The intravenous supplementation type and volume is associated with one-year outcome and the major complications in patients with chronic intestinal failure

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The Home Artificial Nutrition and Chronic Intestinal Failure special interest group of the European Society for Clinical Nutrition and Metabolism (ESPEN)

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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 major complications of home parenteral nutrition/intestinal failure (liver disease and catheter-related blood stream infection) and weaning from home parenteral nutrition are independently associated with the type and volume of the intravenous supplementation required.
- The one-year odds of death is non-significantly associated with the type of intravenous supplementation required; future study is required to determine if the latter significantly impacts on the longer term risk of death in this patient cohort.

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 ongoing 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 admixture (PN). The mean daily IVS volume, calculated on 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. The analysis showed that both IVS type and volume were independently associated with the odds of weaning from HPN (significantly higher for PN <1 L/day than for FE and all the PN >1 L/day), patient's death (lower for FE, p=0.079), presence of IFALD-cholestasis/liver failure and occurrence of CRBSI (significantly higher for PN 2-3 and PN >3 L/day).

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 follow up are reported.

Material and methods

Study design

This was an international survey involving the retrospective collection 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 HPN, weaned from HPN or deceased. The HPN/IF-related complications were described as the occurrence of intestinal failure associated liver disease (IFALD-cholestasis or liver failure), 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 HPN 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 (**Supplemental material 1**) 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) (**Supplemental material 2**). Centers were invited to contact the study coordinator for any additional explanation or instruction.

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. Each patient was labelled with two anonymized identifications: one given by the HPN-center and one given by the database manager. 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

The term HPN described the provision of IVS, either FE or PN, at the patient's home. Weaning from equated to stopping IVS [1]. The clinical classification of CIF consisted of 8 categories, based on the type and volume of IVS, calculated as daily mean of the total volume infused per week: volume per day of infusion × number of infusions per week / 7 (mL/day): FE1 or PN1, ≤1000; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4, >3000, [6].

The pathophysiological mechanisms of IF were classified as short bowel syndrome with end-jejunostomy (SBS-J), with jejuno-colic anastomosis (SBS-JC) or with jejuno-ileal anastomosis and total colon in continuity (SBS-JIC), intestinal dysmotility (Dysmotility), intestinal fistulas (Fistulas), mechanical obstruction (Obstruction) and extensive small bowel mucosa disease (Mucosal disease), [6].

The underlying diseases were grouped as follows: inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis; mesenteric ischemia, comprising mesenteric arterious or venous infarction and non-occlusive ischemia; acute post-surgical complications; chronic intestinal pseudo-obstruction, idiopathic or secondary to intestinal of systemic diseases (CIPO); short bowel syndrome due to causes other than mesenteric ischemia, including intra-abdominal adhesions, volvulus, cured cancer, abdominal trauma, intestinal malformation (Other causes of SBS); radiation enteritis; miscellaneous

(collagenous diseases, intra-abdominal desmoids, intestinal polyposis, autoimmune enteropathy, neurological disease, congenital mucosal disease, celiac disease and other diseases not included in the above categories).

The reasons for weaning from HPN were categorized as medical and surgical, the latter included non-transplant procedures and intestinal transplantation. The odds of weaning from HPN were evaluated by two models of analysis: one including all the weaned patients and one excluding patients weaned because of non-transplant surgery.

HPN/IF-related complications at March 1st 2016 were categorised as follows: IFALD and CVC-VT reported as prevalent cases, when they were already present at baseline, and as incident case, when they developed during the one-year follow up. CRBSI were categorized as incident cases occurring during the one-year follow up. The incident or prevalent nature of CVC-TV was collected at time of filling out the database on March 1st 2016, whereas the incident or prevalent nature of IFALD was collected after receiving the filled out database, by asking a specific question to the participating centers.

Practice variation by HPN-center was weighted by including in the statistical analysis the number of patients enrolled in the study by the individual HPN-center. We also estimated a model with center as a random effect. Although a slight improvement was noted in model fitting (i.e. in terms of percentage of correctly classified subjects, with subjects correctly classified: 81% vs 80%), the random effect was omitted in order to preserve the ease of interpretation of the model.

Data are reported as mean ± standard deviation (SD), median and range, absolute and relative frequencies.

Binomial and multinomial logistic regressions were carried out for multivariate analysis. The odds ratio was used to measure the association between the independent variables and the outcome. A competing risk regression model based on Fine and Gray's proportional subhazards approach was also performed in order to model the time to occurrence of competing outcomes. Subhazard ratios were presented together with the Cumulative Incidence Functions.

Missing data were excluded from the analysis. Two-tailed p-values less than 0.05 were considered as statistically significant. All p-values were not corrected for multiple-hypothesis testing.

The analyses were performed using the IBM SSPS Statistics package for Windows, version 23.0 (BM Co., Armonk, NY, USA), R software for Windows, version 3.5.1 (http://cran.r-project.org) and STATA/IC 16.0 for Windows

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); number of patients by center: ≤19, n. 26 (51.0%) centers, patients n. 198 (9.0% of total); 20-49, n. 8 (15.7%), patients 253 (11.5%); 50-99, n. 10 (19.6%) centers, patients n.657 (29.9%); ≥100 n. 7 (13.7%) centers, patients n. 1086 (49.5%). Nine centers included <5 patients, each.

Table 1 shows the baseline characteristics and the one-year outcome of the cohort of patients with benign-CIF included in the present study. Two-thirds were females. At baseline, the mean±SD, (median; range) patient age, BMI and HPN duration were 51.1±16.2 (56.5;18.0-98.0) years, 22.3±4.4 (21.7; 10.5-59.6) kg/m^2 and 58.0±70.2 (33.2¸0-474) months, 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 1055.8±859.6 mL/day (median 857.1, range 107.1–4800.0) than in those receiving PN 1055.8±859.6 mL/day (median 1785.7, range 81.7-7542.8) (P<0.001).

One-year outcome

On March 1st, 2016, 1740 (79.3%) patients were still on HPN, 298 (13.6%) were weaned from HPN and 156 (7.1%) were deceased (**Table 1**). The reason for weaning from HPN 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.

HPN/IF complications were recorded in 1859 of the 2194 (84.7%) patients. The presence of IFALD-cholestasis/liver failure was reported in 97 patients (4.4%), 66 prevalent and 31 of which were incident

cases: 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%), 23 prevalent and 30 incident cases. 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.

A variation of IVS type and volume between baseline and the end of follow up was observed in 317 (14.4%) patients: 22 patients changed the IVS type from FE to PN (12.6% of FE), 26 patients changed from PN to FE (1.3% of PN) and 269 patients changed PN volume (13.3% of PN) (**Supplemental table 1**).

Table 1. Baseline characteristics and one-year outcome and home parenteral nutrition (HPN)/intestinal failure (IF) – related major complications of adult patients with chronic intestinal failure due to benign disease. (IFALD, intestinal failure associated liver disease: cholestasis or liver failure; CVC-VT, central venous catheter-associated deep vein thrombosis; CRBSI, catheter related bloodstream infections). Data are reported as percentages of cases.

	One-year outcome			One-year HPN/IF major complications		
Baseline patient cohort	**Still on HPN**	**Weaned from HPN**	**Deceased**	**IFALD**	**CVC-VT**	**CRBSI**
n. 2194	**n. 1740**	**n. 298**	**n. 156**	**n. 97**	**n. 53**	**n. 273**
Gender (%)						
Male (n. 811)	77.3	15.4	7.3	6.7	3.1	14.8
Female (n. 1383)	80.5	12.5	7.0	4.4	2.7	14.6
Age, years (%)						
≤29 (n.187)	78.6	19.8	1.6	8.1	1.9	24.2
30-49 (n.575)	80.3	16.2	3.5	5.8	3.1	16.4
50-69 (n.990)	80.2	12.5	7.3	4.4	3.0	12.3
≥70 (n.442)	76.2	10.0	13.8	5.1	2.7	13.8
BMI, kg/m^2, (%)						
≤15 (n.57)	80.7	10.5	8.8	6.3	4.2	14.6
15-18.5 (n.324)	74.4	15.7	9.9	6.3	4.7	14.6
18.5-25 (n.1334)	82.5	10.9	6.6	5.5	2.4	13.3
25-30 (n.363)	75.5	18.7	5.8	3.8	2.5	16.8
≥30 (n.111)	67.6	24.3	8.1	3.0	4.0	25.3
Not reported (n.5)						
Duration of HPN, yrs (%)						
≤1 (n.575)	60	31.7	8.3	5.4	1.3	14.8
1-3 (n.575)	79.1	13.2	7.7	4.9	1.9	16.1
3-10 (n.748)	89.6	4.5	5.9	5.3	4.0	14.7
>10 (n.293)	91.5	1.7	6.8	5.5	4.4	12.2
Not reported (n.3)						

Mechanism of IF (%)						
SBS-J (n.788)	78.3	14.6	7.1	7.5	2.0	14.6
SBS-JC (n.459)	88.2	7.4	4.4	4.0	5.4	12.1
SBS-JIC (n.140)	77.9	17.1	5.0	4.4	2.7	18.6
Fistulas (n.149)	64.4	23.5	12.1	4.0	0.8	16.8
Dysmotility (n.398)	81.7	10.8	7.5	2.9	3.2	15.7
Obstruction (n.104)	70.2	18.3	11.5	5.6	1.1	14.4
Mucosal disease (n.156)	73.7	17.9	8.3	4.6	2.3	14.6
Underlying disease (%)						
IBD (n.480)	79.8	15.0	5.2	4.5	1.9	11.8
CIPO (n.299)	85.6	10.4	4.0	3.4	2.7	18.9
Other causes of SBS (n.178)	80.7	9.6	9.6	5.8	5.1	19.1
Miscellaneous (n.218)	76.4	18.0	5.6	7.3	4.5	19.2
Mesenteric ischemia (n.395)	79.2	10.6	10.1	6.4	4.5	13.4
Radiation enteritis (n.164)	82.3	10.4	7.3	2.3	1.5	9.8
Acute surgical complications (n.306)	70.3	20.6	9.2	7.4	1.2	16.3
Not reported (n.154)						
Clinical classification of CIF						
(IVS volume/day of infusion) (%)						
FE1 (≤1 L) (n.118)	89.8	9.3	0.8	0.9	0.9	6.6
FE2 (1-2 L) (n.40)	77.5	12.5	10.0	2.7	0	10.8
FE3 (2-3 L) (n.10)	80.0	20.0	0	0	22.2	22.2
FE4 (>3 L) (n.6)	83.3	16.7	0	16.7	0	0
PN1 (≤1 L) (n.384)	77.1	16.9	6.0	1.9	4.5	10.7
PN2 (1-2 L) (n.944)	78.9	13.3	7.7	3.8	3.1	15.0
PN3 (2-3 L) (n.482)	78.4	13.5	8.1	8.6	2.0	16.2
PN4 (>3 L) (n.210)	81.4	11.0	7.6	12.4	1.6	22-0
Type of IVS (%)						
Total FE (n.174)	86.2	10.9	2.9	1.9	1.9	8.2
Total PN (n.2020)	78.7	13.8	7.5	12.4	2.9	15.3

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-colic anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileal anastomosis with intact colon in continuity; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture; IBD (inflammatory bowel disease): Crohn's disease n.462, Ulcerative colitis n.18; CIPO (chronic intestinal pseudo-obstruction): primary n.222, secondary n.77; Other causes of SBS: Intra-abdominal adhesions n.72, Volvulus n.46, Cured cancer n.21, Abdominal trauma n.26, Intestinal malformation n.13; Miscellaneous: Collagenous disease n. 40, Intra-abdominal desmoids n.22, Intestinal polyposis n.16, Autoimmune enteropathy n.14, Neurological disease n.11, Congenital mucosal disease n.14, Celiac disease n.8, Other diseases n.93

Factors associated with the patient's one-year outcome and HPN/IF-complications

Weaning from HPN, 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 follow up were considered the dependent variables. The baseline patient's demographics, IF mechanism, underlying disease, IVS characteristics and number of patients enrolled in the study by individual HPN-center were included as independent variables.

Considering the low number of total patients receiving the FE type as well as the very low number of those receiving FE3 and FE4, patients on FE were grouped in a unique cohort for the outcome analyses.

Figure 1 shows the cumulative incidence of weaning off and of death according with the type and the volume of the IVS. When comparing the cumulative incidence function of weaning off and death among groups, non-statistically significant differences were found (p=0.329 and p=0.148 for weaning off and death respectively): incidence of weaning off was greater in PN1 group and lower in PN4 and FE groups; incidence of death was lower in the FE group .

Odds of one-year outcome

The associations with the IVS type and volume were analyzed in comparison with the PN1 category. The odds of weaning from HPN (**Figure 2 and Supplemental table 2**): a) were lower in the FE type category and in the greatest PN volume categories (PN2, PN3 and PN4); b) were lower in the oldest decades of age, in the longest duration of HPN categories and in the miscellaneous group of underlying diseases; c) were higher in the underweight, overweight and obese BMI categories; d) showed no association with the number of patients included in the study by individual HPN-centers.

The results were confirmed when excluding those patients who were weaned because of a non-transplant surgical procedure (**Supplemental table 3**). Furthermore, significant lower odds of weaning off 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 HPN (**Figure 2**): a) showed a non-statistically significant decreased risk for the FE type of IVS with respect to PN1 type ; b) were higher in the oldest age categories and in the lowest BMI categories; c) in comparison with SBS-J mechanism of IF, they were lower in the other SBS types and were higher in the other mechanisms of IF, excepting the extensive mucosal disease; d) were increased in the

mesenteric ischemia and decreased in the CIPO groups of underlying disease; e) showed a negative association with the number of patients included in the study by individual HPN-centers.

The competing risk analysis for the risk of death and of weaning from HPN confirmed the results of the multinomial analysis (**Supplemental table 4**).

Odds of major complications of HPN/IF

The results are reported in **table 2**.

The odds of the presence of IFALD-cholestasis/liver failure: a) were higher in the greatest PN volume categories in comparison with PN1 and were similar between PN1 and the FE type of IVS; b) were lower in dysmotility mechanism of IF; c) were higher in the group with acute surgical complications as underlying disease; d) showed no association with the number of patients included in the study by individual HPN-centers

The odds of the presence of CVC-VT: a) showed no association with the IVS categories; b) were higher in the in the longest HPN duration categories and in the underweight and obese categories of BMI; c) showed a negative association with the number of patients included in the study by individual HPN-centers.

The odds of CRBSI: a) were higher with the increase of the volume of the PN and were similar between PN1 and the FE type of IVS; b) were lower in older patients; c) were higher in the overweight and obese category of BMI and in the CIPO and miscellaneous categories of underlying disease; d) showed a negative association with the number of patients included in the study by individual HPN-centers.

The analyses including only the incident cases of IFALD and of CVC-VT showed non-statistically significant odds ratios (**Supplemental table 5**).

Table 2. Binomial logistic analysis of factors independently associated with the one-year probability of the intestinal failure associated liver disease, cholestasis or liver failure (IFALD), central venous catheter-associated deep vein thrombosis (CVC-VT) and catheter related bloodstream infections (CRBSI) in adult patients on home parenteral nutrition for chronic intestinal failure. Number of analyzed cases due to complete case approach: IFALD-cholestasis/liver failure (presence: 91, absence: 1610), CVC-VT (presence: 49, absence: 1652), CRBSI (presence: 257, absence: 1443).

	IFALD-cholestasis/liver failure			**CVC-VT**			**CRBSI**		
Independent factors	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
IVS type and volume									
PN1 (≤1 L)	1			1			1		
PN2 (1-2 L)	1.824	0.738-4.508	0.193	0.784	0.370-1.663	0.527	1.507	0.967-2.346	0.070
PN3 (2-3 L)	3.794	1.522-9.458	**0.004**	0.513	0.194-1.354	0.178	1.664	1.018-2.721	**0.042**
PN4 (>3 L)	4.828	1.792-13.004	**0.002**	0.437	0.110-1.732	0.239	2.523	1.423-4.475	**0.002**
FE (total)	0.849	0.202-3.569	0.823	0.384	0.078-1.894	0.240	0.743	0.362-1.525	0.418
Gender									
Male	1			1			1		
Female	0.703	0.449-1.099	0.122	0.798	0.434-1.470	0.470	1.066	0.797-1.427	0.666
Age (years)									
≤29	1			1			1		
30-49	0.775	0.355-1.693	0.522	1.875	0.495-7.108	0.355	0.597	0.371-0.961	**0.034**
50-69	0.694	0.317-1.517	0.360	2.017	0.545-7.461	0.293	0.469	0.291-0.756	**0.002**
≥70	0.822	0.339-1.994	0.665	1.657	0.396-6.939	0.489	0.551	0.319-0.952	**0.033**
BMI (kg/m^2)									
18.5-25.0	1			1			1		
≤15.0	1.064	0.233-4.858	0.936	2.705	0.566-12.935	0.212	0.837	0.333-2.106	0.706
15.0-18.5	1.612	0.872-2.983	0.128	2.335	1.093-4.987	**0.028**	1.061	0.697-1.615	0.782
25.1-30.0	0.611	0.310-1.207	0.156	1.134	0.470-2.738	0.779	1.460	1.012-2.108	**0.043**
≥30.0	0.591	0.172-2.036	0.405	3.124	0.829-11.769	0.092	2.769	1.580-4.851	**0.000**
Duration of HPN (years)									
≤1	1			1			1		

1-3	1.025	0.553-1.899	0.938	1.526	0.516-4.515	0.445	1.157	0.787-1.703	0.458
3-10	1.070	0.594-1.929	0.821	2.889	1.093-7.636	**0.032**	1.110	0.762-1.618	0.586
>10	0.982	0.470-2.052	0.962	3.477	1.179-10.256	**0.024**	0.853	0.522-1.393	0.524
Mechanism of IF									
SBS-J	1			1			1		
SBS-JC	0.649	0.338-1.245	0.193	1.926	0.848-4.374	0.117	0.964	0.629-1.479	0.868
SBS-JIC	0.629	0.208-1.902	0.411	0.760	0.189-3.060	0.699	1.377	0.754-2.516	0.298
Fistulas	0.593	0.219-1.607	0.304	0.580	0.071-4.733	0.611	1.207	0.676-2.154	0.525
Dysmotility	0.317	0.115-0.878	**0.027**	1.431	0.428-4.790	0.561	0.759	0.422-1.365	0.357
Obstruction	1.072	0.373-3.083	0.897	0.438	0.050-3.859	0.457	0.800	0.376-1.704	0.563
Mucosal disease	0.712	0.260-1.945	0.507	0.868	0.203-3.713	0.849	0.824	0.445-1.526	0.538
Underlying disease									
IBD	1			1			1		
CIPO	1.459	0.481-4.427	0.505	1.244	0.303-5.113	0.762	2.098	1.092-4.03	**0.026**
Other causes of SBS	1.265	0.501-3.192	0.619	2.308	0.742-7.18	0.149	1.490	0.843-2.634	0.170
Miscellaneous	2.038	0.909-4.567	0.084	2.308	0.723-7.366	0.158	1.712	1.002-2.924	**0.049**
Mesenteric ischemia	1.468	0.732-2.943	0.280	2.063	0.798-5.333	0.135	1.012	0.626-1.635	0.963
Radiation enteritis	0.613	0.170-2.210	0.454	0.824	0.161-4.206	0.816	0.967	0.487-1.918	0.923
Acute surgical complications	2.210	1.089-4.482	**0.028**	0.573	0.142-2.311	0.433	1.143	0.700-1.864	0.593
N. of patients included by center	0.939	0.765-1.153	0.551	0.580	0.451-0.745	**0.000**	0.710	0.626-0.806	**0.000**

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.

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 HPN-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 one-year odds of weaning from HPN and of HPN/IF-associated major complications, as well as with the risk of mortality, albeit the latter observation being based on a non-statistically significant finding 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 (e.g. drugs and dietary prescriptions) 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 HPN-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 multivariate analysis was contemporaneously associated with odds of weaning from HPN, death and 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 into 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, a non-statistically significant decreased risk of death was observed in those receiving the FE type of IVS, but no association was found with the 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. Future studies will clarify whether the association between the current volume categories of IVS and the risk of death will prove to be statistically significant

in the long-term and/or whether a different categorization of the IVS volume will capture any association between IVS volume and risk of death, both in the short and in the long-term.

The one-year probability of weaning from HPN 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 a 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 risk 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. 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, the odds of these complications were higher in the greater PN volume categories. 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 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 HPN 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 incident 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), [2,16]. The same incidence rate can be accounted for the 31 incident cases of IFALD-cholestasis/liver failure. This data is of some relevance as no prospective study has yet been carried out on this HPN/IF complication, [17].

The weakness of the study is mainly represented by the retrospective collection of data prospectively recorded in the previous 12 months, which would imply a risk of some underreporting, and by not using a co-morbidity index to assess the patient's general condition. However, CIF can develop as a complication of a number of gastrointestinal or systemic underlying diseases having different pathogenesis and outcomes, [1]. Therefore, the underlying disease that we collected and included in the statistical analysis, could be considered as a surrogate co-morbidity index, as supported by the finding of an increased risk of death in patients with CIF due to mesenteric ischemia. 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. Considering that CIF is a rare disease, [1] the observation of lower odds of death and of HPN/IF complications in HPN-center which included the larger number of patients in the study would support the importance of creating networks facilitating the referral of CIF patients to few but appropriately organized and experienced centers, [18]. Finally, the agreement between our results and the risk factors, other than 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 risk 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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Figure headings and footnotes

Figure 1. Cumulative one-year incidence of weaning from home parenteral nutrition (HPN) and of death according to the intravenous supplementation (IVS) type and volume. IVS type: FE, fluid and electrolyte alone; PN, parenteral nutrition admixture containing energy. IVS volume (L/day): PN1, ≤1; PN2, 1-2; PN3, 2-3; PN4, >3. FE1, FE2, FE3 and FE4 were grouped in a unique cohort (FE). The patient risk set is reported in **supplemental table 2**.

Figure 2. Forest plot of the analysis of factors associated with the one-year probability of weaning from home parenteral nutrition (HPN) or of death and of home parenteral nutrition /intestinal failure (HPN/IF) in adult patients with chronic intestinal. Number of analyzed cases due to complete case approach: 2035 (Still in HPN: 1610, Weaned from HPN: 278, Deceased: 147).

Footnote figure 2
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.

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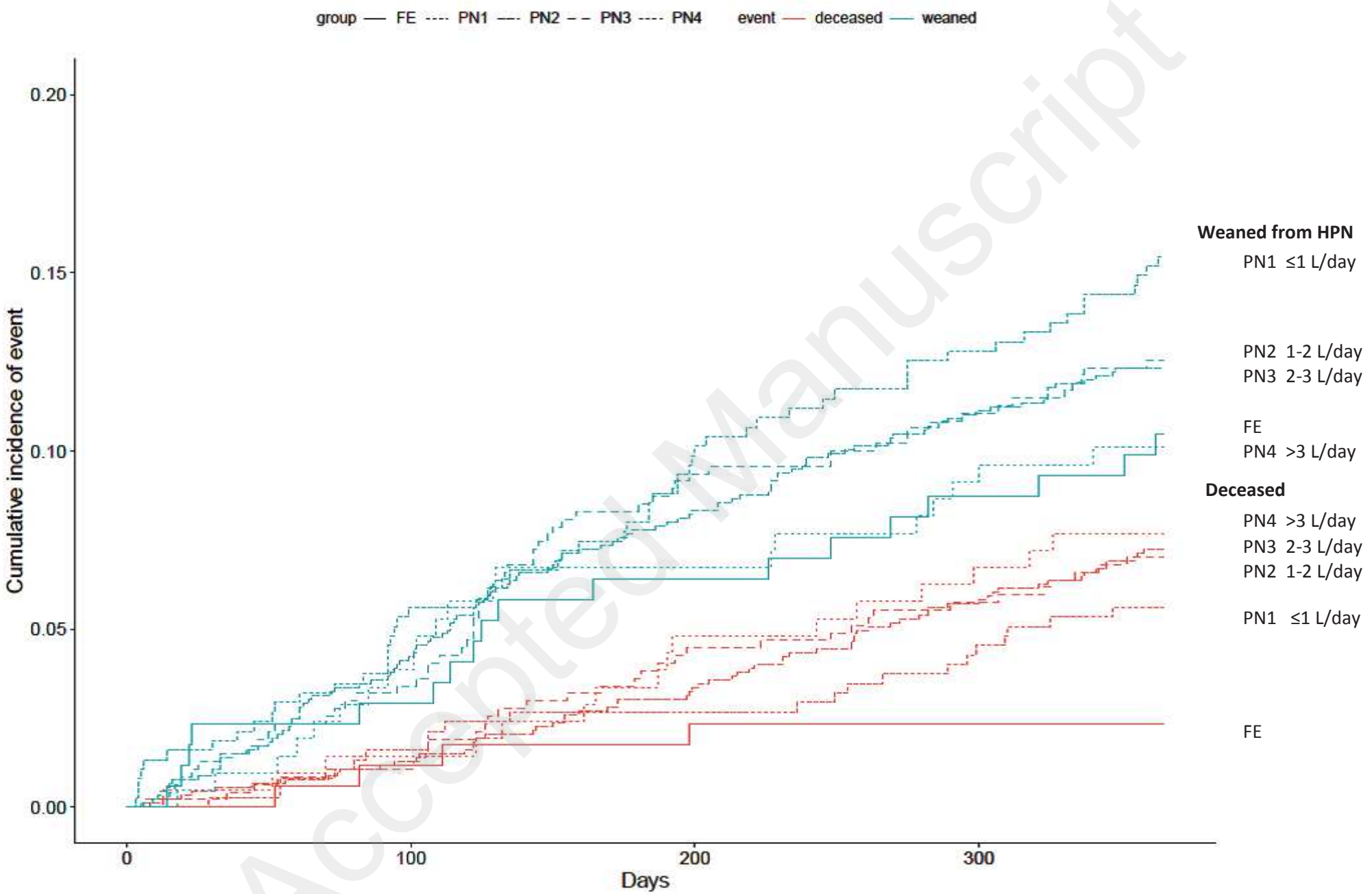
Statement of authorship

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. All the co-Authors participated in the acquisition of data, revised the final analysis, approved the final version of the manuscript and were accountable for all aspects of the work.

Conflict of interest statements

None declared



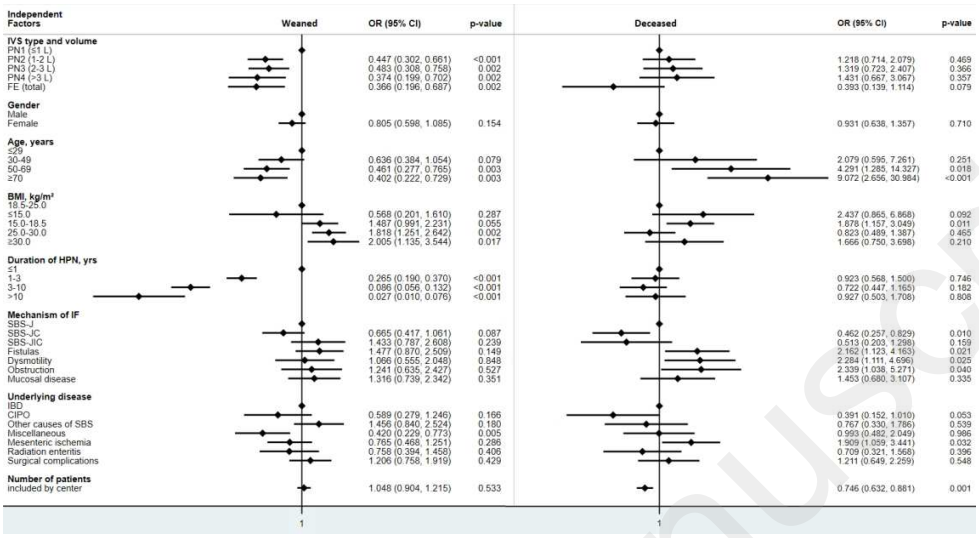


Figure 2

The intravenous supplementation type and volume is associated with one-year outcome and the major complications in patients with chronic intestinal failure

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