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Original article

Clinical classification of adult patients with chronic intestinal failure due to benign disease: An international multicenter cross-sectional survey

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SUMMARY

Background & aims: The aim of the study was to evaluate the applicability of the ESPEN 16-category clinical classification of chronic intestinal failure, based on patients' intravenous supplementation (IVS) requirements for energy and fluids, and to evaluate factors associated with those requirements.
Methods: ESPEN members were invited to participate through ESPEN Council representatives. Participating centers enrolled adult patients requiring home parenteral nutrition for chronic intestinal failure on March 1st 2015. The following patient data were recorded though a structured database: sex, age, body weight and height, intestinal failure mechanism, underlying disease, IVS volume and energy need.
Results: Sixty-five centers from 22 countries enrolled 2919 patients with benign disease. One half of the patients were distributed in 3 categories of the ESPEN clinical classification. 9% of patients required only fluid and electrolyte supplementation. IVS requirement varied considerably according to the pathophysiological mechanism of intestinal failure. Notably, IVS volume requirement represented loss of intestinal function better than IVS energy requirement. A simplified 8 category classification of chronic intestinal failure was devised, based on two types of IVS (either fluid and electrolyte alone or parenteral nutrition admixture containing energy) and four categories of volume.
Conclusions: Patients' IVS requirements varied widely, supporting the need for a tool to homogenize patient categorization. This study has devised a novel, simplified eight category IVS classification for chronic intestinal failure that will prove useful in both the clinical and research setting when applied together with the underlying pathophysiological mechanism of the patient's intestinal failure.

1. Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) recently devised recommendations on the "definition and classification of intestinal failure in adults" [1]. Intestinal failure (IF) was defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth". On the basis of onset, metabolic and expected outcome criteria,

the functional classification identified three types of IF: type I-acute, type II-prolonged acute, and type III-chronic IF (CIF). The "pathophysiological classification" categorized IF into five major mechanisms: short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction and extensive small bowel mucosal disease.

The "clinical classification" of CIF was derived from the common experience of the panel of experts, because no systematic published data were available. Published individual and multicenter series on CIF categorize patient populations in a number of different ways [2,3]. The lack of any systematic categorization of CIF clearly confounds our ability to compare data between IF centers. The ESPEN panel therefore reached a consensus for a classification based on patients' requirements for energy and volume of IVS; sixteen categories were identified (Table 1). A pilot evaluation in two centers, one for patients with CIF due to benign disease and one for patients with CIF due to a cancer, supported its potential applicability [1].

The clinical classification of CIF was intended as an instrument to facilitate communication among professionals through the objective categorization of patients with CIF for ready use in day-to-day clinical practice, as well in the research setting. An international cross-sectional survey was carried out to investigate the applicability of the classification and to evaluate factors associated with the IVS requirements of individual patients. As the previous pilot study suggested that the distribution of patients categorized using the CIF classification differed according to whether their primary underlying condition leading to CIF was benign or malignant, data on patients with benign or malignant disease were analyzed separately; the present paper only details the data of those patients with CIF due to benign disease.

2. Material and methods

This was an international cross-sectional observational study approved by the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF) special interest group of ESPEN [4].

2.1. Participating center recruitment

Invitation to participate in the study occurred via representatives of the national Parenteral and Enteral Nutrition (PEN) Societies of the ESPEN Council, who were asked to send the study protocol to members of their PEN societies. Clinical units caring for patients requiring HPN (HPN centers) expressing an interest in participating were then sent the protocol study, the study database and the instructions for data collection by the study coordinator (L.P.).

Table 1
ESPEN clinical classification of chronic intestinal failure.

IV energy supplementation[b] (kcal/kg body weight/day)	IV volume supplementation[a] (mL/day)			
	≤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

IV, intravenous.
[a] Calculated as daily mean of the total volume infused per week = (volume per day of infusion × number of infusions per week)/7.
[b] Calculated as daily mean of the total energy infused per week = (energy per day of infusion × number of infusions per week)/7/kg body weight.

2.2. Patient inclusion criteria

HPN centers were required to enroll all adult patients (≥18 year old) who were on HPN for CIF on March 1st 2015. Patients with benign and malignant disease were admitted into the study; the terms "benign CIF" and "cancer CIF" were respectively used to define the absence or presence of an active malignant underlying disease as the direct cause of IF. Invasive intra-abdominal desmoid disease was included in the benign group, because of the chronic nature of the condition and reflecting the fact that it is an established indication for intestinal transplantation [5].

2.3. Data collection and schedule

Data were collected into a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database. The following items were gathered: age and gender; body weight and height; underlying disease and its benign or malignant nature; pathophysiological mechanism of CIF; characteristics of the HPN program (duration, provider, number of days of infusion per week, type of parenteral nutrition admixture, IVS volume and energy for each day of infusion). Short bowel syndrome (SBS) was categorized into three recognized types [1,5]: end jejunostomy (SBS-J), jejuno-colonic anastomosis with part of the colon in continuity (SBS-JC) and jejuno-ileal anastomosis with ileo-cecal valve and the entire colon in continuity (SBS-JIC). Patients with an ileostomy were included in the SBS-J group. HPN centers were required to include all patients receiving HPN on March 1st 2015 and to complete the database with relevant data, as sourced from the patients' clinical records on that date.

The deadline to return completed datasets to the study coordinator was May 15th. An extended deadline to June 30th was allowed for some HPN centers with large patient cohorts. As noted above, this paper will report data solely on patients with benign CIF.

2.4. Ethical statement

The research was based on anonymized information taken from patient records at time of data collection. The study was conducted with full regard to confidentiality of the individual patient. Ethical committee approval was obtained by the individual HPN centers according to local regulations. The collected data were used only for the study purpose. Contributing centers have been anonymized for data analysis and presentation.

2.5. Statistical analysis

The daily mean volume and energy of IVS were calculated as follows: daily total volume (mL/day) or energy (kcal/day) = amount per day of infusion × number of infusions per week/7; daily volume or energy per kg of patient body weight (mL/kgBW/day or kcal/kgBW/day) = amount per day of infusion × number of infusions per week)/7/kg patient body weight. The patients' body mass index (BMI) was calculated by Quetelet's formula (weight (kg)/height (m^2).

Data are reported as mean ± standard deviation (SD) and as absolute and relative frequencies. Non-parametric tests were applied where appropriate: Kruskal Wallis test and Spearman's rank correlation. The strength of Spearman's correlation was considered moderate when the r_s value was 0.5–0.7 and high when it was >0.7 [6]. In addition, two multi-way analyses of covariance (ANCOVA) were applied in order to identify factors independently related to IVS volume and energy requirements. In order to avoid multiple comparisons, the simple contrast was used in the ANCOVAs for testing pairs of pathophysiological mechanisms.

The IBM SSPS Statistics package for Windows, version 23.0 (BM Co., Armonk, NY, USA) was used for the analyses. Two-tailed P values less than 0.05 were considered as statistically significant.

3. Results

3.1. Participating centers and enrolled patients

Sixty-five HPN centers from 22 countries participated in the study, enrolling 3362 patients. The number of enrolled patients per center ranged from 1 to 259. The year of starting the HPN activity in the individual center ranged from 1970 to 2013. One hundred and twenty-three patients (3.7%) were excluded from the statistical analysis, because: date of starting HPN occurred after March 1st 2015; age <18 years; missing body weight; missing IVS volume and/or energy; missing definition of benign or cancer CIF status. Three hundred and twenty of the 3239 (9.9%) patients had a diagnosis of cancer CIF. Table 2 demonstrates the distribution of the 2919 patients with benign CIF included in the analysis and stratified according to country of origin; most patients (79.9%) were from European countries, the remainder were from the USA, Israel, South and Central America and Oceania.

3.2. Analysis of patients with chronic intestinal failure due to benign disease

3.2.1. Patient characteristics

The 2919 patients with benign CIF included 1844 females (63.2%). The mean age was 54.9 ± 16.0 years (median 56.0; range: 18.0–98.0). The mean patient BMI was 22.2 ± 4.4 kg/m^2 (median 21.8; range: 10.5–59.6). The number of patients in the BMI categories was: ≤15.0 kg/m^2, n. 70 (2.4%); 15.1–18.5 kg/m^2, n. 439 (15.1%); 18.6–25.0 kg/m^2, n. 1757 (60.3%); 25.1–30.0 kg/m^2, n. 493 (16.9%); >30.0 kg/m^2, n. 153 (5.3%). In particular, 4 patients had BMI <12.0 kg/m^2, 26 had BMI between 12.1 and 14.0 kg/m^2, while 10 patients had BMI between 40.0 and 50.0 kg/m^2 and one patient had BMI >50 kg/m^2. The mean duration of HPN was 58.1 ± 71.5 months (median 33.0; range: 0–474). The number of patients in the HPN duration categories was: ≤12 months, n. 767 (26.4%); 13–36 months, n. 762 (26.2%); 37–120 months, n. 987 (34.0%); >120 months, n. 391 (13.4%).

Table 2
Contributing home parenteral nutrition (HPN) centers and patients with chronic intestinal failure due to benign disease grouped by country of origin.

Country	HPN centers	Patients
UK	10	738 (25.28%)
France	6	441 (15.11%)
Italy	8	326 (11.17%)
Denmark	2	233 (7.98%)
Netherlands	2	229 (7.85%)
Poland	5	224 (7.67%)
Spain	9	40 (1.37%)
Slovenia	1	31 (1.06%)
Sweden	1	24 (0.82%)
Belgium	1	21 (0.72%)
Hungary	4	20 (0.69%)
Bulgaria	1	4 (0.14%)
Croatia	1	3 (0.10%)
Lithuania	1	2 (0.07%)
Germany	1	1 (0.03%)
USA	3	389 (13.33%)
Israel	1	71 (2.43%)
Argentina	1	44 (1.51%)
Brasil	1	7 (0.24%)
Mexico	1	3 (0.10%)
Australia	4	41 (1.40%)
New Zealand	1	27 (0.92%)
Total		2919 (100%)

3.2.2. Pathophysiology of intestinal failure and underlying diseases

SBS was the most frequent pathophysiological mechanism of CIF (64.3% of patients), mostly with an end jejunostomy. Intestinal dysmotility was present in 17.5% of cases. The frequency of intestinal fistulas, mechanical obstruction and extensive mucosal disease ranged from 4.4 to 7.0% (Fig. 1). The most frequent underlying disease was Crohn's disease (22.4%), followed by mesenteric ischemia, surgical complications, chronic intestinal pseudo-obstruction (CIPO) and radiation enteritis (Table 3).

3.2.3. Distribution of patients according to the ESPEN clinical classification of CIF

The mean daily IVS volume and energy requirements were 1877 ± 1016 (range: 82–7543) mL/day and 1088 ± 649 (range: 0–3400) kcal/day, respectively. The mean IVS requirements per kg body weight were 31.5 ± 17.8 (range: 0.9–142.2) mL/kgBW/day and 18.7 ± 11.9 (range: 0.0–74.7) kcal/kg BW/day. The days of IVS per week were <4 in 295 (11.0%), 4 to 6 in 770 (28.8%) and 7 in 1609 (60.2%) patients.

Figure 2 shows patient distribution across all the 16 categories of the clinical classification. Three categories showed the highest frequencies and comprised half of the total group: >20 kcal/kg/day and 1001–2000 mL/day (20.7%), >20 kcal/kg/day and 2001–3000 mL/day (15.7%), 11–20 kcal/kg/day and 1001–2000 mL/day (14.4%). Only 2.8% of patients were allocated into the “extreme” categories (low or no energy with high volume or high energy with low volume): 0 kcal/kg/day and 1001–2000 mL/day (5.8%), >20 kcal/kg/day and ≤1000 mL/day (1.1%), 1–10 kcal/kg/day and >3000 mL/day (0.8%), 0 kcal/kg/day and >3000 mL/day (0.3%). A total of 8.7% of patients received only fluid and electrolyte IVS.

3.2.4. IVS volume and energy requirements according to age, BMI, duration of HPN and pathophysiological mechanism

Univariate analysis demonstrated that total daily IVS volume (mL/day) was associated with patient age (progressive decrease of the volume with the increase of age category), duration of HPN (highest volume in the earliest and in the latest period) and pathophysiological mechanism, but not with patient BMI; total daily IVS energy (kcal/day) was associated with all variables, with a progressive decrease of energy with the increase of BMI category. Furthermore, when daily volume and energy were adjusted for body weight, an association with all variables was demonstrated (Table 4).

In order to better elucidate which factors were independently related to IVS volume and energy requirements in the individual patient, a multivariate analysis was performed, considering the daily total amounts (mL/day or kcal/day) as dependent variables and patient age, patient BMI, duration of HPN and IF pathophysiological mechanism as independent variables. The results are shown in Table 5. Both daily total volume and total energy were dependent on IF pathophysiological mechanism and were negatively associated with patient age. Daily total energy was negatively associated with patient BMI. Daily IVS volume was positively associated with duration of HPN.

The results of the analysis comparing the IVS requirements among pairs of the pathophysiological mechanism cohorts, adjusted for patient age and BMI and HPN duration, are shown in Fig. 3. Daily total IVS volume was significantly associated with the underlying pathophysiological mechanism of CIF: it significantly decreased from SBS-J to SBS-JC to SBS-JIC; patients with SBS-J and the fistula groups showed the highest volume requirements, which were similar between these two groups; the dysmotility and mechanical

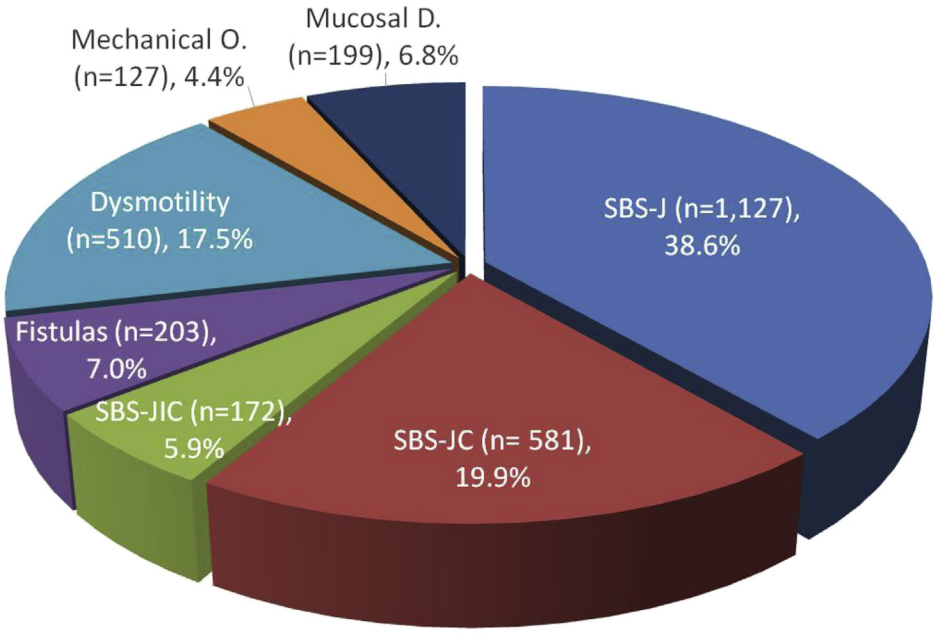


Fig. 1. Pathophysiological mechanism of intestinal failure in adult patients with chronic intestinal failure due to benign disease (n = 2919). SBS-J, short bowel syndrome with an end jejunostomy; SBS-JC, SBS with a jejuno-colonic anastomosis with part of the colon in continuity; SBS-JIC, SBS with jejuno-ileal anastomosis with ileo-cecal valve and the entire colon in continuity. Mechanical O, mechanical obstruction; Mucosal D, extensive small bowel mucosal disease. 40 patients (3.5%) of the SBS-J group had a high output ileostomy.

obstruction cohorts showed similar volume requirements, as did the mucosal disease, the SBS-JC and the SBS-JIC cohorts. Daily total energy provision was more homogeneous: no differences were observed amongst the SBS and mucosal disease cohorts, or amongst the fistula, dysmotility and mechanical obstruction cohorts.

3.2.5. *Correlations between IVS volume and energy requirements in the total group and in the pathophysiological cohorts*

The strength of the correlation between the daily IVS total volume and energy requirements was moderate in the whole population (r_s = 0.604) and in the SBS-J (r_s = 0.598), fistula (r_s = 0.507) and dysmotility (r_s = 0.666) pathophysiological mechanism cohorts, and high in the SBS-JC (r_s = 0.706), SBS-JIC (r_s = 0.757), mechanical obstruction (r_s = 0.702) and mucosal disease (r_s = 0.718) cohorts (Fig. 4).

Table 3
Primary underlying disease in adult patients with chronic intestinal failure due to benign disease (n = 2919).

Disease	No.
Crohn's disease	653 (22.4%)
Mesenteric ischemia	517 (17.7%
Surgical complications	460 (15.8%)
Primary CIPO	283 (9.7%)
Radiation enteritis	212 (7.3%)
Secondary CIPO	86 (2.9%)
Adhesion	84 (2.9%)
Volvulus	71 (2.4%)
Collagenous	53 (1.8%)
Cancer[a]	41 (1.4%)
Trauma	33 (1.1%)
Ulcerative colitis	26 (0.9%)
Desmoid	22 (0.8%)
Intestinal polyposis	23 (0.8%)
Autoimmune enteropathy	17 (0.6%)
Malformation	15 (0.5%)
Neurological disease	15 (0.5%)
Congenital mucosal disease	15 (0.5%)
CVID	12 (0.4%)
Celiac disease	10 (0.3%)
Other	98 (3.4%)
Not reported	173 (5.9%)

CIPO, chronic intestinal pseudo-obstruction.
CVID, common variable immune deficiency.
[a] Cured cancer, no active malignant disease at time of inclusion in the study.

3.2.6. *Revision of the clinical classification of chronic intestinal failure due to benign disease*

Statistical analysis demonstrated that: a) half of the patients were concentrated in 3 of the 16 categories of the ESPEN classification of CIF and half were spread amongst the other 13 categories; b) around 9% of patients were receiving only fluid and electrolyte IVS; c) both IVS volume and energy were associated with the pathophysiological mechanism of IF and d) IVS energy rather than IVS volume was associated with the patient's BMI. Considering these findings, a simplified classification of CIF based on two categories of IVS type: fluid and electrolyte alone or parenteral nutrition admixture containing macronutrients; and four categories of volume was devised (Table 6).

Figure 5 shows the distribution of the patients of the CIF pathophysiological mechanism cohorts according to the revised classification. The need for fluid and electrolyte alone was more frequent in the SBS-J and fistulas cohorts. Looking at SBS types, the frequency of IVS volume ≤1000 mL/day increased and that of >3000 mL/day decreased passing from those with a SBS-J to those with the SBS-JIC. Similar patterns were observed between the SBS-J and fistulas cohorts, between the dysmotility and mechanical obstruction cohorts and between the SBS-JC and the extensive mucosal disease groups.

4. Discussion

The results of this multicenter international survey demonstrate the high variability of IVS volume and energy requirements of patients with CIF due to benign disease, and highlight the important influence of the pathophysiological mechanism of CIF on those requirements. The data further suggest that IVS volume

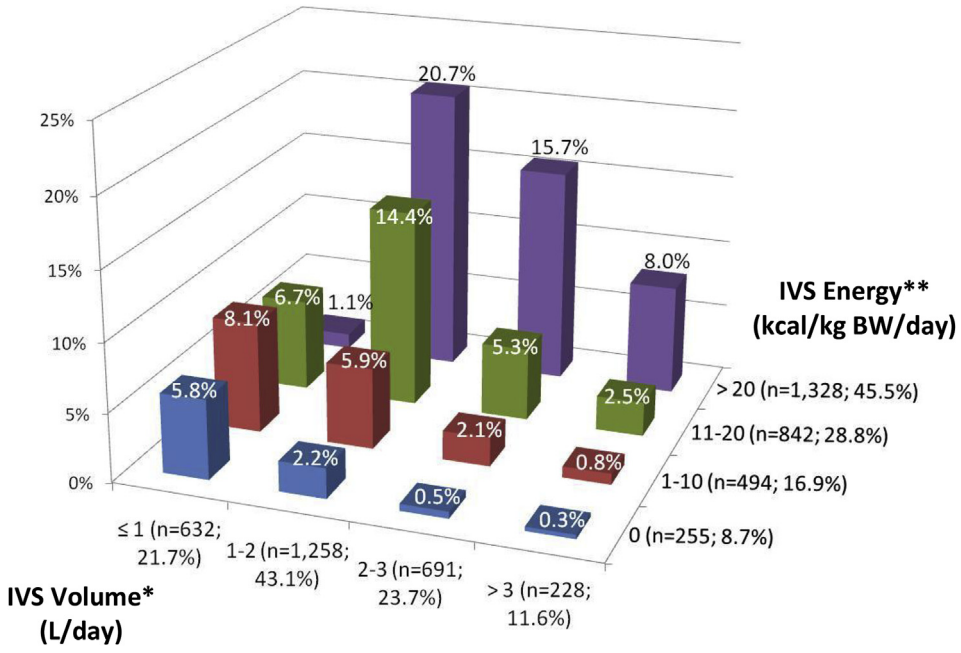


Fig. 2. Distribution of adult patients on home parenteral nutrition due to benign disease into the ESPEN clinical classification categories of chronic intestinal failure. *Volume of the intravenous supplementation, calculated as daily mean of the total volume infused per week = (volume per day of infusion × number of infusions per week)/7. **Energy of the intravenous supplementation, calculated as daily mean of the total energy infused per week = (energy per day of infusion × number of infusions per week)/7/kg body weight.

Table 4
Univariate analysis of the volume and the energy of the intravenous supplementation (IVS) by body mass index (BMI), duration of the home parenteral nutrition (HPN), and the pathophysiological mechanism of intestinal failure (IF). Data as mean ± standard deviation.

	Volume of the IVS		Energy of the IVS	
	mL/day	mL/kg BW/day	kcal/day	kcal/kg BW/day
Age (year)				
≤29 (n = 234)	2005 ± 1036	37.9 ± 20.7	1376 ± 646	26.1 ± 12.6
30–49 (n = 793)	2021 ± 1059	34.1 ± 19.2	1204 ± 651	20.7 ± 12.2
50–69 (n = 1310)	1848 ± 1026	30.2 ± 17.0	1032 ± 638	17.3 ± 11.2
≥70 (n = 578)	1693 ± 889	28.3 ± 15.5	939 ± 611	16.0 ± 11.0
P value	<0.001	<0.001	<0.001	<0.001
BMI (kg/m^2)				
≤15.0 (n = 70)	1822 ± 831	48.4 ± 22.4	1334 ± 491	35.2 ± 12.9
15.1–18.5 (n = 439)	1751 ± 963	37.1 ± 20.1	1207 ± 609	25.6 ± 12.9
18.6–25.0 (n = 1757)	1893 ± 1.021	31.8 ± 17.3	1132 ± 643	19.0 ± 10.8
25.1–30.0 (n = 493)	1946 ± 1.051	26.3 ± 14.1	911 ± 643	12.3 ± 8.6
>30.0 (n = 153)	1842 ± 1.039	20.5 ± 12.0	691 ± 650	7.8 ± 7.3
P value	0.068	<0.001	<0.001	<0.001
HPN duration (year)				
≤1 (n = 767)	1897 ± 929	32.0 ± 17.1	1195 ± 621	20.4 ± 11.5
1.1–3 (n = 762)	1857 ± 991	30.6 ± 17.1	1034 ± 636	17.5 ± 11.4
3.1–10 (n = 987)	1823 ± 1063	30.8 ± 18.4	1028 ± 662	17.9 ± 12.3
>10 (n = 391)	1997 ± 1086	34.1 ± 19.2	1134 ± 658	19.7 ± 12.1
P value	0.002	0.001	<0.001	<0.001
Pathophysiological mechanism of CIF				
SBS-J (n = 1127)	2174 ± 1154	35.6 ± 20.6	994 ± 686	16.6 ± 12.2
SBS-JC (n = 581)	1603 ± 888	26.8 ± 14.8	1038 ± 589	17.5 ± 10.3
SBS-JIC (n = 172)	1395 ± 832	22.9 ± 12.5	1021 ± 610	17.2 ± 10.0
Fistulas (n = 203)	2039 ± 928	33.0 ± 17.6	1216 ± 668	20.1 ± 11.9
Dysmotility (n = 510)	1773 ± 829	31.2 ± 14.9	1289 ± 608	23.2 ± 12.0
Mechanical O. (n = 127)	1889 ± 865	33.5 ± 14.9	1235 ± 579	22.4 ± 11.1
Mucosal D. (n = 199)	1502 ± 707	27.6 ± 15.4	1078 ± 611	20.0 ± 12.4
P value	<0.001	<0.001	<0.001	<0.001

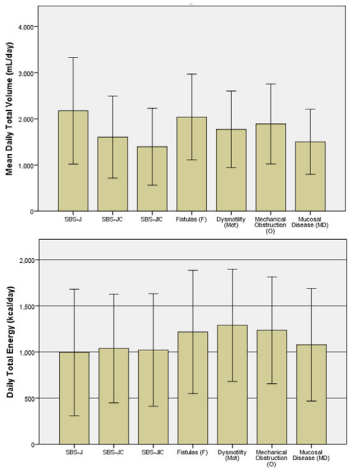
Mechanical O.: mechanical obstruction; Mucosal D.: extensive small bowel mucosal disease.

requirement reflects loss of intestinal function better than energy requirement and suggest a simplified revision of the former 16 category clinical classification of CIF proposed by ESPEN for use in the clinical and research setting. The strength of this study relies on its multicenter and international nature and the size of the patient population included; indeed, this represents the largest cohort of patients with CIF ever investigated. This avoids statistical bias associated with small patient cohorts and reduces the potential bias associated with data from single centers, where the inclusion of patients with malignant disease, as well as differences intrinsic to local and national clinical practice may influence the conclusions drawn [2,3,7,8]. The weakness of the study may pertain to the use of

Table 5
Multivariate analysis of factors associated with the intravenous supplementation daily total volume and daily total energy of patients with chronic intestinal failure due to benign disease.

Dependent variable	Independent variables	ANCOVA	
		Coeff b	P
Daily total volume (mL/day)	Age	−9.176	<0.001
	BMI	8.170	0.050
	Duration of HPN	0.621	0.016
	Pathophysiological mechanism	–	<0.001
Daily total energy (kcal/day)	Age	−6.352	<0.001
	BMI	−26.410	<0.001
	Duration of HPN	0.668	0.070
	Pathophysiological mechanism	–	<0.001

BMI, body mass index.
HPN, home parenteral nutrition.



Daily total volume

	SBS-JC	SBS-JIC	Fistulas	Dysmotility	Mechanical O.	Mucosal D.
SBS-J	<0.001	<0.001	0.134	<0.001	0.002	0.000
SBS-JC		0.004	<0.001	0.061	0.003	0.139
SBS-JIC			<0.001	<0.001	<0.001	0.226
Fistulas				<0.001	0.131	<0.001
Dysmotility					0.073	0.004
Mechanical O.						<0.001

Daily total energy

	SBS-JC	SBS-JIC	Fistulas	Dysmotility	Mechanical O.	Mucosal D.
SBS-J	0.391	0.817	<0.001	<0.001	0.001	0.817
SBS-JC		0.470	<0.001	<0.001	0.008	0.750
SBS-JIC			<0.001	<0.001	0.006	0.725
Fistulas				0.288	0.387	<0.001
Dysmotility					0.930	<0.001
Mechanical O.						0.011

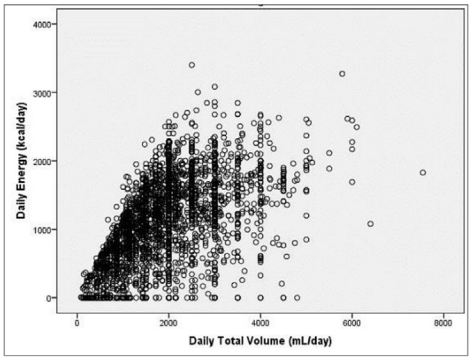
Fig. 3. Intravenous supplementation daily total volume and daily total energy requirements (mean ± SD) among pairs of the pathophysiological mechanisms of intestinal failure cohorts adjusted for patient age, body mass index (BMI) and duration of the home parenteral nutrition (HPN) of patients with chronic intestinal failure due to benign disease (Simple contrasts in ANCOVA). SBS-J, short bowel syndrome with an end jejunostomy; SBS-JC, SBS with a jejuno-colonic anastomosis with part of the colon in continuity; SBS-JIC, SBS with jejuno-ileal anastomosis with ileo-cecal valve and the entire colon in continuity; Mechanical O., Mechanical obstruction; Mucosal D., extensive small bowel mucosal disease.

IVS requirement as a surrogate marker of intestinal function; however, in the absence of an available indicator of the degree of intestinal dysfunction, such as creatinine and SaO_2 for renal or respiratory disease, respectively, IVS provides a readily available and clinically applicable marker. Furthermore, while metabolic balance study techniques, comparing nutrient requirement with nutrient absorption, may represent an optimal means to quantify intestinal failure in the individual patient, very few centers have the facilities for such complex metabolic studies [1]. Centers' participation in this study was on a voluntary basis. Therefore a wide range of experience and management of CIF and HPN was represented.

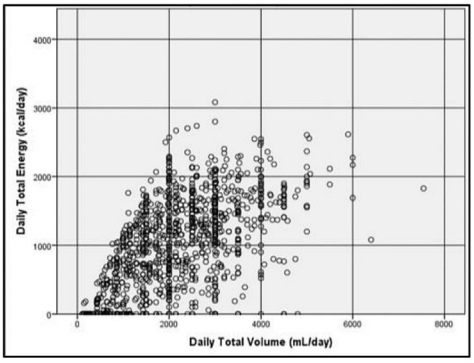
Short bowel syndrome was the most frequent pathophysiological mechanism of IF and Crohn's disease the most frequent underlying disease. Type 1 SBS-J was the most frequent type of SBS. Comparing such data from the present study with those from other individual or multicenter studies of patients with CIF may be hampered by the non-homogeneous patient inclusion criteria and associated clinical categorization adopted [9–20]. Indeed, many previous series have not necessarily distinguished between cancer and benign CIF cohorts, nor have they routinely distinguished pathophysiological mechanism from the underlying disease when detailing the indication for HPN. Short bowel syndrome has been noted to be the most frequent mechanism of CIF in other studies, ranging from 35 to 75% [9–20]; the breakdown of the SBS types has thus far only been reported by one HPN center, which demonstrated type 2 SBS-JC to be the most frequent type [14,19]. Crohn's disease has been reported to be the most frequent underlying disease in most [9,10,13,15–17] but not all surveys published to-date [11,12,14,18–20]. One recent report described a reduction over time of the rate of Crohn's disease as the underlying cause of CIF [20], with advances in medical therapy and/or surgical procedures considered as possible reasons [21]. Thus, the varied nature of previous publications support the potential usefulness of a systematic categorization of CIF to allow an appropriate comparison between centers.

Loss of intestinal function appeared more comprehensively represented by IVS volume requirement than by energy requirement. This was based on the following observations: a) the IVS volume requirements differed consistently with the underlying mechanism of CIF, whereas the energy requirements were more homogeneous; b) IVS energy, but not IVS volume, was statistically significantly associated with the patient's BMI; c) a proportion of patients required only IVS of fluids and electrolytes. It is noteworthy that among the three SBS types, IVS volume progressively decreased from the SBS-J to the SBS-JC and to the SBS-JIC types, but IVS energy requirement did not significantly differ. Furthermore, the strength of the correlations between the daily total IVS volume and energy was lower in those pathophysiological mechanism cohorts characterized by higher intestinal losses, such as SBS-J and

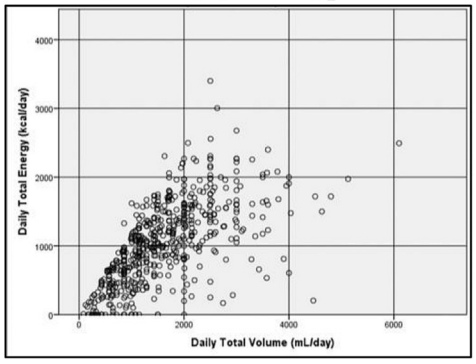
Total group, n=2,919; r_s=0.604; P<0.001



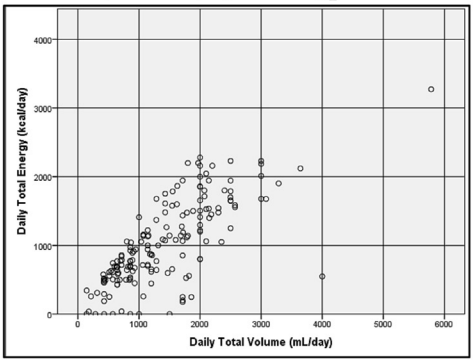
SBS-J, n=1,127; r_s=0.598, p<0.001



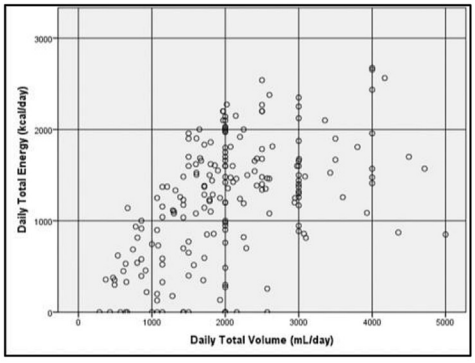
SBS-JC, n=581; r_s=0.706, p<0.001



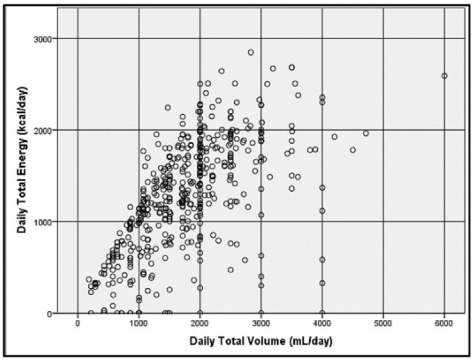
SBS-JIC, n=172; r_s=0.757, p<0.001



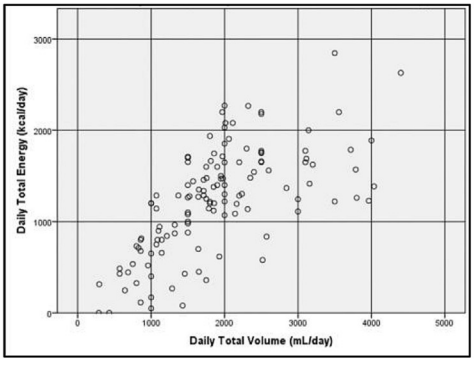
Fistulas, n=203; r_s=0.517, p<0.001



Dysmotility, n=510; r_s=0.666, p<0.001



Mechanical O., n.127; r_s=0.702, p<0.001



Mucosal D., n.199; r_s=0.718, p<0.001

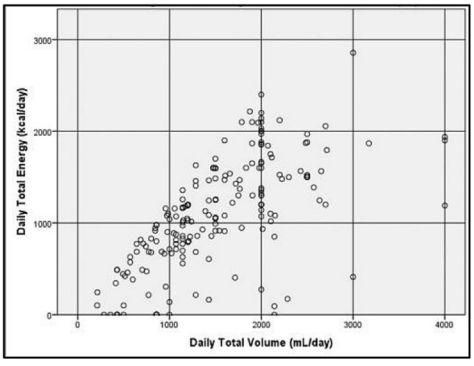
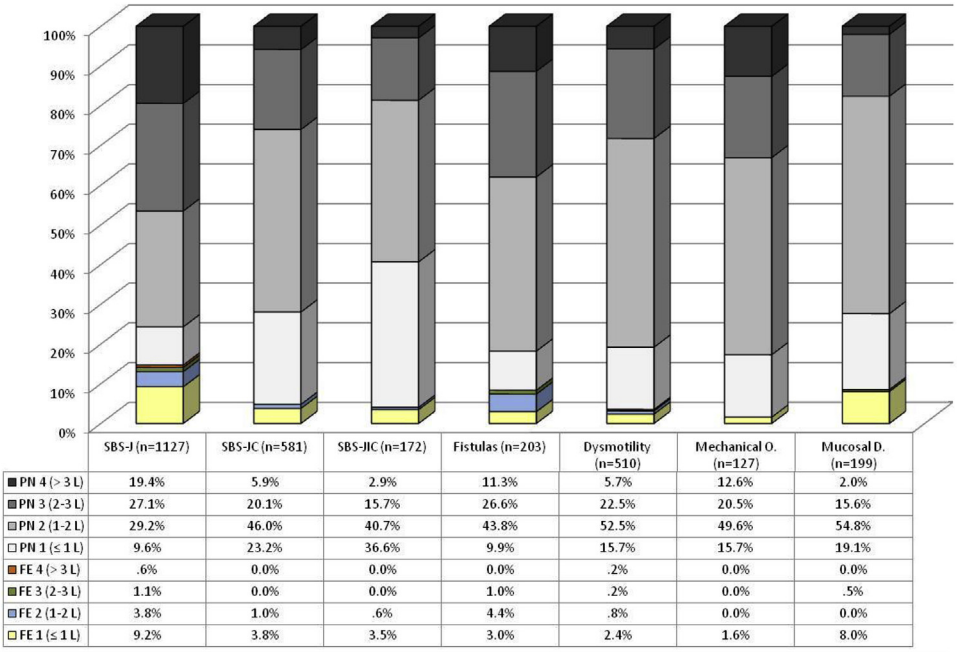


Fig. 4. Spearman rank correlations between daily total volume (mL/day) and daily total energy (kcal/day) of the intravenous supplementation in the total group and in the individual pathophysiological mechanism of intestinal failure cohorts of patients with chronic intestinal failure due to benign disease.

Table 6
Revised ESPEN clinical classification of chronic intestinal failure.

Type of the IVS	Volume of the IVS[a] 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

FE. Fluids and Electrolytes alone.
PN. Parenteral Nutrition Admixture containing also macronutrients.
[a] Calculated as daily mean of the total volume infused per week = volume per day of infusion × number of infusions per week/7.



	SBS-J (n=1127)	SBS-JC (n=581)	SBS-JIC (n=172)	Fistulas (n=203)	Dysmotility (n=510)	Mechanical O. (n=127)	Mucosal D. (n=199)
PN 4 (> 3 L)	19.4%	5.9%	2.9%	11.3%	5.7%	12.6%	2.0%
PN 3 (2-3 L)	27.1%	20.1%	15.7%	26.6%	22.5%	20.5%	15.6%
PN 2 (1-2 L)	29.2%	46.0%	40.7%	43.8%	52.5%	49.6%	54.8%
PN 1 (≤ 1 L)	9.6%	23.2%	36.6%	9.9%	15.7%	15.7%	19.1%
FE 4 (> 3 L)	.6%	0.0%	0.0%	0.0%	.2%	0.0%	0.0%
FE 3 (2-3 L)	1.1%	0.0%	0.0%	1.0%	.2%	0.0%	.5%
FE 2 (1-2 L)	3.8%	1.0%	.6%	4.4%	.8%	0.0%	0.0%
FE 1 (≤ 1 L)	9.2%	3.8%	3.5%	3.0%	2.4%	1.6%	8.0%

Fig. 5. Distribution of adult patients on home parenteral nutrition for chronic intestinal failure due to benign disease into the revised ESPEN clinical classification of chronic intestinal failure categories, according to the pathophysiological mechanism of intestinal failure. FE: fluids and electrolytes alone; PN: parenteral nutrition admixture containing also macronutrients. IVS: volume calculated as daily mean of the total volume infused per week = volume per day of infusion × number of infusions per week/7.

fistulas. Data from the literature also support this feature. Jeppesen and Mortensen clearly demonstrated that energy and wet weight absorption could not be correlated in the individual patient requiring HPN for CIF, and that IF was more accurately measured by wet weight absorption [22]; indeed, they described patients demonstrating an adequate energy absorption, but who required HPN because of reduced wet weight absorption. On the other hand, there were patients who had low energy absorption but did not require HPN because of compensatory hyperphagia [22]. The tighter association between the IVS volume requirement and intestinal function in CIF is also highlighted by the transient need of IVS fluid but not of energy replacement experienced by patients at risk of dehydration because of high intestinal losses [23].

On the basis of our findings, we have devised a simplified clinical classification of CIF, based on two categories of IVS type, either fluid and electrolyte alone or parenteral nutrition admixture with macronutrients, and four categories of daily total volume (Table 6). Furthermore, when describing a patient according to this classification, the underlying pathophysiological mechanism should also be reported because of the clear and clinically relevant correlations noted between the pathophysiological mechanism and IVS volume requirement (Fig. 5). Thus, our data suggest that patients with CIF should be described using three parameters: pathophysiological category, type of IVS and volume of the IVS. This revision of the ESPEN clinical classification of CIF should facilitate day-to-day clinical practice, and organization of centers' HPN programs as well as future research studies. An ESPEN-endorsed prospective study is ongoing to investigate its potential prognostic value as a criterion to estimate the probability of intestinal rehabilitation following medical and/or surgical treatments [5,24,25], as well as patient quality of life and the probability of social and working rehabilitation [26–28].

5. Conclusions

IVS requirements in CIF vary greatly from patient to patient, highlighting the need for an instrument to categorize patients for clinical and research practice in order to facilitate communication and cooperation amongst health care professionals. ESPEN devised a 16 category clinical classification, based on patients' IVS volume and energy requirements. The results of this international and multicenter cross-sectional survey aimed to evaluate the applicability of the ESPEN classification and has enabled the development of a simplified 8 category clinical classification of CIF, while also underscoring the importance of detailing the underlying

pathophysiological mechanism of IF when describing an individual patient with CIF.

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Statement of authorship

LP devised the study protocol, collected the data, analyzed the results and drafted the manuscript. The Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN discussed and approved the protocol study, discussed the results and reviewed the manuscript before submission. According to the authorship rules described in the protocol study, all the coordinators of the participating centers were considered coauthors of the study and received the manuscript upon submission. All authors approved the final version of the manuscript before submission.

Conflict of interest

None declared.

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