The intravenous support type and volume is associated with the outcome and the major complications in patients with chronic intestinal failure

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What is already known on this subject?

Previous studies have demonstrated that several clinical risk factors are associated with outcome and the risk of parenteral nutrition/intestinal failure-related major complications in patients on long-term home parenteral nutrition. However, no objective indicator has yet been identified to categorize the severity of chronic intestinal failure.

What are the new findings?

The one-year odds of death, major complications of parenteral nutrition/intestinal failure (liver disease and catheter-related blood stream infection), and of weaning from home parenteral nutrition are independently associated with the type and volume of the intravenous supplementation required.

How might it impact on clinical practice in the foreseeable future?

The type and the volume of the intravenous supplementation could be indicators to categorize the severity of chronic intestinal failure in clinical and research settings.

Abstract

Background and aim

No marker to categorize the severity of chronic intestinal failure (CIF) has yet been developed. A one-year international survey was carried out to investigate whether the European Society for Clinical Nutrition and Metabolism (ESPEN) clinical classification of CIF, based on the type and the volume of the intravenous supplementation (IVS), could be an indicator of CIF severity.

Methods

At baseline, participating home parenteral nutrition (HPN)-centers enrolled all adults with CIF due to non-malignant disease; demographic data, body mass index, CIF mechanism, underlying disease, HPN duration and IVS category were recorded for each patient. The type of IVS was classified as fluid and electrolyte alone (FE) or parenteral nutrition admixure (PN). The mean daily PN volume, calculated on a weekly basis, was categorized as: <1, 1-2, 2-3, >3 L/day. The severity of CIF was determined by patient outcome (still on HPN, weaned from HPN, deceased) and the occurrence of major HPN/CIF-related complications: intestinal failure associated liver disease (IFALD), catheter-related venous thrombosis (CVC-VT) and catheter-related bloodstream infection (CRBSI).

Results

Fifty-one HPN-centers included 2194 patients. Multiple regression analysis showed that both IVS type and volume were independently associated with the odds of weaning from IVS (higher for PN <1 L/day than for FE and all PN of >1 L/day), patient's death (higher for PN 2-3 and >3 L/day than for FE), presence of IFALD-cholestasis/liver failure and occurrence of CRBSI (progressively higher for PN 2-3 and PN >3 L/day than for FE).

Conclusions

The type and the volume of the IVS required by patients with CIF could be indicators to categorize the severity of CIF in both clinical practice and research protocols.

Introduction

Intestinal failure (IF) is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth [1]. Chronic intestinal failure (CIF) is a long-lasting condition that may be reversible or irreversible. Patients with CIF are metabolically stable and receive IVS at home (home parenteral nutrition, HPN) for months, years or lifelong [2]. Single or multicenter, mostly retrospective, surveys have described risk factors associated with the patient's outcome, such as survival and reversibility of CIF, and with the risk of HPN/IF-related major complications [3-5]. However, no simple indicator, such as creatinine for kidney disease and SaO_2 for respiratory disease, has yet been identified to categorize the severity of CIF. Such an indicator would be a useful criterion for both clinical practice and research protocols.

The European Society for Clinical Nutrition and Metabolism (ESPEN) devised a clinical classification of CIF, to facilitate communication among professionals through an objective categorization of the patients. This was based on patients' requirements for energy and volume of IVS and originally comprised 16 categories [1]. An international cross-sectional survey was carried out to investigate the applicability of this classification and to evaluate factors associated with the IVS requirements of individual patients [6]. In adult patients with CIF due to non-malignant disease (benign-CIF), the loss of intestinal function appeared more comprehensively represented by IVS volume requirement than by energy requirement. The results enabled the derivation of a new simplified 8-category classification of CIF, based on two types of IVS, either fluid and electrolyte alone (FE) or parenteral nutrition admixture containing energy (PN), and four categories of volume [6].

In order to determine whether ESPEN clinical classification categories could be used as indicators of the severity of CIF, a prospective, multi-center international study was carried out to investigate their association with the patient's outcome and the major complications related to HPN/IF. The results of one-year of follow up are reported.

Material and methods

Study design

This was an international survey involving the retrospective analysis of data prospectively recorded during a one-year follow-up period. The severity of CIF was based on both patient outcome and major complications related to HPN/IF. The patient's outcome was categorized as still on IVS, weaned from IVS or deceased. The HPN/IF-related complications were described as the occurrence of intestinal failure associated liver disease cholestasis (IFALD-cholestasis) and of central venous catheter associated vein thrombosis (CVC-VT) or central venous catheter related bloodstream infection (CRBSI) at one-year follow-up [2].

Baseline HPN center enrollment and patient inclusion

The baseline data collection was performed on March 1st, 2015. Details regarding HPN center enrollment and the patient inclusion criteria have been published in the previous cross-sectional survey carried out to evaluate the applicability the clinical classification of CIF [4]. Sixty-five HPN centers from 22 countries enrolled all adult patients (≥18 years old) dependent on IVS for CIF on March 1st ,2015. Patients with either benign or malignant disease were included. Patients with active malignant disease were termed as having "cancer-CIF". Patients without malignant disease at time of inclusion in the study were termed as having "benign-CIF". 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 [2]. A total of 3239 patients, 9.9% with cancer-CIF and 91.1% with benign-CIF were included [4]. For the purpose of the present study, only patients with benign-CIF were investigated.

Follow up data collection

The one-year follow up was carried out on patients enrolled in the 2015 baseline cross-sectional study. In February 2016, the study coordinator (LP) sent an email to the HPN centers that participated in the 2015 cross-sectional survey, to invite them to participate in the follow up. The study protocol and the structured database for the data collection were attached to the invitation letter. Centers were asked to include relevant data from the patient's medical records between March 1st 2015 and March 1st 2016 and details of the patient's outcome on March 1st 2016.

Data were collected into a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database (the ESPEN CIF Action Day database). The items of the questionnaire are shown in **Table 1**.

Ethical statement

The study was approved by the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF) special interest group of ESPEN. 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.

Statistical analysis

Data are reported as mean ± standard deviation (SD), median and range, absolute and relative frequencies. For bivariate analysis involving categorical variables non-parametric tests such as Pearson's chi squared or Fisher's exact test were used, while in case of a categorical and a continuous variable the parametric one-way ANOVA (analysis of variance) or the non-parametric Kruskal-Wallis test were performed.

Logistic regression was carried out for multivariate analysis. The odds ratio was used to measure the association between the variables and the patient outcome or the presence of HPN/IF-complications. Two-tailed p values less than 0.05 were considered as statistically significant.

The analyses were performed using the IBM SSPS Statistics package for Windows, version 23.0 (BM Co., Armonk, NY, USA) and the R software for Windows, version 3.5.1 (http://cran.r-project.org).

Results

Study population

Fifty-one of the 65 HPN-Centers which contributed in the 2015 database collection, participated in the 2016 follow up; this included 2194 of the 2919 benign-CIF (75.1%) patients enrolled in 2015. Most of the patients (79.7%) were from European Countries, the remaining were from Israel, US, Mexico, Argentina, Brazil and Australia. The mean number of patients included in the follow up by center was 43.0 ± 54.1 (median: 19; range: 1-231).

Table 2 shows the baseline characteristics of the cohort of patients with benign-CIF included in the present study. Two-thirds were female. The median (range) patient age, BMI and IVS duration were 56.5 years (18.0-98.0), 21.7 kg/m2 (10.5-59.6) and 33.2 months (0-474), respectively. SBS-J was the most frequent pathophysiological mechanism of IF (35.9% of cases). The most frequent underlying disease was Crohn's disease (21.1%).

The type of IVS was FE in 7.9% of patients and PN in 92.1%. The IVS volume was significantly lower in the subgroup of patients receiving FE (median 857.1 mL/day, range 107.1–4800.0) than in those receiving PN (median 1785.7 mL/day, range 81.7-7542.8) (P<0.001).

One-year outcome

At March 1st, 2016, 1740 (79.3%) patients were still on IVS, 298 (13.6%) were weaned from IVS and 156 (7.1%) were deceased. The reason for weaning from IVS was reported in 272 cases: spontaneous intestinal adaptation in 138 (50.7%), non-transplant surgery in 114 (41.9%); surgical intestinal continuity reconstruction in 97 cases), ITx in 14 (5.1%) and intestinal growth factor therapy in 6 (2.2%) cases. The cause of death was reported in 146 cases: HPN/IF-related in 6 (4.1%) patients (CRBSI 5, IFALD 1), underlying disease-related in 64 (43.8%) (4 due to ITx complications) and other causes (neither HPN/IF nor underlying disease-related) in 76 (52.1%) cases. The bi-variate analysis (**Table 3**) showed that the patient's outcome was associated with the patient's age and BMI, the duration of IVS, the mechanism of IF, the underlying disease and the IVS categories (either FE or PN).

Presence or occurrence of HPN/IF-complications at the end of the one-year follow up

This item was recorded in 1859 of the 2194 (84.7%) patients. The presence of IFALD-cholestasis/liver failure was reported in 97 patients (4.4%): cholestasis 63 (64.9%), impending liver failure 11 (11.3%), overt liver failure 18 (18.6%), not specified 5 (5.1%). A CVC-VT was present in 53 patients (2.9%), 30 of which occurred during the one-year follow up. During the follow up, 273 patients (14.7%) had 344 episodes of CRBSI: one episode in 224 (82.0%); two episodes in 40 (14.7%); three episodes in 5 (1.8%); four episodes in 2 (0.7%); 7 and 10 episodes in 1 (0.4%) patient each one. The bi-variate analysis (**Table 4**) showed that: the presence of IFALD-cholestasis/liver failure was associated with the patient's gender and with both the CIF clinical classification categories of IVS and the type of IVS. The presence of CVC-VT was associated with the duration of IVS, the mechanism of IF and the CIF clinical classification categories of IVS. The occurrence of CRBSI was associated with the patient's age and BMI, the underlying disease and with both the CIF clinical classification categories of IVS and the type of IVS.

Multivariate analysis of factors associated with the patient's one-year outcome and HPN/IF-complications

Weaning from IVS, death, presence of IFALD-cholestasis/liver failure or CVC-VT at the end of the follow up, and occurrence of CRBSI during the one-year of follow up were considered the dependent variables. The baseline demographics, IF mechanism, underlying disease and IVS characteristics were included as independent variables.

The association with either the IVS type or the IVS volume was investigated through two models of analysis:

a) *the IVS type model*, to analyze the association with either FE or PN; because of the statistically significant differences between the total FE and the total PN groups observed in the bivariate analyses, as well as of the low number of patients receiving the FE type, in this analysis the total FE group was considered the comparator group to be compared with the four PN groups;
b) *the PN volume model*, to analyze the association with the volume of the PN type of IVS; in this model, only patients receiving PN were included in the analysis and the lowest PN volume (PN1) was considered as the comparator group

*One-year outcome odds (**Tables 5 and 6**)*

In the whole group of patients, the odds of weaning from IVS (**Table 5**): a) were higher in the smallest PN1 type category (mean volume: 695.3 ± 216.8 mL/day) than in the FE type category (mean volume: 1055.8 ± 859.6 mL/day, P<0.001), while no difference was observed between FE and the other PN volume categories; b) were lower in the greatest PN volume categories (PN2, PN3 and PN4), in comparison with PN1, the smallest PN volume; c) were similar between the two models for all the other independent factors: they were lower in the oldest decades of age, in the longest duration of IVS categories, in the miscellaneous group of underlying diseases and were higher in the underweight, overweight and obese BMI categories. . The multivariate analysis for the odds of weaning from IVS was repeated after excluding those patients who were weaned because of a non-transplant surgical procedure (**Table 6**). The results confirmed the higher odds associated with the PN1 IVS, the patient's age and duration of IVS, but not with the patient's BMI. Significant lower odds of weaning were observed in patients who had SBS-J or SBS-JC as mechanisms of IF and in those who had an underlying disease categorized in the miscellaneous group.

The odds of death on IVS: a) were higher in all the PN volume categories in comparison with the FE type category, even though this was statistically significant only with the greatest PN volumes, but no association was observed when only the PN volume categories were compared; b) were similar between the two models for all the other independent factors: they were higher in the oldest age categories, in the lowest BMI categories; in comparison with SBS-J mechanism of IF, the odds of death were lower in the SBS-JC group and were higher in with the other mechanisms of IF, excepting the extensive mucosal disease; the likelihood of death was increased in the mesenteric ischemia and decreased in the CIPO groups of underlying disease.

*Odds of major complications of HPN/IF (**Table 7)***

The odds of the presence of IFALD-cholestasis/impending or overt liver failure: a) were progressively higher in the greatest PN volume categories (PN3 and PN4), in comparison to both the FE type of IVS and the PN1 and PN2 volumes; b) were similar between the two models of analysis for all the other

independent factors: in comparison with SBS-J, the likelihood of IFALD was lower in dysmotility mechanism of IF and higher in the group with surgical complications as their underlying disease.

The odds of the presence of CVC-VT: a) showed no association with the IVS categories; b) were similar between the two models of analysis for all the other independent factors: they were higher in the in the longest IVS duration categories and in the underweight category of BMI.

The odds of the occurrence of an episode of CRBSI: a) were progressively higher with the increase of the volume of the PN in comparison to both the FE type of IVS and the PN1 and PN2 volumes ; b) were similar between the two models of analysis for all the other independent factors: they were lower in older patients and were higher in the obese category of BMI and in the CIPO underlying disease

Discussion

This is the first study aimed at investigating the association between IVS requirement, CIF outcome and the occurrence of major complications in a very large international cohort of IVS-dependent patients with CIF due to benign underlying disease. The results show that both the type and the volume of the IVS are independently associated with the odds of weaning from IVS at one-year, as well as with the risk of mortality, the occurrence of CRBSI and the presence of IFALD-cholestasis/liver failure. In patients with CIF, the type and the volume of the IVS requirement primarily depends on the degree of the reduction of gut function (6). However, other factors may be involved, such as the patient's metabolic condition and vital organ function, the patient's compliance with the prescribed treatment as well as the treatment protocols of the multidisciplinary team caring for him/her (1,2). Therefore, while any association between IVS characteristics and the patient's outcome or the occurrence of HPN/IF complications may not be considered causal, they may indicate that the type and the volume of the IVS reflect comprehensive odds of morbidity and mortality for IVS-dependent patients, independently from the factors that may have determined their prescription. This is further strengthened by the observation that none of the other independent factors entered in the multiple regression analyses was contemporaneously associated with odds of weaning from IVS, death, or occurrence of IFALD and CRBSI. These data support the potential role of the ESPEN clinical classification of CIF, based on the type and the volume of the IVS, as a potential indicator of CIF severity. Further follow up surveys are required to investigate if this could be translated inot a long-term marker of CIF.

The one-year odds of death depended on the interaction between the IVS type and volume rather than on either characteristic alone. Indeed, an increased likelihood of death was observed in those receiving the greatest volumes of PN rather than those receiving the FE, but no association was found with PN-volume alone; since HPN-related deaths were very rare (3), these results would suggest a less severe clinical condition in patients with CIF requiring only FE supplementation.

The one-year likelihood of weaning from IVS was associated with both the type and volume of IVS. The PN1 volume (≤1 L/day) showed higher odds of weaning than either the greater PN-volumes or FE-type IVS. There could be several reasons for a longer maintenance of low volume FE than of low volume PN IVS:

a more difficult intestinal rehabilitation of fluid and electrolytes than of macronutrient absorption due to concomitant secondary mechanisms of IF causing increased intestinal secretion (1); the concomitant presence of reduced kidney function requiring the maintenance of optimal hydration (2,7); physician's and/or patient's perception of a lower risk of IVS-associated complications with FE than with PN; patient's better acceptance of FE than of PN, because of shorter duration of FE infusion compared to PN (2); the lower cost of FE. All of these factors would make weaning from FE slower/less likely than weaning from PN.

The likelihoods of IFALD and of the occurrence of CRBSIs were also associated with both the type and the volume of the IVS, whereas no association was observed with the presence of CVC-VT (**Tables 4 and 7**). The odds of IFALD and of CRBSI were greater in patients receiving the highest volumes of PN in comparison with the lowest PN-volumes and the FE-type of IVS. Furthermore, there was a progressive increase in likelihood of these complications with increased PN volume. These data are in keeping with previous studies (2,8,9). The pathogenesis of IFALD is multifactorial, including factors related to the IVS, underlying gastrointestinal disease and systemic factors, especially episodes of sepsis (2,10). Intravenous supplementation, overfeeding and a high amount of lipid emulsion are recognized causes of IFALD (2,10). Similarly, CRBSI occurrence has also previously been reported to occur more frequently in those dependent on an increased number of days of IVS (8); this may relate to more frequent handling of the central venous catheter increasing infection risk or the association between macronutrients, vitamins and trace metals affecting microbial growth in the PN admixture (11,12).

Most of the other independent factors found to be associated with patient's outcome and HPN/IF complications (**Tables, 5,6,7**) were in keeping with data from previous studies (2,3,8,10). As expected, non-transplant surgery was the cause of weaning off HPN in a large percentage of patients (13). Notably, data on the causes of death on long-term IVS are consistent with previous observations (3-5,13-15), even though the percentage of HPN-related deaths (4%) was lower than that reported in longer retrospective surveys (10-14%) (3-5,13-15). This could be due to the short duration of the present follow up, as it is known that the rate of the HPN-related death increases with the duration of the treatment (4). The 344 episodes of CRBSI registered in the 1859 patients accounted for a rate of CRBSI of 0.18 per catheter-year, or 0.50 per 1000 catheter-days, a rate that is in the range reported in the literature (2). The 30 new cases of CVC-VT

observed at one-year follow up, accounted for an incidence rate of 0.016 per catheter-year, that is also in the lower range of the literature (0.02-0.09 cases per catheter-year) (2).

The weakness of the study is mainly represented by the retrospective analysis of data prospectively recorded in the previous 12 months, which would imply a risk of some underreporting. However, the strength of the study is clearly reflected by its international multicenter structure and by the study population, which is the largest cohort of patients with CIF ever enrolled in a single survey. These characteristics should avoid the potential bias associated with the analysis of individual center cohorts, which could be influenced by local practice and expertise, and mitigate the impact of the above possible weakness on statistical analyses. Furthermore, the agreement between our results and the risk factors, (other than quantified IVS), reported by previous studies would support the overall reliability of our findings.

In conclusion, the type of the IVS, either FE or PN, and the volume of the PN-admixture, as categorized by the ESPEN clinical classification of CIF, were found to be independently associated with the one-year likelihoods of death, of weaning from HPN and of major complications of HPN/IF. These results support the ESPEN categorization of the IVS as potential marker of the severity of CIF.

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Table 1. Items of the "Chronic Intestinal Failure (CIF) Action Day" database of the European Society for Clinical Nutrition and Metabolism (ESPEN) used for the follow up survey on patient outcome and home parenteral nutrition/chronic intestinal failure major complications.

At baseline

- Patient characteristics
  - Gender
  - Age (year)
  - Body height (cm)
  - Body weight (kg)
  - Body mass index (BMI) [body weight (kg)/height (m^2)]
- CIF characteristics
  - Pathophysiological mechanism of intestinal failure
    - Short bowel syndrome with end-jejunostomy (SBS-J)
    - SBS with jejuno-colic anastomosis (SBS-JC)
    - SBS with jejuno-ileal anastomosis and total colon in continuity (SBS-JIC)
    - Dysmotility
    - Intestinal fistulas (Fistulas)
    - Mechanical obstruction (Obstruction)
    - Extensive small bowel mucosa disease (Mucosal disease)
  - Underlying disease which causes the intestinal failure
- HPN program characteristics
  - HPN duration at patient first inclusion in the database (months)
  - Intravenous supplementation (IVS)-admixture type
  - IVS-volume per day of infusion
  - IVS-total energy per day of infusion
  - IVS-days of infusion per week

- Clinical classification of CIF, based on the IVS type and volume:

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

- * calculated as daily mean of the total volume infused per week = volume per day of infusion x number of infusions per week / 7
- FE, Fluids and Electrolytes alone
- PN, Parenteral Nutrition Admixture containing also macronutrients

At follow up

Patient outcome

- Still on HPN:
  - On standard treatment
  - On intestinal growth factor
  - After intestinal transplantation (ITx)
- Weaned from HPN:
  - spontaneous adaptation
  - non-transplant surgery
  - intestinal growth factor therapy
  - ITx
- Deceased:
  - HPN/CIF complication (CRBSI, CVC-VT, IFALD-cholestasis)
  - underlying disease complication (gastrointestinal disease, systemic disease, post-ITx complications or other) (specify)
  - other causes (specify)
- Lost to follow up

HPN/IF major complications

- Presence of intestinal failure associated liver disease-cholestasis (IFALD-cholestasis) or liver failure:
  - Cholestasis: total bilirubin >1 mg/dL (>17.1 μmol/L) and direct bilirubin >0.3 mg/dL (>5.2 μmol/L)
  - Impending liver failure: total bilirubin >3 mg/dL (>54.3 μmol/L) with direct bilirubin above the upper normal value, progressive thrombocytopenia and splenomegaly
  - Overt liver failure: portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis
- Presence of central venous catheter venous-associated venous thrombosis (CVC-VT)
- Occurrence of catheter related bloodstream infection (CRBSI), diagnosed according to local protocol, between baseline and follow up

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438 **Table 2.** Baseline patient cohort characteristics

Categories	N. of patients (%)	Mean ± SD
Gender		
Male	811 (37.0)	
Female	1383 (63.0)	
Age (years)		55.1 ± 16.2
≤29	187 (8.5)	
30-49	575 (26.2)	
50-69	990 (45.1)	
≥70	442 (20.1)	
BMI (kg/m^2)		22.3 ± 4.4
≤15	57 (2.6)	
15-18.5	324 (14.8)	
18.5-25	1334 (60.8)	
25-30	363 (16.5)	
≥30	111 (5.1)	
Missing	5 (0.2)	
Duration of IVS (years)		4.8± 5.8
≤1	575 (26.2)	
1-3	575 (26.2)	
3-10	748 (34.1)	
>10	293 (13.4)	
Missing	3 (0.1)	
Mechanism of IF		
SBS-J	788 (35.9)	
SBS-JC	459 (20.9)	
SBS-JIC	140 (6.4)	
Fistulas	149 (6.8)	
Dysmotility	398 (18.1)	
Obstruction	104 (4.7)	
Mucosal disease	156 (7.1)	
Underlying disease		
Crohn's disease	*462*	
Ulcerative colitis	*18*	
Total IBD	480 (21.9)	
Mesenteric ischemia	395 (18.0)	
Surgical complications	306 (13.9)	
CIPO primary	*222*	
CIPO secondary	*77*	
Total CIPO	299 (13.6)	

Intra-abdominal adhesions	*72*	
Volvulus	*46*	
Cured cancer	*21*	
Abdominal trauma	*26*	
Intestinal malformation	*13*	
Total other causes of SBS	178 (8.1)	
Collagenous	*40*	
Intra-abdominal desmoid	*22*	
Intestinal polyposis	*16*	
Autoimmune enteropathy	*14*	
Neurological disease	*11*	
Congenital mucosal disease foglio2	*14*	
Celiac disease	*8*	
Other diseases	*93*	
Total miscellaneous	218 (9.9)	
Radiation enteritis	164 (7.5)	
Missing	154 (7.0	
Clinical classification of CIF (volume/day of infusion)		
FE1 (≤1 L)	118 (5.4)	
FE2 (1-2 L)	40 (1.8)	
FE3 (2-3 L)	10 (0.5)	
FE4 (>3 L)	6 (0.3)	
Total FE	174 (7.9)	1055.8 ± 859.6
PN1 (≤1 L)	384 (17.5)	
PN2 (1-2 L)	944 (43.0)	
PN3 (2-3 L)	482 (22.0)	
PN4 (>3 L)	210 (9.6)	
Total PN	2020 (92.1)	1872.6 ± 972.1

BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal pseudo-obstruction; CIF, chronic intestinal failure; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture

445 **Table 3**. Bivariate analysis of factors associated with the one-year outcome of adult patients on home intravenous support for chronic intestinal failure due to
446 benign disease.

	Patients n.	**Still on HPN** n. (%)	**Weaned from HPN** n. (%)	**Deceased** n. (%)	**P**
Gender (n.)					0.144
Male	811	627 (77.3)	125 (15.4)	59 (7.3)	
Female	1383	1113 (80.5)	173 (12.5)	97 (7.0)	
Age (years)					<0.001
≤29	187	147 (78.6)	37 (19.8)	3 (1.6)	
30-49	575	462 (80.3)	93 (16.2)	20 (3.5)	
50-69	990	794 (80.2)	124 (12.5)	72 (7.3)	
≥70	442	337 (76.2)	44 (10.0)	61 (13.8)	
BMI (kg/m^2)					0.008
≤15	57	46 (80.7)	6 (10.5)	5 (8.8)	
15-18.5	324	241 (74.4)	51 (15.7)	32 (9.9)	
18.5-25	1334	1100 (82.5)	146 (10.9)	88 (6.6)	
25-30	363	274 (75.5)	68 (18.7)	21 (5.8)	
≥30	111	75 (67.6)	27 (24.3)	9 (8.1)	
Duration of IVS (years)					<0.001
≤1	575	345 (60)	182 (31.7)	48 (8.3)	
1-3	575	455 (79.1)	76 (13.2)	44 (7.7)	
3-10	748	670 (89.6)	34 (4.5)	44 (5.9)	
>10	293	268 (91.5)	5 (1.7)	20 (6.8)	
Mechanism of IF (n.)	788				<0.001
SBS-J	459	617 (78.3)	115 (14.6)	56 (7.1)	

SBS-JC	140	405 (88.2)	34 (7.4)	20 (4.4)	
SBS-JIC	149	109 (77.9)	24 (17.1)	7 (5.0)	
Fistulas	398	96 (64.4)	35 (23.5)	18 (12.1)	
Dysmotility	104	325 (81.7)	43 (10.8)	30 (7.5)	
Obstruction	156	73 (70.2)	19 (18.3)	12 (11.5)	
Mucosal disease	788	115 (73.7)	28 (17.9)	13 (8.3)	
Underlying disease (n.)					<0.001
Total IBD	480	383 (79.8)	72 (15.0)	25 (5.2)	
Mesenteric ischemia	395	313 (79.2)	42 (10.6)	40 (10.1)	
Surgical complications	306	215 (70.3)	63 (20.6)	28 (9.2)	
Total CIPO	299	256 (85.6)	31 (10.4)	12 (4.0)	
Other causes of SBS	178	176 (80.7)	21 (9.6)	21 (9.6)	
Miscellaneous	218	136 (76.4)	32 (18.0)	10 (5.6)	
Radiation enteritis	154	135 (82.3)	17 (10.4)	12 (7.3)	
Clinical classification of CIF (n.)					0.190
FE1 (≤1 L)	118	106 (89.8)	11 (9.3)	1 (0.8)	
FE2 (1-2 L)	40	31 (77.5)	5 (12.5)	4 (10.0)	
FE3 (2-3 L)	10	8 (80)	2 (20.0)	0	
FE4 (>3 L)	6	5 (83.3)	1 (16.7)	0	
PN1 (≤1 L)	384	296 (77.1)	65 (16.9)	23 (6.0)	
PN2 (1-2 L)	944	745 (78.9)	126 (13.3)	73 (7.7)	
PN3 (2-3 L)	482	378 (78.4)	65 (13.5)	39 (8.1)	
PN4 (>3 L)	210	171 (81.4)	23 (11.0)	16 (7.6)	
Type of IVS (n.)					0.032
Total FE	174	150 (86.2)	19 (10.9)	5 (2.9)	
Total PN	2020	1590 (78.7)	279 (13.8)	151 (7.5)	

BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture

Table 4. Bivariate analysis of factors associated with the major home parenteral nutrition/ intestinal failure complications during a one-year follow up in adult patients on home intravenous support for chronic intestinal failure due to non malignant disease, categorized according to clinical, home parenteral nutrition and referral center characteristics (IFALD, intestinal failure associated liver disease: cholestasis of impending/overt liver failure; CVC-VT. Central venous catheter-associated deep vein thrombosis; CRBSI, catheter related bloodstream infections)

	Patients	**Presence of IFALD***		**Patients**	**Presence of CVC-VT**		**Patients**	**Occurrence of CRBSI**	
	n.	n. (%)	**P**	n.	n. (%)	**P**	n.	n. (%)	**P**
Gender (n.)			0.029			0.689			0.886
Male	642	46 (6.7)		667	21 (3.1)		585	102 (14.8)	
Female	1120	51 (4.4)		1139	32 (2.7)		1000	171 (14.6)	
Age (years)			0.253						0.001
≤29	148	13 (8.1)		158	3 (1.9)	0.855	122	39 (24.2)	
30-49	456	28 (5.8)		469	15 (3.1)		404	79 (16.4)	
50-69	801	37 (4.4)		813	25 (25)		735	103 (12.3)	
≥70	357	19 (5.1)		366	10 (2.7)		324	52 (13.8)	
BMI (kg/m^2)			0.533			0.281			0.019
≤15	45	3 (6.3)		158	2 (4.2)		41	7 (14.6)	
15-18.5	238	16 (6.3)		469	12 (4.7)		217	37 (14.6)	
18.5-25	1075	63 (5.5)		813	27 (2.4)		986	151 (13.3)	
25-30	303	12 (3.8)		366	8 (2.5)		262	53 (16.8)	
≥30	96	3 (3.0)		158	4 (4.0)		74	25 (25.3)	
Duration of IVS (years)			0.980			0.010			0.549
≤1	442	25 (5.4)		461	6 (1.3)		398	69 (14.8)	
1-3	449	23 (4.9)		463	9 (1.9)		396	76 (16.1)	
3-10	611	34 (5.3)		619	26 (4.0)		550	95 (14.7)	
>10	257	15 (5.5)		260	12 (4.4)		238	33 (12.2)	

Mechanism of IF (n.)			0.540			0.038		0.674
SBS-J	633	51 (7.5)		670	14 (2.0)		584	100 (14.6)
SBS-JC	357	15 (4.0)		352	20 (5.4)		326	45 (12.1)
SBS-JIC	108	5 (4.4)		110	3 (2.7)		92	21 (18.6)
Fistulas	120	5 (4.0)		124	1 (0.8)		104	21 (16.8)
Dysmotility	335	10 (2.9)		334	11 (3.2)		291	54 (15.7)
Obstruction	85	5 (5.6)		89	1 (1.1)		77	13 (14.4)
Mucosal disease	124	6 (4.6)		670	3 (2.3)		111	19 (14.6)
Underlying disease (n.)			0.156			0.060		0.023
Total IBD	406	19 (4.5)		417	8 (1.9)		375	50 (11.8)
Mesenteric ischemia	294	20 (6.4)		300	14 (4.5)		272	42 (13.4)
Surgical complications	238	19 (7.4)		254	3 (1.2)		215	42 (16.3)
Total CIPO	255	9 (3.4)		257	7 (2.7)		214	50 (18.9)
Other causes of SBS	129	8 (5.8)		130	7 (5.1)		110	26 (19.1)
Miscellaneous	164	13 (7.3)		169	8 (4.5)		143	34 (19.2)
Radiation enteritis	129	3 (2.3)		130	2 (1.5)		119	13 (9.8)
Clinical classification of IF (n.)			<0.001			0.005		0.005
FE1 (≤1 L)	105	1 (0.9)		105	1 (0.9)		99	7 (6.6)
FE2 (1-2 L)	36	1 (2.7)		37	0		33	4 (10.8)
FE3 (2-3 L)	9	0		7	2 (22.2)		7	2 (22.2)
FE4 (>3 L)	5	1 (16.7)		6	0		6	0
PN1 (≤1 L)	302	6 (1.9)		294	14 (4.5)		275	33 (10.7)
PN2 (1-2 L)	768	30 (3.8)		773	25 (3.1)		678	120 (15.0)
PN3 (2-3 L)	374	35 (8.6)		401	8 (2.0)		342	66 (16.2)
PN4 (>3 L)	163	23 (12.4)		183	3 (1.6)		145	41 (22.0)
Type of IVS (n.)			0.050			0.452		0.016
Total FE	155	3 (1.9)		155	2 (1.9)		145	13 (8.2)
Total PN	1607	94 (5.5)		1701	50 (2.9)		1440	260 (15.3)

455 BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with
456 jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease,
457 CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral
458 nutrition-admixture
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Table 5. Multivariate analysis of factors independently associated with the likelihoods of weaning from IVS and of death in adult patients with CIF

	Patients weaned form HPN				**Patients deceased**			
	Association with IVS type (n. 278)		**Association with PN volume (n. 259)**		**Association with IVS type (n. 147)**		**Association with PN volume (n. 142)**	
Independent factors	P	OR	P	OR	P	OR	P	OR
IVS type and volume								
Total FE1	Comparator				Comparator			
PN1 (≤1 L)	**0.002**	**2.726**	Comparator		0.066		Comparator	
PN2 (1-2 L)	0.539		**<0.001**	**0.428**	**0.025**	**3.001**	0.665	
PN3 (2-3 L)	0.335		**0.002**	**0.491**	**0.016**	**3.343**	0.456	
PN4 (>3 L)	0.907		**0.002**	**0.372**	**0.019**	**3.611**	0.420	
Gender								
Male	Comparator							
Female	0.173		0.081		0.684		0.848	
Age (years)								
≤29	Comparator							
30-49	0.086		0.057		0.244		0.233	
50-69	**0.003**	**0.462**	**0.006**	**0.484**	**0.015**	**4.531**	**0.017**	**4.433**
≥70	**0.002**	**0.393**	**0.001**	**0.353**	**<0.001**	**9.602**	**<0.001**	**9.412**
BMI (kg/m^2)								
18.5-25.0	Comparator							
≤15.0	0.281		0.338		0.063		0.074	
15.0-18.5	0.057		**0.034**	**1.573**	**0.006**	**1.960**	**0.011**	**1.891**
25.1-30.0	**0.002**	**1.835**	**0.002**	**1.850**	0.440		0.416	
≥30.0	**0.017**	**2.010**	**0.001**	**2.826**	0.174		0.223	

Duration of IVS (years)								
≤1	Comparator							
1-3	**<0.001**	**0.266**	**<0.001**	**0.268**	0.545		0.411	
3-10	**<0.001**	**0.086**	**<0.001**	**0.080**	0.081		**0.041**	**0.605**
>10	**<0.001**	**0.028**	**<0.001**	**0.030**	0.607		0.609	
Mechanism of IF								
SBS-J	Comparator							
SBS-JC	0.095		0.082		**0.008**	**0.452**	**0.007**	**0.438**
SBS-JIC	0.214		0.272		0.216		0.263	
Fistulas	0.147		0.154		**0.022**	**2.162**	**0.014**	**2.347**
Dysmotility	0.696		0.411		**0.021**	**2.344**	**0.019**	**2.401**
Obstruction	0.391		0.300		**0.043**	**2.333**	**0.045**	**2.335**
Mucosal disease	0.396		0.282		0.246		0.194	
Underlying disease								
Total IBD	Comparator							
Total CIPO	0.153		0.099		**0.033**	**0.354**	0.052	
Other causes of SBS	0.160		0.168		0.753		0.949	
Miscellaneous	**0.008**	**0.436**	**0.011**	**0.442**	0.866		0.704	
Mesenteric ischemia	0.298		0.483		**0.025**	**1.946**	**0.013**	**2.164**
Radiation enteritis	0.514		0.718		0.406		0.595	
Surgical complications	0.408		0.587		0.521		0.414	

BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture

Table 6. Multivariate analysis of factors independently associated with the likelihoods of weaning from IVS without an intestinal surgical procedure in adult patients with CIF

	Patients weaned form HPN			
	Association with IVS type (n. 174)		**Association with PN volume (n. 162)**	
Independent factors	P	OR	P	OR
IVS type and volume				
Total FE1	Comparator			
PN1 (≤1 L)	**0.049**	**2.094**	Comparator	
PN2 (1-2 L)	0.862		**<0.001**	**0.433**
PN3 (2-3 L)	0.762		**0.002**	**0.419**
PN4 (>3 L)	0.459		**0.011**	**0.327**
Gender				
Male	Comparator			
Female	0.760		0.554	
Age (years)				
≤29	Comparator			
30-49	**0.031**	**0.543**	**0.024**	**0.517**
50-69	**0.002**	**0.408**	**0.003**	**0.425**
≥70	**0.001**	**0.296**	**<0.001**	**0.251**
BMI (kg/m^2)				
18.5-25.0	Comparator			
≤15.0	0.367		0.420	
15.0-18.5	0.096		0.076	
25.1-30.0	0.097		0.053	
≥30.0	0.173		0.056	

Duration of IVS (years)				
≤1	Comparator			
1-3	**<0.001**	**0.332**	**<0.001**	**0.320**
3-10	**<0.001**	**0.139**	**<0.001**	**0.123**
>10	**<0.001**	**0.047**	**<0.001**	**0.049**
Mechanism of IF				
SBS-J	Comparator			
SBS-JC	0.318		0.236	
SBS-JIC	**<0.001**	**3.459**	**<0.001**	**3.684**
Fistulas	**<0.001**	**3.387**	**<0.001**	**3.710**
Dysmotility	**0.011**	**2.707**	**0.002**	**3.536**
Obstruction	**0.049**	**2.387**	**0.026**	**2.762**
Mucosal disease	**0.003**	**2.699**	**0.001**	**3.165**
Underlying disease				
Total IBD	Comparator			
Total CIPO	0.087		**0.042**	**0.403**
Other causes of SBS	0.859		0.871	
Miscellaneous	**0.013**	**0.427**	**0.013**	**0.417**
Mesenteric ischemia	0.237		0.338	
Radiation enteritis	0.119		0.193	
Surgical complications	0.540		0.346	

469 BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with
470 jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease,
471 CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral
472 nutrition-admixture
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474 **Table 7.** Multivariate analysis of factors associated with the likelihoods of major HPN/IF complications in adult patients with CIF

Independent factors	Presence of IFALD-cholestasis/impending or overt liver failure				Presence of CVC-vein thrombosis				Occurrence of CRBSI			
	Association with IVS type (n.91)		Association with PN volume (n.88)		Association with IVS type (n.49)		Association with PN volume (n.47)		Association with IVS type (n.257)		Association with PN volume (n.244)	
	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR
IVs type and volume												
Total FE1	Comparator				Comparator				Comparator			
PN1 (≤1 L)	0.831		Comparator		0.246		Comparator		0.362		Comparator	
PN2 (1-2 L)	0.227		0.175		0.380		0.530		**0.024**	**2.079**	0.071	
PN3 (2-3 L)	**0.017**	**4.437**	**0.004**	**3.881**	0.746		0.183		**0.015**	**2.264**	**0.043**	**1.654**
PN4 (>3 L)	**0.007**	**5.692**	**0.001**	**5.008**	0.827		0.329		**<0.001**	**3.543**	**0.001**	**2.614**
Gender												
Male	Comparator											
Female	0.121		0.205		0.482		0.326		0.658		0.566	
Age (years)												
≤29	Comparator											
30-49	0.486		0.499		0.329		0.392		**0.046**	**0.620**	**0.047**	**0.616**
50-69	0.358		0.306		0.228		0.217		**0.005**	**0.507**	**0.007**	**0.516**
≥70	0.637		0.615		0.419		0.482		0.058		0.093	
BMI (kg/m^2)												
18.5-25	Comparator											
≤15	0.916		0.947		0.188		0.183		0.834		0.806	
15-18.5	0.116		0.196		**0.011**	**2.643**	**0.009**	**2.746**	0.569		0.785	
25-30	0.152		0.220		0.757		0.713		0.054		0.117	
≥30	0.404		0.310		0.123		0.064		**0.001**	**2.583**	**0.012**	**2.199**
Duration of HPN (years)												

≤1	Comparator								
1-3	0.94		0.867		0.405	1.573	0.227	2.006	0.426		0.317
3-10	0.839		0.667		0.054	2.540	**0.035**	**3.025**	0.669		0.798
>10	0.949		0.931		**0.036**	**3.105**	**0.019**	**3.873**	0.516		0.405
Mechanism of IF											
SBS-J	Comparator										
SBS-JC	0.190		0.23		0.215		0.168		0.722		0.994
SBS-JIC	0.434		0.513		0.874		0.969		0.191		0.180
Fistulas	0.304		0.421		0.578		0.678		0.542		0.603
Dysmotility	**0.026**	**0.314**	**0.036**	**0.330**	0.654		0.590		0.290		0.428
Obstruction	0.917		0.878		0.470		0.563		0.470		0.558
Mucosal disease	0.526		0.556		0.948		0.895		0.769		0.972
Underlying disease											
Total IBD	Comparator										
Total CIPO	0.510		0.598		0.889		0.848		**0.041**	**1.982**	0.074
Other causes of SBS	0.581		0.686		0.077		0.156		0.080		0.132
Miscellaneous	0.079		0.105		0.123		0.109		**0.034**	**1.775**	0.055
Mesenteric ischemia	0.273		0.323		0.111		0.099		0.796		0.976
Radiation enteritis	0.454		0.421		0.799		0.928		0.857		0.722
Surgical complications	**0.027**	**2.219**	0.112		0.557		0.658		0.470		0.455

BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileo anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture