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## Characteristics of adult patients with chronic intestinal failure due to short bowel syndrome

*An international multicenter survey*

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Original article

## Characteristics of adult patients with chronic intestinal failure due to short bowel syndrome: An international multicenter survey

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## SUMMARY

**Background and aims:** The case-mix of patients with intestinal failure due to short bowel syndrome (SBS-IF) can differ among centres and may also be affected by the timeframe of data collection. Therefore, the ESPEN international multicenter cross-sectional survey was analyzed to compare the characteristics of SBS-IF cohorts collected within the same timeframe in different countries.

**Methods:** The study included 1880 adult SBS-IF patients collected in 2015 by 65 centres from 22 countries. The demographic, nutritional, SBS type (end jejunostomy, SBS-J; jejuno-colic anastomosis, SBS-JC; jejunoileal anastomosis with an intact colon and ileocecal valve, SBS-JIC), underlying disease and intravenous supplementation (IVS) characteristics were analyzed. IVS was classified as fluid and electrolyte alone (FE) or parenteral nutrition admixture (PN). The mean daily IVS volume, calculated on a weekly basis, was categorized as <1, 1–2, 2–3 and >3 L/day.

**Results:** In the entire group: 60.7% were females and SBS-J comprised 60% of cases, while mesenteric ischaemia (MI) and Crohn' disease (CD) were the main underlying diseases. IVS dependency was longer than 3 years in around 50% of cases; IVS was infused  $\geq 5$  days/week in 75% and FE in 10% of cases. *Within the SBS-IF cohort:* CD was twice and thrice more frequent in SBS-J than SBS-JC and SBS-JIC, respectively, while MI was more frequent in SBS-JC and SBS-JIC. *Within countries:* SBS-J represented 75% or more of patients in UK and Denmark and 50–60% in the other countries, except Poland where SBS-JC prevailed. CD was the main underlying disease in UK, USA, Denmark and The Netherlands, while MI prevailed in France, Italy and Poland.

**Conclusions:** SBS-IF type is primarily determined by the underlying disease, with significant variation between countries. These novel data will be useful for planning and managing both clinical activity and research studies on SBS.

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## 1. Introduction

In adults, short bowel syndrome (SBS) occurs due to extensive surgical resection leaving less than 200 cm of small intestine,

measured from the ligament of Treitz [1,2]. Patients typically present with diarrhea, malnutrition and dehydration [1,2]. In some patients, SBS can occur despite a post-resection small intestine length >200 cm due to impairment of remnant bowel function

(functional SBS) [1–3]. SBS is the main cause of chronic intestinal failure (CIF), which is defined as “the persistent reduction of the 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” [4]. For patients with CIF, IVS is provided at patient’s home through home parenteral nutrition (HPN) programs [4]. The international multicenter cross-sectional survey carried out by the European Society for Clinical Nutrition and Metabolism (ESPEN), demonstrated that around two thirds of all CIF cases resulted from SBS (SBS-IF) [3].

Individual centre surveys have shown that the case-mix of patients with SBS-IF can differ between IF centres. Mesenteric ischemia (MI) and Crohn’s disease (CD) accounted for 58.0% (MI 20.5%, CD 37.5%) of the Salford cohort in the UK [5], 59.4% (MI 35.0%, CD 24.40%) of the Copenhagen cohort in Denmark [6], 49.0% (MI 43.0%, CD 6.0%) of the Paris cohort in France [7] and 53.1% (MI 29.1%, CD 24.0%) of the Bologna cohort in Italy [8]. Also, the type of SBS differed among centres, with ranges of 18–82% for SBS-J, 6.2–67% for SBS-JC and 1.1–15% for SBS-JIC [5–8]. However, the study design and the time-frame of data collection varied amongst these reports and could have contributed to the observed differences. The British, Danish and Italian studies were cross-sectional observations of patients who were on HPN in 2017, 2017 and 2020, respectively [5,6,8]. The French study included all patients with SBS-IF treated from 1980 to 2006 [7]. Despite these findings, it is currently unknown if these SBS-IF patient characteristics are comparable in other countries and/or whether they have remained consistent over time. Therefore, the SBS-IF cohort of the ESPEN international multicenter cross-sectional survey [3] was analyzed in order to compare patient characteristics at the same time in different countries.

## 2. Materials and methods

### 2.1. Data collection and patient population

The ESPEN international cross-sectional observational study on CIF [3] was the baseline of a prospective survey developed by the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF) special interest group of ESPEN, aimed at investigating the outcome of patients with CIF [9]. Invitation to participate in the study occurred via representatives of the national Parenteral and Enteral Nutrition (PEN) societies of the ESPEN Council, who were asked to send the study protocol to members of their PEN societies. Sixty-five HPN centers from 22 countries were interested in participating in the study and enrolled all adult patients ( $\geq 18$ -year-old) who were dependent on HPN for either benign-CIF or malignant-CIF on March 1st, 2015 [3]. The term malignant-CIF indicates the presence of active malignant disease [3]. Data were collected in a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database, termed “the CIF Action day” [3,9]. Demographic, clinical, CIF, underlying disease, IVS and HPN program characteristics were collected. A total of 3362 patients were enrolled: 320 with malignant CIF and 2919 with benign CIF. The mechanisms of benign CIF were SBS-IF in 64.3%, enterocutaneous fistulas in 7.0%, intestinal dysmotility in 17.5%, mechanical obstruction in 4.4% and extensive mucosal disease in 6.8% [3]. For the purpose of the present study, only patients with benign SBS-IF were analyzed.

### 2.2. 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.

### 2.3. Statistical analysis

Depending on the anatomy of the remnant bowel, SBS was categorized as: end jejunostomy (SBS-J); jejunocolic anastomosis (SBS-JC); jejunoleal anastomosis with an intact colon and ileocecal valve (SBS-JIC) [2,3]. Patients who required IVS because of a high output ileostomy were defined “functional SBS” and were included in the SBS-J group. The severity classification of CIF was based on the type and volume of IVS, calculated as daily mean of the total volume infused per week and consisted of eight categories: volume per day of infusion  $\times$  number of infusions per week/7 (mL/day): FE1 or PN1,  $\leq 1000$ ; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4,  $>3000$  [9]. 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  $\times$  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  $\times$  number of infusions per week/7/kg patient body weight. The patient’s body mass index (BMI) was calculated by Quetelet’s formula (weight (kg)/height (m<sup>2</sup>)).

Data are reported as mean  $\pm$  standard deviation (m $\pm$ SD), minimum–maximum range and percentage.

The IBM SSPS Statistics package for Windows, version 23.0 (BM Co., Armonk, NY, USA) was used for the analyses.

## 3. Results

### 3.1. Total population

The total cohort consisted of 1880 SBS-IF patients, included by 65 centres from 22 countries: 1559 patients (82.9%) were from European countries, the remainder were from the USA (n. 221, 11.8%), Israel (n.21, 1.1%), South and Central America (n. 35, 1.9%) and Oceania (n.44, 3.3%); 7 countries (Denmark, France, Italy, Poland, The Netherlands, UK, USA) enrolled more than 100 patients and 4 countries (Australia, Argentina, Spain, and Israel) each enrolled between 20 and 40 patients.

Table 1 shows the characteristics of the total group and of the gender cohorts.

Around two-thirds of patients were females (60.7%), aged over 50 years (69%) and mostly with a BMI within the normal range (61.9%).

The SBS types were SBS-J in 1127 patients (40 of whom had a functional SBS), SBS-JC in 581 and SBS JIC in 172. Three-fourths of the underlying diseases were represented by CD, MI, post-surgical complications, and radiation enteritis. CD and MI equally contributed to the majority (53.8%) of total cases.

The duration of IVS was less than 3 years in around one-half of patients and longer than 10 years in one-sixth. Three-fourths of patients received IVS infusion 5 or more days per week (7 days in more than one-half). The type of IVS was FE in around 10% of patients, PN  $< 2$  L/day in one-half and PN  $> 2$  L/day in one-third.

The most evident differences between the gender cohorts were in body height and weight, shorter and lower in females, as expected, and in radiation enteritis as underlying disease, which was more frequent in females.

### 3.2. Characteristics of the SBS type cohorts

Patient characteristics are summarized in Fig. 1 and extensively reported in supplementary table 1.

**Table 1**

Demographic nutritional status, intravenous supplementation, anatomical characteristics, and underlying diseases of patients with chronic intestinal failure due to short bowel syndrome.

	Total n. 1880	Males n. 738	Females n. 1142
Age, yr. ( <i>m ± SD</i> )	56.7 ± 15.3	55.5 ± 15.6	57.5 ± 15.0
range	18.0–92.0	18.0–88.0	19.0–92.0
Age-class, yr (%)			
≤29	5.7	7.1	4.7
30–49	25.3	26.4	24.4
50–69	46.9	47.1	46.8
≥70	22.1	19.4	24.0
Body weight, kg ( <i>m ± SD</i> )	62.8 ± 13.8	69.5 ± 12.9	58.5 ± 12.7
range	24.5–119.0	30.0–110.9	24.5–119.0
Body weight-class, kg (%)			
<40	1.9	0.8	2.5
40–49	14.8	4.6	21.5
50–59	28.0	15.9	35.8
60–69	26.8	30.8	24.2
70–79	17.2	28.6	9.8
80–89	6.5	11.4	3.4
90–99	3.6	6.8	1.6
100–109	1.0	1.1	1.0
≥110	0.2	0.1	0.3
Body height, cm ( <i>m ± SD</i> )	166.2 ± 9.9	174.1 ± 8.3	161.1 ± 7.1
range	132–201	138–201	132–193
Body height-class, cm (%)			
≤160	32.6	6.2	49.7
161–170	35.9	27.0	41.7
171–180	23.0	45.7	8.2
>180	8.5	21.1	0.4
BMI, kg/m <sup>2</sup> ( <i>m ± SD</i> )	22.7 ± 4.2	22.9 ± 3.7	22.5 ± 4.6
range	10.5–46.8	13.5–39.3	10.5–46.8
BMI-class, kg/m <sup>2</sup> (%)			
≤15.0	1.6	1.4	1.8
15.1–18.5	12.6	9.0	15.0
18.6–25.0	61.9	64.6	60.2
25.1–30.0	18.2	21.2	16.3
>30	5.6	3.9	6.7
SBS type (%)			
SBS-J	60.0	58.1	61.1
SBS-JC	30.9	32.4	30.0
SBS-JIC	9.1	9.5	8.9
Underlying disease (%)			
Adhesion	2.3	2.0	2.5
Cancer	1.3	1.9	0.9
CIPO	2.2	2.3	2.2
Crohn's disease	27.1	28.5	26.3
Mesenteric Ischemia	26.7	30.8	24.1
Polyposis-Gardner's	2.2	2.4	2.1
Radiation enteritis	6.3	1.9	9.1
Surgical complications	16.7	14.8	18.0
Trauma	1.5	2.2	1.1
Ulcerative colitis	1.3	1.8	1.0
Volvulus	3.7	4.2	3.3
Other	3.1	2.6	3.5
Not reported	5.5	4.7	6.0
IVS			
Duration, mo ( <i>m ± SD</i> )	65.2 ± 77.4	65.7 ± 81.2	64.9 ± 75.0
range	0–474.0	0–474.0	0–463.1
Duration-class, yr (%)			
≤1	22.8	25.0	21.4
1.1–3	26.0	24.4	27.0
3.1–10	35.4	35.0	35.4
>10	15.8	15.6	16.2
Infusion			
Days/week, n. ( <i>m ± SD</i> )	5.8 ± 1.6	5.9 ± 1.5	5.8 ± 1.6
range	1–7	1–7	1–7
Days/week-class (%).			
<3	3.1	2.9	3.3
3–4	19.8	19.1	20.3
5–6	20.3	19.4	20.8
7	56.8	58.7	55.5
Volume mL/week, ( <i>m ± SD</i> )	13,585 ± 7668	14,580 ± 8096	12,777 ± 7296
Range	572–52,800	572–52,800	750–38,500
Volume mL/day ( <i>m ± SD</i> )	1926 ± 1095	2083 ± 1157	1825 ± 1042
Range	82–7543	82–7543	107–5500
Volume, mL/kg/day, ( <i>m ± SD</i> )	31.8 ± 19.0	31.0 ± 18.6	32.3 ± 19.3

Table 1 (continued)

	Total n. 1880	Males n. 738	Females n. 1142
Range	0.9–142.2	0.9–142.2	1.3–115.4
Energy, kcal/week ( <i>m</i> ± <i>SD</i> )	7074 ± 4560	8221 ± 4842	6333 ± 4208
Range	0–23,803	0–23803	0–21021
Energy, kcal/day ( <i>m</i> ± <i>SD</i> )	1011 ± 651	1174 ± 692	905 ± 601
Range	0–3400	0–3400	0–3003
Energy, kcal/kg/day, ( <i>m</i> ± <i>SD</i> )	17.0 ± 11.5	17.8 ± 11.2	16.5 ± 11.7
Range	0–74.7	0–55.6	0–74.7
IF-class, volume/day of infusion (%)			
FE1 (≤1 L)	7.0	4.9	8.4
FE2 (1–2 L)	2.7	2.8	2.5
FE3 (2–3 L)	0.6	0.8	0.5
FE4 (>3 L)	0.4	0.4	0.4
PN1 (≤1 L)	16.3	12.6	18.7
PN2 (1–2 L)	35.4	36.4	34.8
PN3 (2–3 L)	23.9	25.9	22.6
PN4 (>3 L)	13.7	16.1	12.2

BMI, body mass index. IVS, intravenous supplementation. IF, intestinal failure. CIPO, chronic intestinal pseudo-obstruction. SBS, short bowel syndrome. SBS-J, end jejunostomy. SBS-JC, jejunocolic anastomosis. SBS-JIC, jejunioileal anastomosis with an intact colon and ileocecal valve. FE, fluid and electrolytes alone. PN, parenteral nutrition-admixture.

The three cohorts were similar for gender, age and BMI categories. Females were 61.9%, 58.9% and 59.3%, and age was lower than 50 years in 31.8%, 28.0% and 37.2% of the SBS-J, SBS-JC and SBS-JIC cohorts, respectively. BMI was below normal in 13%, 15.9%, 17.1%, within the normal range in 60.7%, 63.6%, 64.1%, and above normal in 26.3%, 20.5%, 18.5%, of the SBS-J, SBS-JC and SBS-JIC cohorts, respectively.

Differences were observed in the underlying diseases and IVS characteristics (Fig. 1). CD was more frequent in SBS-J, and MI prevailed in SBS-JC and SBS-JIC. The duration of IVS was shorter in SBS-J (less than 3 years in more than one-half), whereas it was

longer than 3 years in 61.4% of SBS-JC and in 52.3% of SBS-JIC. The number of days of IVS infusion per week and the percentage of patients requiring the FE type of IVS were greater in the SBS-J group. The volume of IVS was also higher in SBS-J than in SBS-JC and SBS-JIC, whereas no differences between the SBS types were observed in IVS energy.

### 3.3. SBS patient cohorts in the different countries

Country-based data are shown in Fig. 2 and are extensively reported in supplementary table 2.

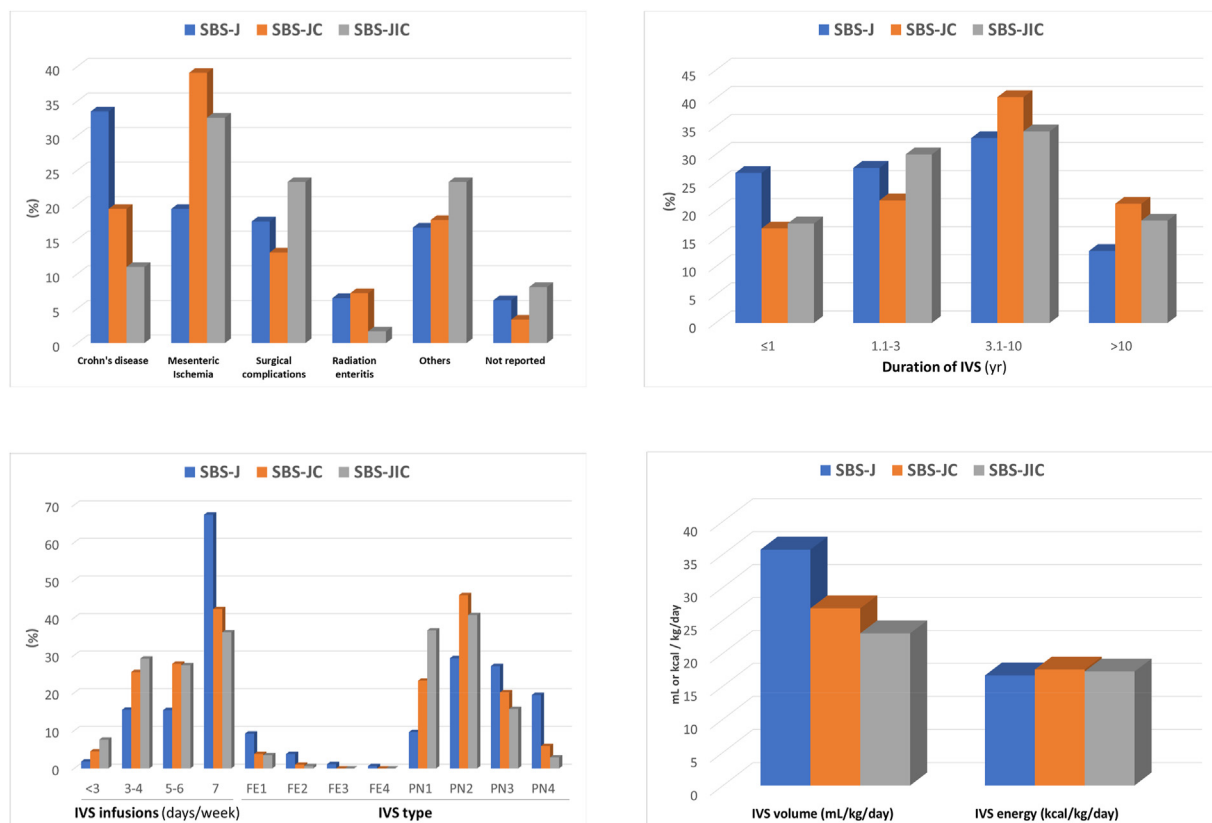
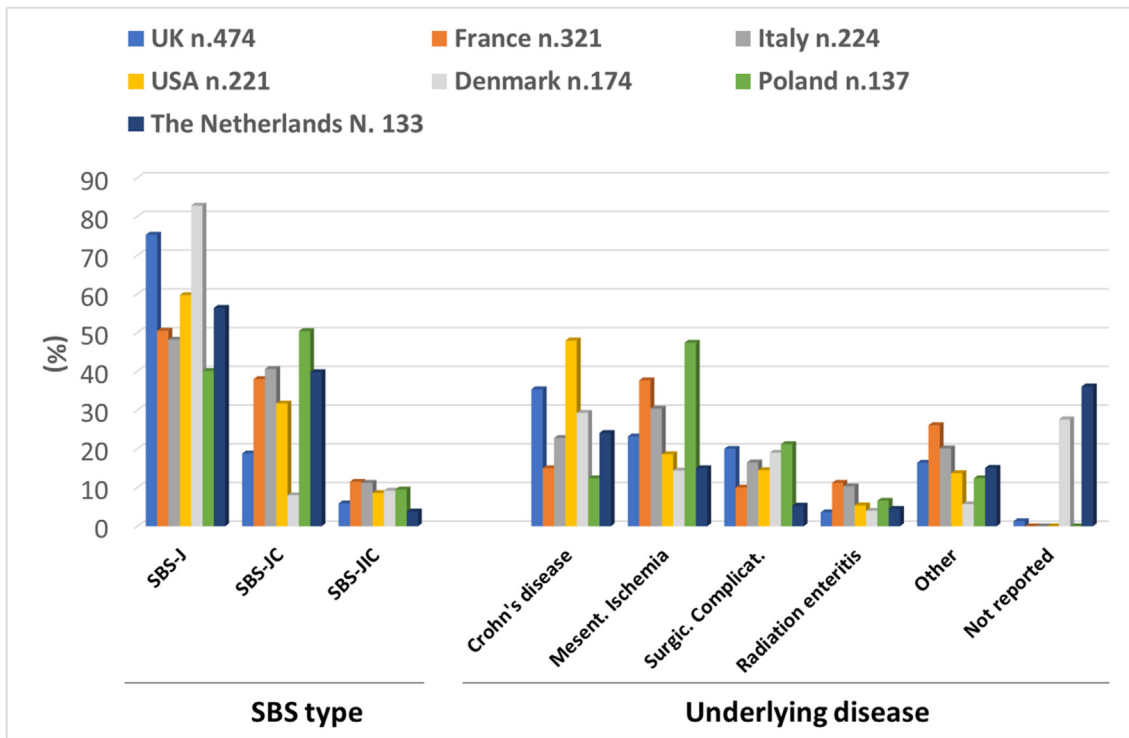


Fig. 1. Characteristics of the SBS type cohorts. (SBS, short bowel syndrome; SBS-J, end jejunostomy; SBS-JC, jejunocolic anastomosis; SBS-JIC, jejunioileal anastomosis with an intact colon and ileocecal valve; IVS, intravenous supplementation).

A)



B)

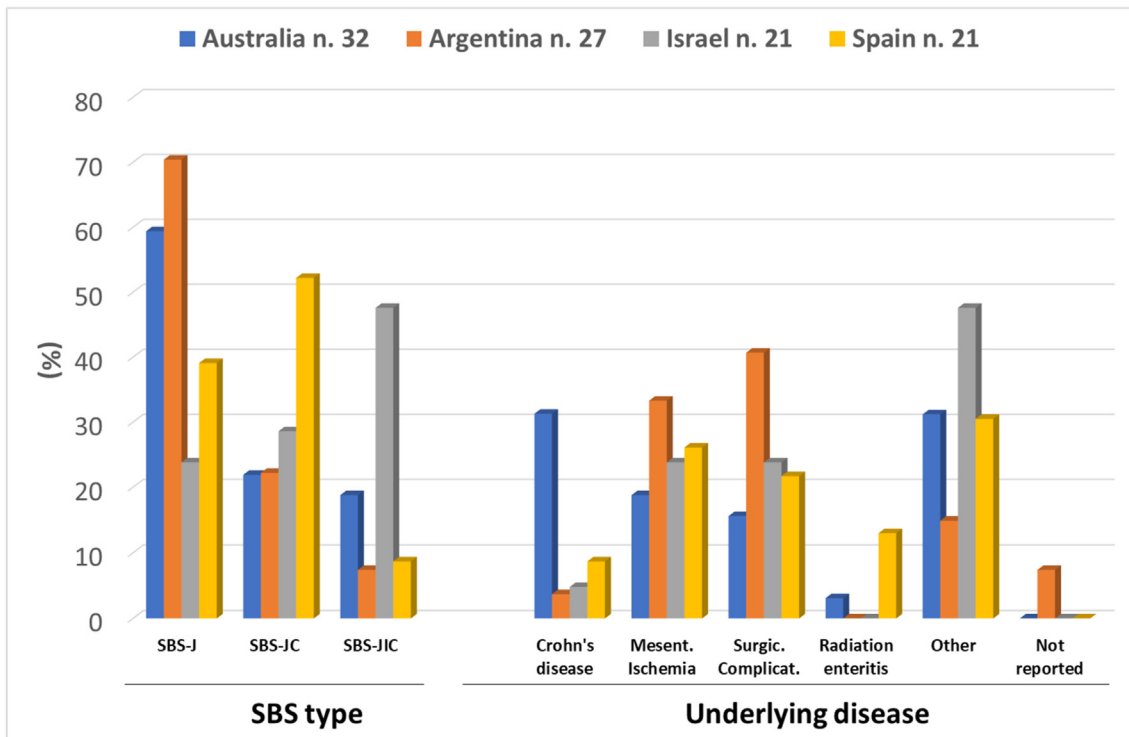


Fig. 2. SBS patient cohorts in the different countries. (SBS, short bowel syndrome; SBS-J, end jejunostomy; SBS-JC, jejunocolic anastomosis; SBS-JIC, jejunoleal anastomosis with an intact colon and ileocecal valve).

In the 7 countries that included more than 100 patients each: females comprised greater than 50% of patients in all cohorts; France and USA reported the youngest cohorts, with 36.7% and 38.0% of patients aged less than 50 years, respectively; malnutrition (BMI < 18.5 kg/m<sup>2</sup>) was more frequent in the French (21.9%), Danish (23.8%) and Polish (18.9%) groups and overweight and obesity in the British group (34.4%).

SBS-J represented 75% or more of patients in the UK and Denmark cohorts, and 50–60% of patients in the other countries, with the exception of Poland where it comprised 40% and where SBS-JC was the most frequent SBS type. CD was the main underlying disease in the UK, USA, Denmark and The Netherlands, whereas MI prevailed in France, Italy and Poland (Fig. 2A).

The shortest durations of IVS were reported in USA and Poland, where it was less than 3 years in 51.5% and 60.6% of patients, respectively; in four countries (USA, Denmark, Poland and The Netherlands), 70% or more patients received the IVS infusion 7 days per week. The greatest percentages of FE type of IVS were observed in France (20.5%) and The Netherlands (21.3%); no patient received the FE type in Poland.

Differences in type of SBS, underlying diseases, duration of IVS, number of days of IVS infusion per week and type of IVS were observed among the cohorts of the 4 countries which included 20 to 40 patients (Australia, Argentina, Spain, and Israel) and are demonstrated in Fig. 2B. Differences were also apparent among the countries which each included less than 20 patients (Supplementary table 1).

#### 4. Discussion

The data represent the largest study to-date demonstrating that clinically-relevant differences exist in SBS-IF types and underlying diseases between different countries, collected from multiple international centres at the same time point. Notably, the dataset also confirms differences between genders and SBS types, while also providing a global picture of the characteristics of SBS-IF cohorts within different countries of origin. In the whole group, the female to male ratio was 2:1, SBS-J was the prevalent type of SBS, MI and CD were the more frequent underlying diseases, BMI was normal in most patients, IVS dependency was longer than 3 years in around one-half of the cases, IVS was infused 5 days or more per week in three-fourth and consisted of FE in around 10%.

The highest percentage of females was also observed in all three SBS-types, as well as in the individual country cohorts, a finding supported by older investigations noting that normal human small intestinal length tends to be shorter in women [1]. An individual study reported a small bowel length range of 488–785 (mean 637) cm in men and of 335–716 (mean 592) cm in women [10]. Furthermore, a previous review of eight studies demonstrated a correlation between intestinal length (range 275–850 cm) and body height in men [11]. Thus, since we also and predictably observed a shorter body height in females, a shorter baseline bowel length in women could be an explanation for the higher frequency of SBS noted in our study in females. However, recent data on the bowel length in healthy adults measured by modern technologies are lacking. Moreover, our gender cohorts did not differ in any other characteristics, except a higher frequency of radiation enteritis in females, probably due to the more frequent use of radio-therapy in treating gynaecological malignancy.

The main differences among the SBS-type cohorts were those between the SBS-J and both SBS-JC and SBS-JIC. In SBS-J, CD, as the underlying disease, was twice and thrice more frequent than in SBS-JC and SBS-JIC, respectively, whereas the opposite was observed for MI. In parallel, we also noted a higher percentage of patients with SBS-J having an IVS duration shorter than 1 year and a

lower percentage on very long term (>10 years) IVS. The reasons for these findings are not directly evident in the present survey. Possible explanations could be the higher 1-year risk of death on HPN observed in patients with SBS-J [9] and/or the creation of an SBS-J as a transient solution for safety reasons during abdominal surgery, with subsequent restoration of intestinal continuity leading these individuals ultimately weaning off IVS [12]. The observed highest number of days of IVS per week, of IVS volume and of FE type in SBS-J are, of course, consistent with the greatest intestinal fluid and electrolyte losses in SBS without a colon in continuity [1,2,4].

The patient cohorts included by countries differed significantly in a number of characteristics. CD was the main underlying disease in UK (35.4%), USA (48.0%), Denmark (29.3%) and Poland (24.1%). The same countries had the highest percentages of SBS-J (UK, 75.3%; USA, 59.7%; Denmark, 82.8%; Poland, 56.4%), thus confirming the association between the underlying disease and type of SBS. The difference in CD percentages is perhaps most relevant; assuming that the prevalence and the severity of CD were the same in all the countries participating in the survey, the differences in the percentages of patients with SBS-IF due to CD could be determined by the disease treatment strategies adopted by different countries and/or centers contributing to the ESPEN database. Insight into the relative types of SBS and underlying diseases are clearly important for planning national healthcare system resources for both HPN provision and SBS therapy. Indeed, as outlined earlier, IVS needs of patients with SBS-J are greater than those of the other SBS types with colon in continuity [3]; greater IVS needs, being surrogate marker of CIF severity, are, in turn, associated with poorer outcome and greater risk of major IF/HPN-related complications [9]. Furthermore, highest IVS volume requires more days of IVS infusion per week and more hours of infusion per day, with a resultant negative impact on a patient's quality of life [13].

Therapy for SBS aims to improve the function of the remnant bowel and to reduce the need of IVS with possible weaning from HPN, thus decreasing the risk of complications and outcome and quality of life [4]. The most recent advance in pharmacological treatment for SBS-IF has been the approval of teduglutide, an analogue of glucagon like peptide-2, by the European Medical Agency and by the Food and Drug Administration. Teduglutide enhances post-resection intestinal adaptation in SBS by stimulating intestinal mucosal growth and slowing gastrointestinal transit time, thus increasing intestinal absorption and decreasing intestinal losses in patients with SBS [14–18]. The response to treatment with teduglutide, with the consequent reduction in IVS requirements, has been shown to be greater in SBS-IF with the highest baseline IVS volume requirement [19,20] and in those with SBS-J [19]. Furthermore, the decision to use teduglutide in SBS-IF due to CD, the main cause of SBS-J in the present study, must take into account associated therapeutic precautions related to the presence of active disease, fistulas, strictures and the concomitant use biologic drugs [5,21]. It is also important to recognize that other differences among countries noted in IVS characteristics may have not only been determined by SBS-types or underlying disease, but also by the established variation that is known to exist in the approach adopted by individual countries and centres to the organization and management of CIF and HPN [22,23]. This variability can influence the epidemiology of both CIF and HPN provision. The lack of standardization of regulations and procedures for CIF is probably unique in the panorama of all chronic organ failures and requires resolution [24].

The strength of the study is reflected by its international multicentre structure and by the study population, which is the largest cohort of SBS-IF patients ever enrolled in a single survey. Limitations to be considered are the voluntary participation of the HPN



centres as well as the date of data collection, that was 6 years before this sub-analysis. These limitations may imply that, notwithstanding the fact that the participating HPN centres were among the largest of their countries, they may not be representative of the entire country's experience, and that the epidemiology of SBS-IF in 2021 may differ from that of 2016, even though a significant change in SBS-IF pathogenesis seems unlikely within a 6-year timeframe. In conclusion, the analysis of the SBS-IF cohorts of patients included in the ESPEN CIF database provides useful information for planning and managing both clinical activity and research studies on SBS. Overall, SBS-IF was twice as frequent in females and SBS-J was the most frequent type of SBS. Significant variations among countries were observed in underlying diseases and IVS characteristics, which may be determined by differences in clinical practice, as well as in service organization for managing CIF and HPN.

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#### Statement of authorship

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

#### Declaration of competing interest

None declared.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2021.07.004>.

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