

HOME PARENTERAL NUTRITION PROVISION MODALITIES FOR CHRONIC INTESTINAL FAILURE IN ADULT PATIENTS: AN INTERNATIONAL SURVEY

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

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Abstract

Background and aim. The safety and effectiveness of an HPN program depends on both the expertise and the management procedures of the HPN center. We aimed to know the modalities needed to provide the home parenteral nutrition (HPN)-program and the types of intravenous supplementation (IVS)-admixture supplied to patients with chronic intestinal failure (CIF) in different countries.

Methods. In March 2015, 65 centers from 22 countries enrolled 3239 patients (benign disease 90.1%, malignant disease 9.9%), recording the patient, CIF and HPN characteristics in a structured database. The HPN-provider was categorized as health care system local pharmacy (LP) or home care company (HCC). The IVS-admixture was categorized as fluids and electrolytes alone (FE) or parenteral nutrition, either commercially premixed (PA) or customized to the individual patient (CA), alone or plus extra FE (PAFE or CAFE).

Results. HPN-provider: HCC 66%, LP 34%; no difference between benign-CIF and malignant-CIF. LP was the main modality in 11 Countries; HCC prevailed in 4 European countries, Israel, USA, South America and Oceania ($p < 0.001$). IVS-admixture: FE 10%, PA 17%, PAFE 17%, CA 38%, CAFE 18%. PA+PAFE use was greater in malignant-CIF and CA+CAFE use was greater in benign-CIF ($p < 0.001$). PA+PAFE prevailed in those Countries where LP was the main HPN-provider and CA+CAFE prevailed where the main HPN-provider was HCC ($p < 0.001$).

Conclusions. The HPN provision and the IVS-admixture types differ greatly among countries, among HPN centers and between benign-CIF and malignant-CIF. As both HPN provider and IVS-admixture types may play a role in the safety and effectiveness of HPN therapy, criteria to homogenize HPN programs are needed, to give patients the same opportunity to receive appropriate HPN therapy.

Keywords: Intestinal failure, home parenteral nutrition, management, intravenous supplementation, cancer.

Introduction

Home parenteral nutrition (HPN) is the primary and life-saving treatment for patients with chronic intestinal failure (CIF) [1]. 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” [2]. Chronic IF can be due to five pathophysiological mechanisms (short bowel, intestinal fistulas, intestinal dysmotility, intestinal mechanical occlusion, or extensive small bowel mucosa disease) which can originate from either non-malignant (benign-CIF) or malignant (malignant-CIF) diseases [2]. Patients with CIF require IVS for months, years or lifelong [1,2]. They are discharged onto HPN programs which aim to provide evidence-based therapy, to prevent HPN-related complications, such as central venous catheter (CVC)-related infections and metabolic complications, and to maximize the patient/family quality of life (QoL) [3,4]. The European Society for Clinical Nutrition and metabolism (ESPEN) guidelines on benign-CIF recommend that at discharge: patients are metabolically stable, able physically and emotionally to cope with the HPN therapy, and have an adequate home environment; patients should be cared for by a multidisciplinary team with skills and experience in IF and HPN management; patient/caregiver training for HPN management should be patient-centered with a multidisciplinary approach, together with written guidelines; HPN patients should have access to infusion pumps or devices with specified safety features together with ancillary products, safe compounding and delivery systems. Thus, the safety and effectiveness of a HPN program depends on the expertise and the management modalities of the HPN center.

It is known that the management and the provision of HPN programs differ greatly among countries and among HPN centers. However, only one study, performed in 2010, objectively described this feature [5]. Using the ESPEN database for CIF, we have carried out an international

cross-sectional survey to know the modalities used to provide the HPN-program and the types of IVS-admixtures supplied to patients with CIF.

Materials and methods

This international cross-sectional observational study comprises the largest study protocol approved by the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF) special interest group of ESPEN, which aims to investigate the applicability of the clinical classification of CIF [6]. The HPN centers' recruitment, the patient inclusion criteria, the modalities of data collection and the recorded items have been already extensively described [6] and are summarized below.

Participating centers and patient enrollment criteria

Sixty-five HPN centers from 22 countries enrolled all adult patients (≥ 18 year old) who were on HPN for either benign-CIF or malignant-CIF on March 1st 2015. The term malignant-CIF indicates the presence of an active malignant disease at time of enrollment on the study (and thus excludes, for example, patients with IF as a result of radiotherapy in whom the malignancy has been cured; these patients were surveyed within the benign-CIF group).

Data collection and schedule

Data were collected into a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database, termed "the CIF Action day", available at the web page of the HAN&CIF group on the ESPEN website [7].

Demographic, clinical, CIF, underlying disease, IVS and HPN program characteristics were gathered, and the clinical classification of CIF was calculated for each patient [6]. The HPN-provider was categorized as health care system local pharmacy (LP) or home care company (HCC). By HPN-provider was meant the supplier to the patient of the IVS-admixture, the infusion pump or regulatory device and the ancillaries for infusion-line management and CVC medication. The IVS-admixture was categorized as: fluids and electrolytes (FE); commercially premixed ready-to-use parenteral nutrition admixture (PA); commercially premixed parenteral nutrition admixture plus extra FE (PAFE);

parenteral nutrition admixture customized (tailored) to the individual patient requirements (CA);
parenteral nutrition admixture customized to the individual patient requirements alone or plus extra
FE (CAFE).

Ethical statement

The research was based on anonymized information taken from patient records at the 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. The identity of the contributing centers has also been anonymized for data analysis and presentation.

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 x 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 x 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 (m²).

Data are reported as mean ± standard deviation (SD) and as absolute and relative frequencies. The non-parametric Kruskal Wallis test, the Fisher's exact test and the Chi-square test were applied where appropriate.

The IBM SPSS 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.

Results

Participating centers and patient cohorts

A total of 3239 patients were included, 2919 benign-CIF (90.1%) and 320 malignant-CIF (9.9%) (**Table 1**). All the HPN centers enrolled benign-CIF patients, while only 45 of them enrolled malignant-CIF. The malignant-CIF cohort had statistically significant older age, lower BMI, shorter duration of HPN, IVS of greater daily volume and energy, and a 10 times greater percentage of patients with IF due to mechanical occlusions, (**Table 2**). In both benign-CIF and malignant-CIF, two-thirds of patients were female.

In the benign-CIF cohort, the underlying diseases were Crohn's disease 22.4%, mesenteric ischemia 17.7%, surgical complications 15.8%, primary chronic intestinal pseudo-obstruction 9.7%, radiation enteritis 7.3%, others (<3% each-one) 21.3%, and not reported 5.9%. In the malignant-CIF cohort, the type of cancer was not specified 62%, gastrointestinal 28%, extra-abdominal 10%. Concurrent enteritis due to radio- or chemo-therapy was described in 5% of cases, and peritoneal carcinomatosis was reported in 12%.

HPN-providers and IVS-admixture types in the total group

The HPN-provider was not reported in 11 cases and was LP in 1111 (34.4%) and HCC in 2117 (65.6%) cases. The IVS-admixture type was FE in 312 (9.7%), PA in 556 (17.2%) and PAFE in 541 (16.8%), CA in 1227 (37.9%) and CAFE in 595 (18.4%) cases. The IVS-admixture types significantly differed between the two modalities of HPN provision. When the HPN was provided by a HCC, the IVS-admixtures were CA or CAFE in two-thirds of cases, while PA or PAFE accounted for more than 50% of the IVS-admixtures provided by the LPs (**Table 3**).

HPN-providers and IVS-admixture types by countries

HCCs provided all HPN in the UK and Israel, were almost exclusive providers ($\geq 80\%$ of patients) in the USA, Mexico and South America, and were the main providers (56-63% of cases) in France, Italy, Poland and Oceania. LPs provided all the HPN programs in Denmark, two thirds of programs in The Netherlands and more than 90% of cases in the other 9 European countries which contributed to the survey (**Figure 1**).

In those countries, excepting Poland, where most or all the HPN programs were provided by a HCC, CA and CAFE represented more than 50% of the IVS-admixtures. Where the LP was the main HPN-provider, PA and PAFE prescription prevailed (**Figure 2**).

HPN-providers and IVS-admixture types by the nature of the underlying disease

The percentage split of the two HPN-providers did not differ between benign-CIF and malignant-CIF, while CA and CAFE were the IVS-admixture types in almost two-thirds of benign-CIF and PA and PAFE were the IVS-admixture types in more than 50% of malignant-CIF (**Figure 3**).

Discussion

This international survey shows that the modalities of HPN provision and the type of IVS-admixture supplied significantly differ among countries and between benign-CIF and malignant-CIF. Although it is well known that HPN management is not homogeneous among countries or among HPN centers within an individual country, this is the first study that gives objective data on this aspect. The strengths of the study are the large numbers of participating countries, and the worldwide distribution of contributing HPN-centers and enrolled patients. The main limitation of the study is the relatively small number of malignant-CIF patients, in comparison with those with benign-CIF (**Table 1**). Actually, the percentage of enrolled patients with malignant-CIF is lower than that expected on the basis of previous early and recent surveys on HPN [8-13]. This could be due to the voluntary basis of the HPN center participation, that could have attracted primarily those centers mainly caring for benign-CIF. Indeed, it may be that in individual countries, most of the patients on HPN for cancer are managed by specialists other than those caring for CIF, such as oncologists or internists. Another explanation could be that, in previous surveys on HPN prevalence, a percentage of patients with a diagnosis of cancer may have not had CIF, being on HPN because of refusal of an otherwise working gut, or just because they already had a CVC positioned for chemotherapy. However, as expected, the benign-CIF and the malignant-CIF cohorts of the present study consistently differed for all the clinical and IVS characteristics, thus supporting the representativeness of the malignant-CIF cohort (**Table 2**).

Overall, the prescribed IVS-admixture type and the HPN-providers looked associated. Commercially PA or PAFE were more frequently used when the LP was the HPN-provider, while CA or CAFE were more frequently used when the HPN-provider was a HCC (**Table 3**). This would indicate that, when required, a HCC makes it easier to supply a tailored IVS-admixture. Indeed, as CIF is a rare

condition, not all the LP may have developed the expertise and/or implemented the facilities to produce CA in a sufficient quantity to overcome the production costs.

The data confirm that the HPN provision modalities differ greatly among the individual countries, with a range of 0 to 100% of cases for both HCC and LP (**Figure 1**). The association between the HPN provision modality and the IVS-admixture types reported in the total cohort, was observed also in the individual countries (**Figure 2**). The primary aims of an HPN program are prevention of HPN-related complications and maximization of the patient/family QoL [3]. The protocol for patient/caregiver training and the facilities and ancillaries for IVS management may be very relevant to the CVC-related complications, and the availability of a portable infusion pump may significantly change the QoL of patients [3]. Differences between means of HPN provision may therefore have implications to the safety and efficacy of an HPN program. This suggests that criteria for the implementation of HPN provision should be formally devised, in order to homogenize this feature of the HPN program and to give patients the same opportunity to receive appropriate HPN therapy regardless of where they live.

The results showed that IVS-admixture types but not the HPN-provider differed between benign-CIF and malignant-CIF. The IVS-admixtures tailored to the patient requirements (CA and CAFE) were mainly used in benign-CIF, while premixed, ready-to-use, IVS-admixture (PA and PAFE) were mainly used in malignant-CIF (**Figure 3**). This difference may be due to the characteristics of the two patient populations, in terms of pathophysiological mechanisms of IF as well as in the aims of the HPN program and the expected patient outcome. The clinical scenarios of benign-CIF and malignant-CIF are quite different. In malignant-CIF, the cause of IF was more homogeneous, being represented by mechanical obstruction in almost 50% of cases, often due to peritoneal carcinomatosis. In benign-CIF, the mechanisms of IF were represented by SBS and fistula in almost 70% of patients. The oral food

and beverage intakes and the intestinal fluid and electrolytes losses may greatly differ among patients [6]. Patients with benign CIF have a high survival probability, may have good probabilities of intestinal rehabilitation and programs aim for social-working-familial rehabilitation and good QoL. Most of the patients are independent from a caregiver and do not need any home healthcare assistance [3]. This scenario often needs a fine tuning of the HPN program, requiring tailored IVS-admixture in order to maximize the prevention of long-term metabolic complications as well as the daily time free of IVS infusion. In patients with malignant-CIF, HPN may be required while waiting for or during cancer-directed treatment, on symptomatic treatment, and/or receiving palliative care [4]. The expected duration of HPN is much shorter, either because of a transient need related to cancer treatment plans or to short life expectancy of advanced cancer. These patients are often home-bound, dependent on a caregiver and require home healthcare assistance. Safety of the line infusion is a priority of any HPN program, while the risk of metabolic complications may be lower in the short term. In this scenario, premixed ready-use IVS-admixtures may adequately fit with the requirements of the patient with malignant-CIF. The lack of differences in HPN-provider between benign-CIF and malignant-CIF was probably due to the bias in the enrollment of the HPN centers, that were mostly devoted to benign-CIF, so that the same HPN provider may have been used for the few patients with malignant-CIF enrolled.

In conclusion, the HPN provision modalities and the IVS-admixture types differ greatly among countries and between benign-CIF and malignant-CIF. As both HPN provider and IVS-admixture types may play a role in the safety and effectiveness of a HPN program, these data indicate the need to devise criteria to homogenize these essential features of HPN, in order to give all patients with CIF the same opportunity to receive this life-saving therapy in the appropriate modality.

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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

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Conflict of interest statements

None declared.

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Table 1. Patients on home parenteral nutrition for chronic intestinal failure (CIF) due to non-malignant (benign) or malignant disease, enrolled by countries contributing in the survey.

| | Total n. | Benign-CIF n. (%) | Malignant-CIF n. (%) |
|-----------------|---------------------|------------------------------|---------------------------------|
| UK | 781 | 738 (94.5) | 43 (5.5) |
| France | 478 | 441 (92.3) | 37 (7.7) |
| Italy | 362 | 326 (90.1) | 36 (9.9) |
| Poland | 283 | 224 (79.2) | 59 (20.8) |
| Denmark | 262 | 233 (88.9) | 29 (11.1) |
| The Netherlands | 257 | 229 (89.1) | 28 (10.9) |
| Spain | 43 | 40 (93.0) | 3 (7.0) |
| Slovenia | 39 | 31 (79.5) | 8 (20.5) |
| Sweden | 25 | 24 (96.0) | 1 (4.0) |
| Hungary | 22 | 20 (90.9) | 2 (9.2) |
| Belgium | 21 | 21 (100) | 0 |
| Germany | 10 | 1 (10) | 9 (90) |
| Bulgaria | 5 | 4 (80) | 1 (20) |
| Croatia | 3 | 3 (100) | 0 |
| Lithuania | 3 | 2 (66.7) | 1 (33.3) |
| USA | 429 | 389 (90.7) | 40 (9.3) |
| Israel | 90 | 71 (78.9) | 19 (21.1) |
| Mexico | 4 | 3 (75) | 1 (25) |
| Argentina | 44 | 44 (100) | 0 |
| Brasil | 7 | 7 (100) | 0 |
| Australia | 44 | 41 (93.2) | 3 (6.8) |
| New Zealand | 27 | 27 (100) | 0 |
| Total | 3239 | 2919 (90.1) | 320 (9.9) |

Table 2. Characteristics of the cohorts of patients with chronic intestinal failure (CIF) enrolled in the study: patients without malignant disease (Benign-CIF), n. 2919; patients with a malignant disease (Malignant-CIF), n.320.

| | Benign-CIF | Malignant-CIF | P |
|----------------------------------------------|---------------|---------------|--------|
| Gender | | | 0.202 |
| Males | 36.8% | 39.45 | |
| Females | 63.2% | 60.6% | |
| Age, years | 54.9±16.0 | 60.6±13.5 | <0.001 |
| BMI, kg/m ² | 22.2±4.4 | 21.5±4.4 | 0.002 |
| HPN duration, months | 58.1±71.5 | 17.1±30.9 | <0.001 |
| Pathophysiological mechanism of IF | | | <0.001 |
| SBS-J | 38.6% | 28.8% | |
| SBS-JC | 19.9% | 9.7% | |
| SBS-JIC | 5.9% | 2.8% | |
| Fistulas | 7.0% | 3.4% | |
| Dysmotility | 17.5% | 3.4% | |
| Mechanical Obstruction | 4.4% | 45.9% | |
| Mucosal Disease | 6.8% | 5.9% | |
| IVS volume, mL/day | 1877.0±1016.6 | 1967.6±817.8 | 0.004 |
| IVS energy, kcal/day | 1088.0±649.4 | 1315.9±560.9 | <0.001 |
| Clinical classification of CIF (IVS, mL/day) | | | <0.001 |
| FE1, ≤1000 | 5.8% | 3.1% | |
| FE2, 1001-2000 | 2.2% | 1.3% | |
| FE2, 2001-3000 | 0.5% | 0 | |
| FE4, >3000 | 0.3% | 0 | |
| PN1, ≤1000 | 15.9% | 10.3% | |
| PN2, 1001-2000 | 40.9% | 47.2% | |
| PN3, 2001-3000 | 23.1% | 29.4% | |
| PN4, >3000 | 11.3% | 8.8% | |

BMI, body mass index; HPN, home parenteral nutrition; SBS-J, short bowel syndrome with end jejunostomy; SBS-JC, short bowel syndrome with jejunocolon anastomosis; SBS-JIC, short bowel syndrome with jejunocolon anastomosis and total colon; IVS, intravenous supplementation; FE, fluid and electrolytes; PN, parenteral nutrition

Table 3. Intravenous supplementation (IVS)-admixture type by home parenteral nutrition (HPN)-provider in patients with chronic intestinal failure (P<0.001)

| | Total n. | FE n. (%) | PA n. (%) | PAFE n. (%) | CA n. (%) | CAFE n. (%) | P |
|------------|--------------------|---------------------|---------------------|-----------------------|---------------------|-----------------------|----------|
| HCC | 2117 | 224 (10.5) | 149 (7.0) | 304 (14.3) | 906 (42.8) | 534 (25.2) | <0.001 |
| LP | 1111 | 88 (7.9) | 407 (36.6) | 237 (21.3) | 318 (28.6) | 61 (5.4) | |

HCC, home care company

LP, health care system local pharmacy

FE, fluids and electrolytes

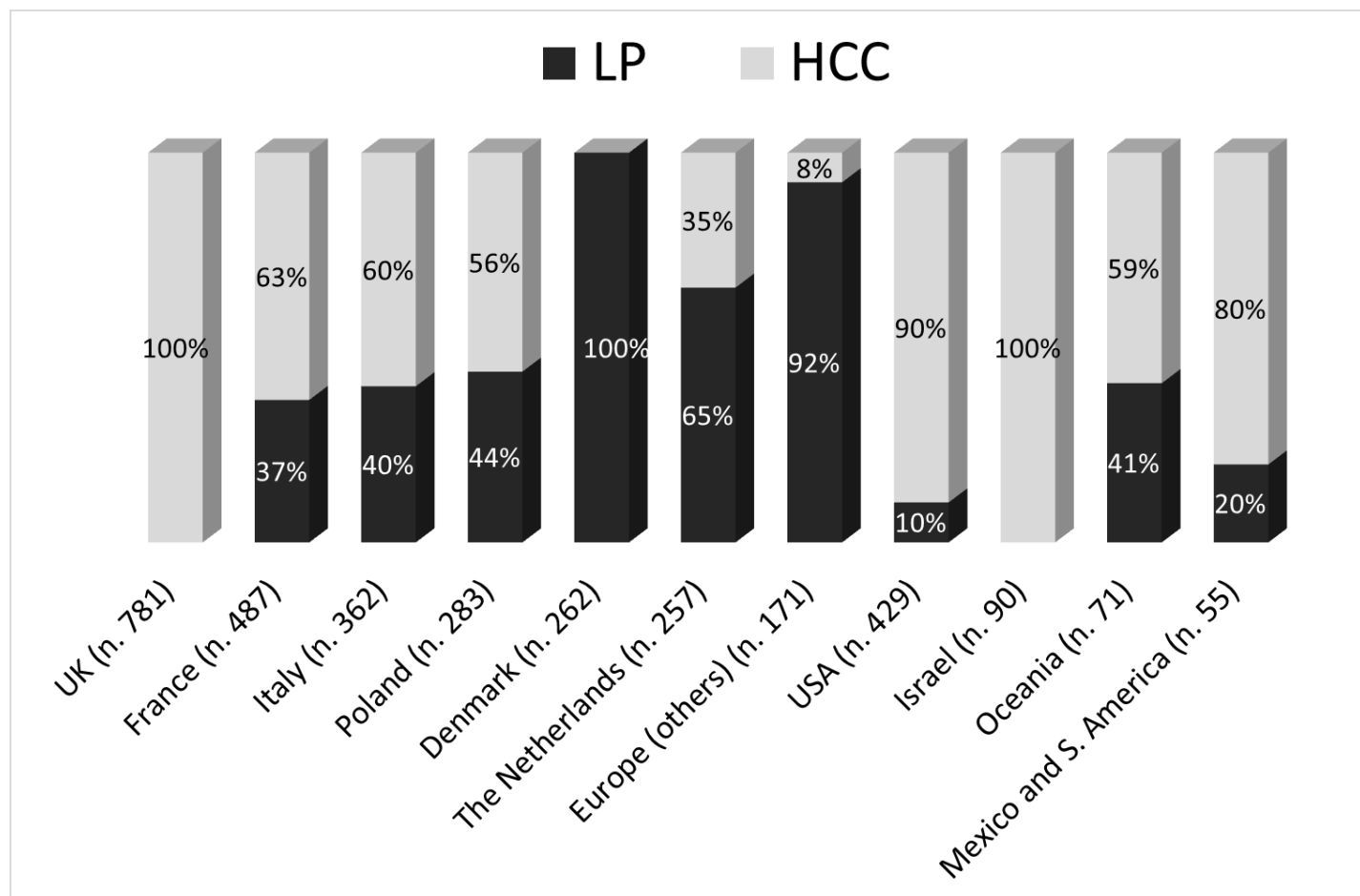
PA, commercially premixed ready-to-use parenteral nutrition admixture

PAFE, commercially premixed ready-to-use parenteral nutrition admixture plus extra fluids and electrolytes

CA, parenteral nutrition admixture customized (tailored) to the individual patient requirements

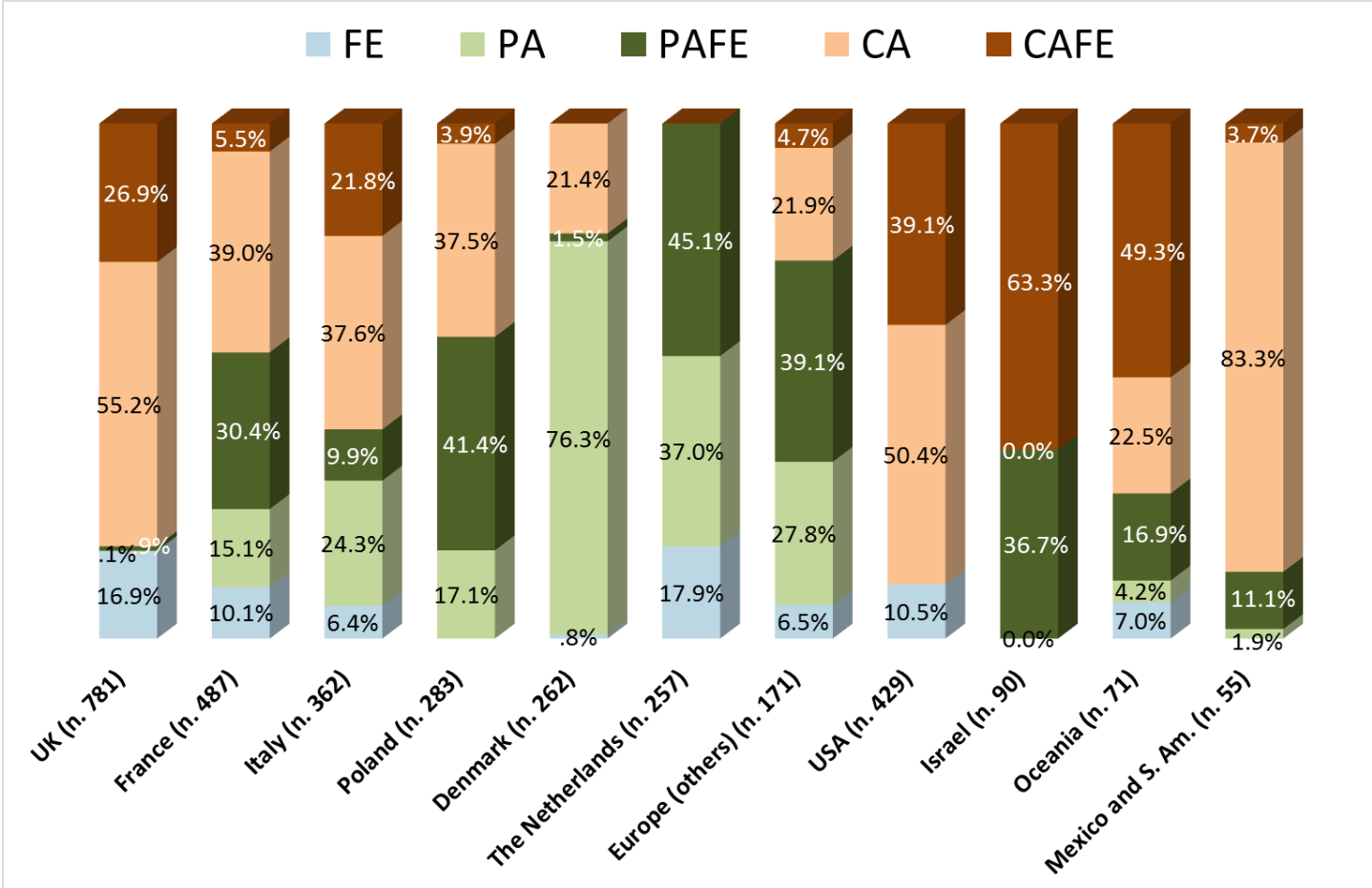
CAFE, parenteral nutrition admixture customized (tailored) to the individual patient requirements plus extra fluids and electrolytes

Figure 1. Home parenteral nutrition (HPN)-providers by countries in patients with chronic intestinal failure. **LP**, health care system local pharmacy. **HCC**, home care company. (P<0.001)



Europe others: Belgium, Bulgaria, Croatia, Germany, Hungary, Lithuania, Slovenia, Spain, Sweden. **Oceania:** Australia, New Zealand
S. America: Argentina, Brasil

Figure 2. Intravenous supplementation (IVS)-admixture type by countries in patients with chronic intestinal failure. **FE**, fluids and electrolytes; **PA**, commercially premixed ready-to-use parenteral nutrition admixture; **PAFE**, commercially premixed ready-to-use parenteral nutrition admixture plus extra fluids and electrolytes; **CA**, parenteral nutrition admixture customized (tailored) to the individual patient requirements; **CAFE**, parenteral nutrition admixture customized (tailored) to the individual patient requirements plus extra fluids and electrolytes (P<0.001)



Europe others: Belgium, Bulgaria, Croatia, Germany, Hungary, Lithuania, Slovenia, Spain, Sweden. **Oceania:** Australia, New Zealand
S. Am.: Argentina, Brasil

Figure 3. Home parenteral nutrition (HPN)-provider (P=0.083) and intravenous supplementation (IVS)-admixture type (P<0.001) by nature of the underlying disease in patients with chronic intestinal failure.

HPN-provider: LP, health care system local pharmacy. HCC, home care company.

IVS-admixture: FE, fluids and electrolytes; PA, commercially premixed ready-to-use parenteral nutrition admixture; PAFE, commercially premixed ready-to-use parenteral nutrition admixture plus extra fluids and electrolytes; CA, parenteral nutrition admixture customized (tailored) to the individual patient requirements; CAFE, parenteral nutrition admixture customized (tailored) to the individual patient requirements plus extra fluids and electrolytes

