]. It aims to categorize the medical care, the professional expertise, the management, the treatment setting as well as the organization, logistic and administrative issues required for the treatment of IF.

Acute type I and type II IF have been extensively reviewed [20,28]. **Type I** IF is a common, short and often self limiting, condition, estimated to occur in about 15% patients in the perioperative setting after abdominal surgery or in association with critical illnesses such as head injury, pneumonia and acute pancreatitis. While intestinal function recovers, short-term parenteral fluid and nutrition support can be required. Post-operative ileus usually spontaneously resolves within a few days. This duration can be shortened by multimodal enhanced recovery techniques aiming to promote early mobilization and early introduction of oral nutrition [32]. Such patients are usually managed in surgical wards, although some patients in critical care environments also fit into this category.

Type II IF is an uncommon condition, most often seen in the setting of an intra-abdominal catastrophe (like peritonitis due to visceral injury) and is almost always associated with septic, metabolic and complex nutritional complications. Renal impairment may be present. It is originally an acute event, often occurring in a previously healthy subject (mesenteric ischaemia, volvulus or abdominal trauma) or complicating intestinal surgery (anastomotic leak; inadvertent and unrecognized intestinal injury) and necessitating massive enterectomy and/or resulting in one or more enterocutaneous fistulae, with or without a proximal stoma. Less frequently, it may be the complication of a type III chronic IF, representing a condition of "acute on chronic" IF. Type II IF requires prolonged parenteral nutrition over periods of weeks or months. These patients often initially need the facilities of an intensive care or high dependency unit and to be managed by a multi-professional specialist IF team for part or most of their stay in hospital. Using a

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Table 4
Pathophysiological classification of intestinal failure.

Condition	Primary mechanism of intestinal failure	Concomitant mechanisms
Short bowel	Reduced absorptive mucosal surface	• Increased intestinal losses of fluids and electrolytes (adjunctive mechanism in the case of end-jejunostomy) • Restricted oral/enteral nutrition (to reduce intestinal losses) • Disease-related hypophagia • Lack of adaptive hyperphagia • Accelerated gastrointestinal transit time • Small bowel bacterial overgrowth
Intestinal fistula	By pass of large areas of absorptive mucosal surface	• Increased intestinal losses of fluids and electrolytes • Disruption of the entero–hepatic cycle • Restricted oral/enteral nutrition or total fasting (bowel rest) to decrease fistula output • Impaired intestinal peristalsis and increased metabolic demand related to concomitant sepsis and inflammation
Intestinal dysmotility	Restricted oral/enteral nutrition or total fasting from intolerance due to feeding-related exacerbation of digestive symptoms or to episodes of non-mechanical intestinal obstruction	• Malabsorption due to small bowel bacterial overgrowth • Increased intestinal secretion of fluids and electrolytes in the obstructed segments • Increased intestinal losses of fluids and electrolytes due to vomiting, gastric drainage and/or diarrhoea
Mechanical obstruction	Incomplete or total fasting (bowel rest)	• Increased intestinal secretion of fluids and electrolytes in the obstructed segments • Increased intestinal losses of fluids and electrolytes with vomiting or gastric drainage
Extensive small bowel mucosal disease	Inefficient absorptive and/or nutrient losing mucosal surface.	• Increased intestinal losses of fluids and electrolytes • Restricted oral/enteral nutrition • Disease-related hypophagia

requirement for parenteral nutrition of 28 days or more as a surrogate marker, the annual incidence of Type II IF has been estimated to be 9 patients per million population [6]. Outcome is most frequently represented by full intestinal rehabilitation (about 40%), enteral nutrition including distal feeding (10%) or type III IF requiring prolonged HPN (50%). An in-hospital mortality as high as 9.6%–13% has been reported. In the majority of deaths the underlying process is sepsis, which can be intra-abdominal but distant sites such as bone, cardiac and the central nervous system as well as the intravenous feeding catheter have all been implicated. Specialist in–patient intestinal failure units, with multidisciplinary teams are recommended [33–35].

Type III IF is a chronic condition (CIF) in a metabolically stable patient, which usually requires long-term HPN. CIF may be the evolution of a type II acute IF, the result of progressive and devastating gastrointestinal or systemic benign diseases, often requiring multiple intestinal resections (such as Crohn's disease, radiation enteritis, familiar polyposis, chronic intestinal pseudo-obstruction, intestinal lymphangectasia, or systemic sclerosis), the main clinical feature of congenital digestive diseases (such as gastroschisis, intestinal atresia, microvillous inclusion disease and intestinal epithelial dysplasia), or the end stage of intra-abdominal or pelvic cancer [5,36].

CIF due to benign disease may be a reversible condition. Weaning from HPN after 1–2 years of starting may occur in 20%–50% of the patients, depending on the characteristics of the CIF [5]. Patients with CIF due to benign disease have a high probability of long-term survival on HPN (about 80% in adults and 90% in children at 5 years) [5]. Overall, about two thirds of patients may have partial or total social and working rehabilitation as well as a good family life [37–39]. On the other hand, CIF may be associated with life-threatening complications and the condition itself may be highly disabling and impairs the quality of life [5,23]. Treatment of CIF is based on complex technologies and requires multidisciplinary and multiprofessional activity and expertise [23]. The outcome of patients with benign CIF, in terms of reversibility, treatment-related morbidity and mortality, and survival probability is strongly dependent on care and support from an expert specialist team [5,23]. Patients with irreversible CIF are destined to need life-long HPN or ITx. On the basis of data on safety and efficacy, HPN is considered the primary treatment for CIF, whereas ITx is reserved for those patients at risk of death because of life-threatening complications related to HPN or to the underlying gastrointestinal disease [5]. In Europe, the prevalence of HPN for CIF due to benign disease has been estimated to range from 5 to 20 cases per million population [36,40–43]. CIF due to benign disease has been included in the 2013 Orphanet list of rare diseases [44].

Treatment with HPN for CIF due to end stage malignant disease is controversial [45,46]. HPN patients with cancer varies from 60% in Italy to 20–30% in Spain, France and Belgium, and only 8% in UK [36,40–43]. This wide range may be due to different medical and social attitudes toward palliative care. Other factors that play a role include different regulation and funding of the various national health care systems and/or to the inappropriate use of a central venous catheter, previously positioned for chemotherapy. Many such patients could be adequately managed by enteral nutrition. Overall, the scientific society guidelines have not recommended HPN for patients with a short life expectancy due to the malignancy (generally considered inappropriate if this is less than 2–3 months) [47].

3.3. Pathophysiological classification

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

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

The first classification of IF, based on the underlying causes, was described in 1991 [33] and further developed in 1995 [10,11], 2006 [2,20], 2008 [6] and 2010 [27]. The panel has termed this classification “pathophysiological”, to underline the main mechanisms that, alone or in association, can determine the development of an IF (Table 4).

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Table 5
Gastrointestinal or systemic diseases that may determine the pathophysiological conditions of intestinal failure. The list may not be exhaustive of all the possible causes.

Condition	Most frequent underlying diseases
Short bowel	Extensive surgical resection for: • Mesenteric infarction (arterial or venous thrombosis) • Crohn's disease • Radiation enteritis • Surgical complications • Intestinal volvulus • Familial polyposis • Abdominal trauma • Intestinal angiomatosis • Necrotizing enterocolitis • Complicated intussusception Congenital: • Gastroschisis • Intestinal atresia • Intestinal malformation • Omphalocoele
Intestinal fistula	• Inflammatory (Crohn's disease, diverticular disease, pancreatic disease, radiation enteritis) • Neoplastic (colon cancer, ovarian cancer, small bowel malignancy) • Iatrogenic (operation, percutaneous drainage) • Infectious disease (tuberculosis, actinomycosis) • Trauma • Foreign body
Intestinal dysmotility	Acute: post-operative, systemic inflammatory or neurological reaction associated with critical illnesses; Ogilvie syndrome (acute colonic non-mechanical obstruction) Chronic Intestinal Pseudo-Obstruction (obstructive symptoms for at least 6 months): • Primary/idiopathic (with no underlying disorder) – Neuropathic: inflammatory or degenerative injury to the enteric nervous system (ENS) – Myopathic: damage of the smooth muscle (congenital, familial, or sporadic); familial visceral myopathy is classified as type 1 (autosomal dominant), type 2 (autosomal recessive with associated ptosis and ophthalmoplegia), or type 3 (autosomal recessive with the presence of gastrointestinal tract dilatation) – Mesenchymopathy: injury of the interstitial cells of Cajal • Secondary (due to an underlying disorder); may be also classified as neuropathy, myopathy or mesenchymopathy – Collagen vascular diseases: primary systemic sclerosis, systemic lupus erythematosus, dermatomyositis/polymyositis, periarteritis nodosa, rheumatoid arthritis, mixed connective tissue disorders, Ehlers-Danlos syndrome – Endocrine disorders: diabetes, hypothyroidism, hypoparathyroidism, hyperparathyroidism – Neurologic disorders: Parkinson disease, Alzheimer disease, Shy-Drager syndrome, Chagas disease, Hirschsprung disease (intestinal hypoganglionosis), dysautonomia (familial or sporadic), Von Recklinghausen's disease – Medication associated: tricyclic antidepressants, anticholinergic agents, ganglionic blockers, anti-Parkinsonian agents, clonidine, phenothiazines – Paraneoplastic: central nervous system neoplasms, lung microcytoma, brochial carcinoid, leiomyosarcomas, carcinoid, thymoma – Miscellaneous: celiac disease, infiltrative disorders (amyloidosis, lymphoma), alcohol abuse, post-infectious processes (viral, bacterial, parasitic), radiation, vascular insufficiency, metabolic (hypokalaemia, hypomagnesemia), postsurgical, post–organ transplant, mitochondrial disorders
Mechanical obstruction	• Obturation (polypoid tumors, intussusception, gallstones, foreign bodies, bezoars, feces) • Intrinsic bowel lesions (stenosis or strictures: neoplastic, inflammatory bowel disease, chemical, anastomotic) • Extrinsic lesions (abdominal adhesions: previous surgery, previous peritonitis, frozen abdomen; hernias; neoplasia: desmoid tumors, peritoneal carcinomatosis; volvulus; congenital bands)
Extensive small bowel mucosal disease	• Microvillous inclusion disease (or microvillous atrophy) • Tufting enteropathy (or intestinal epithelial dysplasia) • Tricho-hepato-enteric syndrome (or syndromic diarrhoea or phenotypic diarrhoea) • Intractable diarrhea of infancy • Severe food allergy in children • Autoimmune enteropathy • Intestinal lymphangectasia • Waldman disease and other protein-losing enteropathies • Common variable immunodeficiency • Crohn's disease • Celiac disease • Radiation enteritis • Chemotherapy related enteritis • Congenital diseases (such as glucose-galactose malabsorption, congenital defects of glycosylation, primary bile acid malabsorption, chloride diarrhea, sodium diarrhoea)

A **short bowel** may be the result of extensive surgical resections or of congenital diseases of the small intestine (Table 5). In adults, normal small intestinal length, measured from the duodenojejunal flexure at autopsy or surgery, varies from about 275 cm to 850 cm [15,22,48]. The clinical feature associated with a remaining small bowel in continuity (even though the total small bowel length including that bypassed may be normal) of less than 200 cm is defined as short bowel syndrome (SBS) [15,22]. SBS has been reported to be the main cause of type III CIF, accounting for about 75% of adults and 50% of children on HPN in Europe [36].

The primary pathophysiological mechanism of IF in the patient with SBS is the reduced intestinal absorptive surface area (Table 4). The likelihood of developing an SBS-associated IF depends on the residual small bowel length in continuity and on several "concomitant pathophysiological mechanisms" related to the anatomy, integrity, function and adaptive potential of the small bowel remnant as well as to the underlying clinical condition [15,22,49]. The post-resection intestinal adaptation is a spontaneous process that attempts to ensure a more efficient absorption of nutrients per unit length of the remaining bowel [15,22]. This occurs partly by increasing the absorptive area (structural adaptation) and/or by slowing the gastrointestinal transit (functional adaptation). It is promoted by the presence of nutrients in the gut lumen, by the pancreatic and biliary secretions and by gut hormones mainly produced by the ileum and colon, and usually takes place over 1 or 2 years. Post-operative intestinal adaptation appears to be absent or impaired in the presence of an end-jejunostomy [15,22].

In adults, a high risk for developing IF due to inadequate length of small bowel in continuity has been reported when there is less than 35 cm small bowel with a jejunoileal anastomosis with an intact colon, less than 60 cm small bowel with a jejunocolic anastomosis or less than 115 cm small bowel with an end-jejunostomy [22]. Other mechanisms contributing to IF may be, excessive fluid and electrolyte intestinal losses in the presence of an end jejunostomy, restriction of oral nutrient intake in an attempt to decrease the intestinal losses, reduced oral intake because of underlying disease-related hypophagia and failure to develop the post-resection adaptive hyperphagia [22,49].

SBS-associated IF may be reversible because of the intestinal adaptation process and/or intestinal rehabilitation programs [4]

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based on medical and surgical tretments. The probability of weaning off HPN has been reported to be about 50% in adults and up to 73% in children. Complete weaning off HPN in patients with SBS is unlikely (<10%) to occur after 2–3 years have elapsed since the most recent intestinal resection [5,50,51].

Intestinal fistulas are abnormal communications between two parts of the gastrointestinal tract, between the gut and the other organs (eg the bladder), or between the gastrointestinal tract and the skin (enterocutaneous fistulas, EC) [10,34,35,52–54]. About 75–85% of EC fistulas form after surgery as a result of bowel injury, inadvertent enterotomy and/or anastomotic leakage, in the presence of malignancy or inflammatory bowel disease, and with attempted surgical division of dense adhesions. In the remaining 15–25%, EC fistulas form spontaneously secondary to underlying pathology, in particular Crohn's disease. Other causes include radiation enteritis, diverticular disease, malignancy, intra-abdominal sepsis and trauma. Anatomically, an EC fistula is identified by the segment of the gut from which it originates (eg, gastrocutaneous, enterocutaneous) (Table 5). EC fistulas are classified by their aetiology, anatomy and output volume. In general, a fistula with an output >500 mL/day in the fasting state is generally regarded as a high output fistula [55].

In EC fistulas, the enteric content is prematurely lost from the small bowel lumen. The primary mechanism of IF is the bypass of a large area of intestinal absorption surface [10,34,35,52–55], a condition resembling a short bowel (Table 4). The onset of an EC fistula is often an acute event, associated with intra-abdominal abscess collection, systemic sepsis and the related metabolic derangement, as well as with high intestinal fluid and electrolyte losses with the fistula effluent. Exposure of the skin around the fistula to the corrosive effect of the enteric content can lead to rapid tissue breakdown in this area and may be a major treatment challenge. Concomitant pathophysiological mechanisms contributing to EC fistula-associated IF may be the impairment of gastrointestinal motility and the metabolic alterations associated with systemic sepsis or intra-abdominal inflammation, the excessive intestinal losses of fluids and electrolytes, the disruption of the entero–hepatic cycle of bile acids, and the restricted or abolished ("bowel rest") oral/enteral nutrition to decrease the fistula output and/or to favor spontaneous fistula closure.

In adults, EC fistulas are among the most common causes of type II, prolonged acute IF. Parenteral nutrition has a key role in the early days of treatment, often characterized by metabolic instability. When metabolic stability has been achieved, nutrition support through fistuloclysis [56] or re-feeding enteroclysis [57] may be attempted, when a double enterostomy is present. In this case there are a proximal stoma representing the EC fistula or a surgically placed transient enterostomy and a distal stoma representing the intestine segment totally excluded from the chime transit. Fistuloclysis is a method of enteral nutrition through the intestine distal to the fistula. Re-feeding enteroclysis consists in chyme collection from the proximal stoma and re-infusion down the distal stoma. Fistuloclysis and re-feeding enteroclysis may allow weaning off parenteral nutrition and intravenous electrolyte supplementation [56,57]. As a consequence the underlying intestinal derangement passes from IF to intestinal insufficiency/deficiency. Nevertheless, EC fistulas account for about 2% of patients with reversible type III IF, requiring intravenous supplementation in hospital or at home for a period of 3–12 months before undergoing planned reconstructive surgery [36].

The term **intestinal dysmotility** is used to indicate the presence of disorders of the propulsion of the gut content in the absence of fixed occluding lesions. It may be loco-regional, affecting only one bowel segment, as in achalasia, gastroparesis, colonic obstruction and Hirschprungs' disease, or multi-regional, involving more than one part of the GI tract, especially the small bowel. Acute intestinal dysmotility is the primary pathophysiological cause of type I IF due to post-operative or acute critical illness associated ileus, and a frequent concomitant cause of type II IF, due to the impaired gastrointestinal motility associated with systemic or intra-abdominal inflammation. Permanent intestinal dysmotility is termed chronic intestinal pseudo-obstruction (CIPO), where the modifier "pseudo" is used to underline the absence of occluding lesions [58–60].

CIPO may be congenital or acquired (Table 5). Congenital disorders can be sporadic or familial. Acquired forms can be secondary to a variety of insults, such as infections, autoimmune processes, mitochondrial dysfunction, and side effects of medications. However in the majority of cases, CIPO is an idiopathic disorder of unknown aetiology. Acquired forms are more prevalent in adults, while congenital forms predominate in children. Whatever the underlying cause, CIPO can be subdivided histologically into 3 categories: neuropathies (involving the enteric nervous system and/or the autonomic nervous system, either the sympathetic or parasympathetic), myopathies (involving the smooth muscle), or mesenchymopathies (involving the interstitial cells of Cajal). Some patients may have other coexisting pathology [58–60].

In intestinal dysmotility, the primary pathophysiological mechanism is intolerance to oral or enteral nutrition resulting in inadequate nutritional intake. The mucosal surface is generally intact (Table 4). "Secondary pathophysiological mechanisms" include nutrient malabsorption due to small bowel bacterial overgrowth, and increased intestinal secretion and/or losses of fluids and electrolytes, occurring in the dilated bowel segments, or after intestinal resection and venting or end-ostomy performed to relieve symptoms. CIPO-associated IF represents approximately 20% of both adults and children on HPN for type III chronic IF [36]. The reversibility of IF in patients with CIPO is lower than that reported in SBS, having been reported in 25–50% in adults and 25–38% in children, with a 78% 5 year survival probability for adults on HPN [5,51,61].

Mechanical obstruction of the intestinal lumen results from a physical abnormality affecting the intestine, which may be intraluminal, intrinsic or extrinsic, of benign or malignant origin (Table 5). It may be an acute event encompassing a feature of type I IF, that resolves in a few days through conservative medical treatment or a surgical procedure. It may also be a prolonged feature, determining a type II or III IF, as in patients with extensive adhesions ("frozen abdomen"), or in those with peritoneal carcinomatosis associated with late-stage intra-abdominal malignancy. The primary pathophysiological mechanism of IF in obstruction is the spontaneous or prescribed ("bowel rest") abolished oral or enteral nutrition (Table 4). Secondary mechanisms include the increased intestinal secretion of fluids and electrolytes in the obstructed segment, and increased intestinal losses of fluids and electrolytes with vomiting or naso-gastric drainage.

Extensive small bowel mucosal disease indicates a condition characterized by an intact or almost intact, although inefficient, mucosal surface [3,5,17] (Table 5). The reduction of nutrient absorption and/or the loss of nutrients through the intestinal mucosa to the point where the body's requirements are no longer met, are the most frequent primary mechanisms of IF (Table 4). Rarely, increased intestinal secretion of fluids and electrolytes can be present as a concomitant mechanism. The most frequent diseases causing extensive mucosal damage are reported in Table 5. Extensive small bowel mucosal disease has been reported to be the cause of CIF in about 25% of children and 5% of adult patients on long term HPN. In adults with type III IF due to extensive mucosal disease, weaning from HPN rarely occurs [5,51].

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3.4. Clinical classification of chronic intestinal failure

On the basis of the requirements for energy and the volume of the intravenous supplementation, IF can be categorized into 16 subtypes

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

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

The panel discussed the need for and the feasibility of a severity classification of IF, as for failure of the other organs. Unfortunately, there are no simple indicators of the degree of intestinal absorption and/or metabolic balance. Therefore, a "general classification of the severity of IF" could not be devised. In addition, the severity of the clinical picture of the individual patient can be influenced by a number of extra-intestinal factors, including the metabolic–inflammatory reaction, nutritional compromise, abdominal and systemic lesions and symptoms, the response to treatments, as well as psycho-social factors. Therefore, a severity classification should be defined for each individual functional and/or pathophysiological cause of IF, as already described for EC fistulas [34,52–54], SBS [15,23,62] and CIPO [58–60].

However, the panel agreed on the need for a "clinical classification" of IF, aiming to facilitate communication and cooperation among professionals through a more objective categorization of patients, to be used in clinical practice, management/administrative organization, epidemiological surveys and clinical research. Considering that no published data were available to be used as a starting point, the development of a "clinical classification" was based on the common experience of the panel of experts. Furthermore, because of the already mentioned difficulty in summating the many variables that could play a role in the individual patient, the panel decided to devise a clinical classification only for type III CIF, because of the greater metabolic stability and the longer duration of this condition than expected in types I and II IF.

Starting from the given definition of IF, the panel reached a consensus on a "clinical classification of chronic IF" based on the intravenous "energy and volume" requirements. As it is not truly a severity classification, the panel emphasize that this has no implication in the level of optimization of care required by the patients, which must be the same for all the patients regardless of their classification.

Table 6 reports the results of the cross sectional investigation on two samples of randomly selected patients, currently on HPN for type III CIF due to either benign or active malignant disease, which aimed to verify the applicability of the clinical classification. As expected, almost all the categories were represented, with the exception of the rather unusual, though not improbable, requirements of high volume of fluid and electrolytes with no or minimal energy (categories B4 and A2-A4). The range of the patient distribution within the categories of the "clinical classification" was wider in CIF for benign disease than in CIF for active cancer. This was in agreement with the different causes, clinical features and expected outcomes of the two patient populations. Patients with benign disease have greater variability in the pathophysiological causes of IF and of activity-related energy expenditure, the last being dependent on the degree of physical rehabilitation. In patients with active cancer, intestinal dysmotility or mechanical obstruction due to the cancer are the most frequent causes of the IF, and physical activity is often limited to a chair-to-bed life. Allowing a simple and easy-to-do categorization of patients with CIF, the proposed "clinical classification" should facilitate communication and cooperation among professionals. The panel recognizes the need for prospective studies to investigate its potential prognostic value.

Table 6
Clinical classification of adult patients on home parenteral nutrition for chronic intestinal failure due to benign disease (a) or to active cancer (b).

IV energy supplementation[b] (kcal/kg Body Weight)	Volume of the IV supplementation[a] (ml)			
	≤ 1000 [1]	1001–2000 [2]	2001–3000 [3]	> 3000 [4]
a) Distribution of the patients with CIF due to benign disease (n = 114; mean age±standard deviation: 47.2 ± 15.5 years; pathophysiology of IF: short bowel 65, entero-cutaneous fistula 10, intestinal dysmotility 29, extensive small bowel mucosal disease 10)				
0 (A)	2			
1–10 (B)	6	4	2	
11–20 (C)	9	10	10	2
> 20 (D)	2	37	20	10
b) Distribution of the patients with CIF due to active cancer (n = 50; mean age±standard deviation: 62.4 ± 12.6 years; pathophysiology of IF: mechanical occlusion 39; intestinal dysmotility, 11)				
0 (A)				
1–10 (B)	5			
11–20 (C)	12	6		
>20 (D)	3	21	3	

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

4. Conclusions

IF is a well recognized organ failure, but no formal definition and classification of IF had been devised before. These ESPEN endorsed recommendations on "definition and classification of IF in adults" (Table 3) aims to facilitate communication and cooperation among professionals in clinical practice, organization, management and research.

Contributors and authorship

All Authors have materially participated in the conception of the position paper and in the Dephi rounds, live meetings and manuscript revisions needed to devise the article. All Authors have approved the final version of the article.

Conflict of interest

None declared.

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