Presentation of a nationwide multicenter Registry of Intestinal Failure and Intestinal Transplantation

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ABSTRACT

Background & aims

Exact data on Dutch patients with chronic intestinal failure (CIF) and after intestinal transplantation (ITx) have been lacking. To improve standard care of these patients, a nationwide collaboration has been established. Objectives of this study were obtaining an up-to-date prevalence of CIF and characterizing these patients using the specially developed multicenter web-based Dutch Registry of Intestinal Failure and Intestinal Transplantation (DRIFT).

Methods

Cross-sectional study. CIF was defined as type 3 intestinal failure in which >75% of nutritional requirements were given as home parenteral nutrition (HPN) for ≥ 4 weeks in children and > 50% for ≥ 3 months in adults. All patients with CIF receiving HPN care by the three Dutch specialized centers on January 1, 2013 and all ITx patients were registered in DRIFT (https://drift.darmfalen.nl).

Results

In total, 195 patients with CIF (158 adults, 37 children) were identified, of whom 184 were registered in DRIFT. The Dutch point prevalence of CIF was 11.62 per million (12.24 for adults, 9.56 for children) on January 1, 2013. Fifty-seven patients (31%) had one or more indications for ITx, while 12 patients actually underwent ITx since its Dutch introduction. Four patients required transplantectomy of their intestinal graft and 3 intestinal transplant patients died.

Conclusion

The multicenter registry DRIFT revealed an up-to-date prevalence of CIF and provided nationwide insight into the patients with CIF during HPN and after ITx in the Netherlands. DRIFT will facilitate the multicenter monitoring of individual patients, thereby supporting multidisciplinary care and decision-making.

INTRODUCTION

Intestinal failure (IF) is characterized by the inability to maintain protein-energy, fluid, electrolyte and/or micronutrient balance, resulting from anatomic reduction or functional failure of the gut.[1] Patients with chronic and/or irreversible IF (CIF) depend on parenteral nutrition (PN) to survive, which can be provided at home. Home parenteral nutrition (HPN) is rare with a European prevalence ranging from 2-40 per million in adults[2] and 0.34-8.92 in children.[3] The treatment of IF requires a multidisciplinary approach which includes members specialized in (pediatric) surgery, (pediatric) gastroenterology, dieticians and nurse specialists. Intestinal transplantation (ITx) has become an alternative for patients with life-threatening complications of PN. Due to the lower survival rates after intestinal transplantation (ITx) than on HPN, HPN is still the treatment of choice.

A good collaboration between centers for HPN and transplant centers is the cornerstone of the management of patients with CIF. It has been shown that early referral to the transplant center is related to higher survival.[4] However, the optimal timing to refer is difficult to determine by caregivers in HPN centers, while the exact medical status including detailed documentation of complications is often unclear to the transplant professionals. To improve standard care of these patients, a nationwide collaboration has been established. The last registration of patients with CIF in the Netherlands has been performed in 2004, with a prevalence of long-term PN of at least 5.1 per million adults and 0.6 per million children.[5] An up-to-date registration including an actual overview of the individual patient is therefore necessary. For this purpose the web-based Dutch Registry of Intestinal Failure and Transplantation (DRIFT) was developed. The objectives of this study were to obtain an up-to-date prevalence of CIF and to characterize the Dutch patients with CIF and after ITx by using the multicenter registry DRIFT.

METHODS

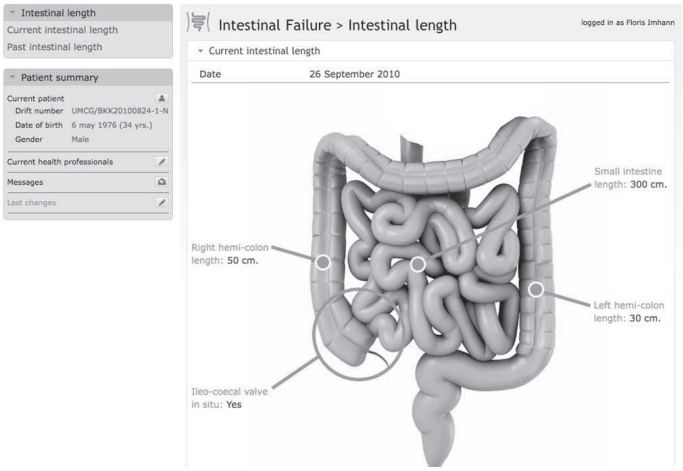
Study design

HPN care in the Netherlands is coordinated by three specialized centers, located in Amsterdam (Academic Medical Center) and Nijmegen (Radboud University Medical Center) for adults and children and in Rotterdam (Erasmus Medical Center - Sophia Children's Hospital) for children only. Adults and children with CIF receiving HPN care provided by these centers on January 1, 2013 were included in DRIFT. Patients from Maastricht University Medical Center were only taken into account for the calculation of the Dutch CIF prevalence, since this center does not participate in the nationwide collaboration because of geographical reasons. CIF was defined as type 3 IF: chronic IF requiring long-term nutritional support in the form of HPN.[6] We specified this adding that > 75% of nutritional requirements had to be given as HPN for ≥ 4 weeks in children (in line with the definition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)) and > 50% for ≥3 months in adults.[7] Patients who were receiving HPN in the absence of IF or as a bridge to a gastrointestinal continuity procedure were excluded. All patients who underwent ITx in the single Dutch transplant center (University Medical Center Groningen) were included.

Data collection & registration

Data for this cross-sectional study were obtained using medical patient records. Data known on January 1, 2013 were registered in DRIFT. This registry is available online in English at https://drift.darmfalen.nl (see supplement). **Figure 1** shows how data are displayed in DRIFT. Patient safety was ensured according to ISO-27001 and Dutch Data Protection Act standards.

Figure 1. DRIFT



Data definitions

- Catheter-related bloodstream infection (CRBSI) was defined as a positive central venous catheter (CVC) blood culture or positive peripheral blood culture in patients who met the clinical criteria of sepsis, while another focus was highly unlikely.
- Critical loss of vascular access was defined as occlusion of ≥2 from the 4 primary veins (jugular and subclavian) for the placement of a vascular access, confirmed by ultrasound or phlebography.[7]
- We used total bilirubin (along with information of the last hepatic ultrasound and liver biopsy) as documented at last follow-up to assess liver dysfunction, since this value is also used in the ITx criteria. Patients who were clinically unstable or with liver dysfunction unrelated to PN were excluded for the analysis.
- Potential ITx candidates were identified using the indications defined by the USA Center for Medicare and Medicaid Services[8] and the American Society of Transplantation.[9] We specified the definitions of pending liver dysfunction (total bilirubin > 50 µmol/L), overt liver failure (signs of portal hypertension, liver fibrosis or cirrhosis) and CIF with high morbidity (≥3 hospitalizations per year, with each a minimal duration of 7 days) since the description of these indications could be interpreted in various ways (supplementary **Table 1**).

Statistics

Patients were categorized in two groups, adults (≥ 18 years) and children (< 18 years). The national point prevalence was calculated from the latest estimate for the population in the Netherlands (Statistics Netherlands). Data were described as mean and standard deviation (if distributed normally) and median and range (if not distributed normally) it continuous and absolute frequencies and percentages if categorical. Analyses were performed using SPSS version 20 for Windows (IBM, Armonk, NY, USA).

RESULTS

In total, 195 Dutch CIF patients (158 adults and 37 children) were identified (supplementary **Figure 2**). This provides a point prevalence of 11.62 per million (12.24 for adults, 9.56 for children) on January 1, 2013.

Patient characteristics of the 184 patients included in DRIFT are presented in **Table 2**. Fifty-seven patients (31%, 39 adults and 18 children) had one or more indications for ITx (supplementary **Table 3**). Since 2001, 12 patients underwent ITx (**Table 4**). Indication for ITx was insufficient vascular access due to CVC-related thrombosis of ≥ 2 central veins in 5 patients, frequent CVC-related sepsis (2 patients), liver failure (2 patients), insufficient vascular access and frequent CVC-related sepsis combined (1 patient), frequent CVC-related sepsis and a depressed quality of life combined (1 patient) and depressed quality of life (1 patient). The indication for a combined small bowel and kidney transplantation was pre-emptive in 2 patients and chronic renal failure due to post-infectious glomerulonephritis in the third patient. Four patients (33.3%) suffered from severe rejection requiring transplantectomy of the intestinal graft after a median time of 8.56 months (range 2.33 – 23.00). Three patients died because of sepsis, euthanasia and massive psoas bleeding after a median time of 23.89 months (range 15.11 – 35.98). There were no patients on the waiting list for ITx on January 1, 2013.

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht)

		Adults (n = 147)	Children (n = 37)
Gender	N (%)		
Female		102 (69.4)	14 (37.8)
Male		45 (30.6)	23 (62.2)
Cause of intestinal failure	N (%)		
Short bowel syndrome		75 (51.0)	14 (37.8)
Motility disorder		57 (38.8)	15 (40.5)
Enteropathy		8 (5.4)	6 (16.2)
Combined*		7 (4,8)	2 (5.4)
Underlying disease	N (%)		
Motility disorder other than CIPO		41 (27.9)	3 (8.1)
Inflammatory bowel disease		25 (17.0)	0 (0)
Ischemic bowel		29 (19.7)	0 (0)
Tumor		11 (7.5)	0 (0)
CIPO		11 (7.5)	11 (29.7)
Radiation enteritis		9 (6.1)	0 (0)
Adhesions/fistulas		9 (6.1)	0 (0)
Volvulus/malrotation/mechanical obstruction		8 (5.4)	3 (8.1)

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht) (continued)

		Adults (n = 147)	Children (n = 37)
Trauma		2 (1.4)	0 (0)
Graft versus host disease		2 (1.4)	0 (0)
Necrotizing enterocolitis		0 (0)	5 (13.5)
Microvillus inclusion disease		0 (0)	4 (10.8)
Gastroschisis		0 (0)	3 (8.1)
Intestinal atresia		0 (0)	3 (8.1)
Meconium ileus		0 (0)	1 (2.7)
Long gap oesophageal atresia		0 (0)	1 (2.7)
Congenital absorption disorder		0 (0)	2 (5.4)
Cloacal exstrophy		0 (0)	1 (2.7)
Age at January 1, 2013	Median (range), years	54.04 (18.04 – 78.67)	3.82 (0.35 – 16.95)
Age at start PN	Median (range), years	49.23 (7.11 – 75.77)	0.04 (0.00 – 11.90)
Duration on PN	Median (range), years		
General		2.92 (0.28 – 36.42)	3.04 (0.35 – 11.97)
Short bowel syndrome		3.25 (0.36 – 36.42)	2.62 (0.36 – 9.54)
Motility disorder		2.92 (0.28 – 19.50)	3.82 (0.35 – 11.97)
Enteropathy		1.18 (0.44 – 4.92)	2.96 (1.55 – 8.88)
Combined*		2.39 (0.96 – 11.09)	4.58 (3.13 – 6.03)
Duration on PN	N (%)		
< 1 year		32 (21.8)	6 (16.2)
1 – 5 years		70 (47.6)	21 (56.8)
5 – 10 years		27 (18.4)	9 (24.3)
10 – 20 years		14 (9.5)	1 (2.7)
> 20 years		4 (2.7)	-
Remaining small bowel			
Whole small bowel in situ	N (%)	56 (38.1)	17 (45.9)
≥ 1 small bowel resections	N (%)	91 (61.9)	20 (54.1)
Small bowel length documented	N (%)	64 (70.3)	15 (75.0)
Small bowel length	Median (range), cm	70.00 (0 – 250)	32.00 (5 – 90)
≤ 50 cm		26 (40.6)	10 (66.7)
50 - 100 cm		18 (28.1)	5 (33.3)
100 - 200 cm		19 (29.7)	0 (0)
200 - 300 cm		1 (1.6)	0 (0)
Colon in continuity			
Yes		47 (51.6)	14 (70.0)
No		44 (48.4)	6 (30.0)
Presence of ileocoecal valve	N (%)		
Yes		63 (42.9)	25 (67.6)
No		76 (51.7)	12 (32.4)

Table 2. Patient characteristics of adults and children with chronic intestinal failure (CIF) receiving home parenteral nutrition (HPN) on January 1, 2013 (data excludes patients from Maastricht) (continued)

		Adults (n = 147)	Children (n = 37)
Unknown		8 (5.4)	0 (0)
Stoma	N (%)		
Jejuno- or ileostomy		59 (40.1)	7 (18.9)
Colostomy		10 (6.8)	1 (2.7)

Legend: * Combination of short bowel syndrome and motility disorder or enteropathy.
Abbreviations: CIPO, chronic intestinal pseudo-obstruction; PN, parenteral nutrition.

Table 4. Characteristics of patients who underwent intestinal transplantation (ITx)

		Adults (n = 7)	Children (n = 5)
Gender	N		
Female		6	1
Male		1	4
Type of intestinal failure	N		
Short bowel syndrome		6	1
Motility disorder		1	1
Enteropathy			3
Underlying disease	N		
Mesenteric artery thrombosis		5	-
Microvillus inclusion disease		-	2
Chronic intestinal pseudo-obstruction		1	-
Volvulus		-	1
Total aganglionosis		-	1
Complicated surgery		1	-
Absorption disorder not specified		-	1
Duration on PN	Median, range (years)	6.21 (0.85 – 15.24)[a]	4.59 (2.50 – 5.46)
Age at ITx	Median, range (years)	43.05 (35.50 – 54.64)	4.80 (2.50 – 5.46)
Type of ITx	N		
Isolated		4	3
Small bowel with kidney		4[a]	-
Combined liver-small bowel		-	2
Outcome	N		
Alive with functioning graft		4[a]	2
Alive without functioning graft		1	2
Deceased		2	1

Legend: [a] One patient underwent re-transplantation (after 0.85 years on parenteral nutrition).
Abbreviations: ITx, intestinal transplantation; PN, parenteral nutrition.

DISCUSSION

This report presents the web-based registry DRIFT and describes the first results of registration of patients with CIF and patients after ITx in the Netherlands. To improve standard care of these patients, a nationwide collaboration has been established. To facilitate this nationwide collaboration, up-to-date data on Dutch patients with CIF and after ITx were necessary. Until the development of DRIFT, these data have been lacking. DRIFT has a multicenter and multidisciplinary nature, since both patients receiving HPN and after ITx in different centers can be registered. As far as we know, such a nationwide multicenter and multidisciplinary registry has not been described before. Registration in DRIFT has provided a point prevalence of CIF of 11.62/million inhabitants on January 1, 2013. The increase in CIF patients with HPN[2,5] might reflect both increasing numbers of patients and increased experience in specialized HPN centers with improvement of overall HPN survival rates. However, previous insufficient documentation might be partially responsible as well. Comparing this prevalence with other countries is difficult since different definitions of CIF and indications for HPN are used. In the Netherlands, patients with end-stage cancer rarely receive HPN, in contrast to the United States and Mediterranean countries, where the prevalence of HPN in those cases is higher.[5,10] However, the Dutch CIF-patient population seems similar to populations reported in Europe, Canada and earlier Dutch reports.[2,5]

Thirty-one percent of the CIF patients receiving HPN met the criteria for screening for ITx. The discrepancy with the number of patients who actually underwent ITx in the Netherlands is explained by the conscious and cautious-restrictive policy in the Dutch transplant center. This policy is based on the current superiority of HPN care over ITx in the Netherlands. However, this discrepancy suggests also that an update of the indications for ITx is necessary, as has been indicated by other professionals in the field.[11] With DRIFT, these vulnerable patients can be monitored closely in order to decide whether they should be referred to the transplant center or not.

One of the limitations of this study is that we chose to apply a strict definition in line with definitions earlier described by Lal et al.[6], Beath et al.[7] and ESPGHAN, which might have led to an underestimation of the prevalence of CIF and HPN. We expect that some of the 41 patients that did not meet the criteria for CIF on January 1, 2013, will not be able to wean from HPN and therefore deserve to be included. Furthermore, data were incomplete for some patients, because information was not available or specific measurements had not been performed.

In conclusion, the novel, English language web-based registry DRIFT provided an up-to-date prevalence of CIF and a nationwide insight into patients with CIF during HPN and after ITx in the Netherlands. DRIFT will facilitate the monitoring of individual patients by

functioning as a national Electronic Patient Register (EPR), thereby supporting multidisciplinary care and decision-making in this clinically complex patient population. DRIFT will be used as a quality instrument between the different Dutch centers. Our aim is to extend this registry to other countries.

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SUPPLEMENTARY MATERIAL

Table 1. Indications to identify potential intestinal transplantation (ITx) candidates in our population of patients with chronic intestinal failure (CIF) on home parenteral nutrition (HPN)

Indications[8,9]
Failure of HPN - Insufficient vascular access due to CVC-related thrombosis of ≥ 2 central veins (subclavian or jugular veins) - Frequent (≥ 2/year) episodes of CRBSI - Liver dysfunction Pending: -Total bilirubin > 50 µmol/l Overt: - ≥ 1 of the following criteria; - Signs of portal hypertension - Liver fibrosis or cirrhosis
High risk of death attributable to underlying disease Intra-abdominal invasive desmoid tumours Congenital enteropathy Ultra-short bowel syndrome (gastrostomy, duodenostomy, remaining small bowel length < 10 cm in children and < 20 cm in adults)
CIF with high morbidity Need for frequent hospitalization because of HPN related complications (≥3 hospitalizations per year, with each a minimal duration of 7 days) Severe impairment of Quality of Life (disregarded in this research)

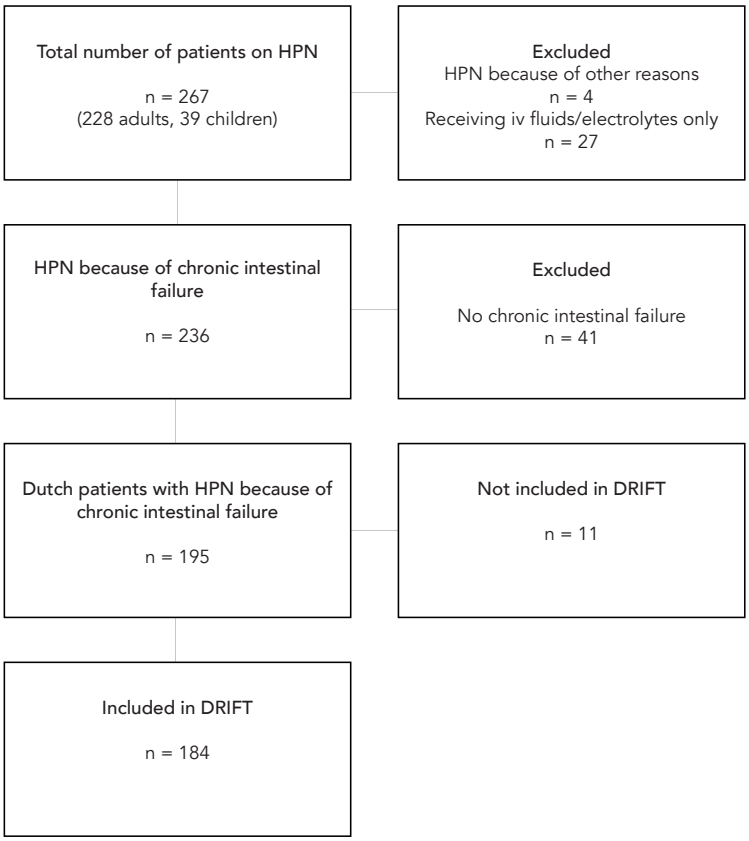
Abbreviations: CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

Table 3. Identification of potential intestinal transplantation (ITx) candidates

Indication (n, (%))	**Patients (n = 184)**	**Adults (n = 147)**	**Children (n = 37)**
Treatment failure of HPN			
Insufficient vascular access	10 (5.4)	8 (5.4)	2 (5.4)
Liver dysfunction			
Pending	5 (2.7)	5 (3.4)	0 (0.0)
Overt	17 (9.2)	10 (6.8)	7 (18.9)
Splenomegaly	14 (7.6)	9 (6.1)	5 (13.5)
Splenomegaly with ascites	3 (1.6)	1 (0.7)	2 (5.4)
Fibrosis/cirrhosis	0 (0)	0 (0)	0 (0)
Frequent CRBSI	32 (17.4)	24 (16.3)	8 (21.6)
High risk of death attributable to underlying disease			
Desmoid tumor	1 (0.5)	1 (0.7)	0 (0.0)
Congenital enteropathy	6 (3.3)	0 (0)	6 (16.2)
Ultra-short bowel syndrome	15 (8.2)	12 (8.2)	3 (8.1)
CIF with high morbidity			
≥ 3 hospitalizations per year	5 (2.7)	2 (1.4)	3 (8.1)
Total	57 (31.0)	39 (26.5)	18 (48.6)

Abbreviations: CIF, chronic intestinal failure; CRBSI, catheter-related bloodstream infection; HPN, home parenteral nutrition.

Figure 2. Patient inclusion flowchart



Abbreviation: HPN, home parenteral nutrition.