Acute intestinal failure

International multicenter point-of-prevalence study

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ACUTE INTESTINAL FAILURE: INTERNATIONAL MULTICENTER POINT-OF-PREVALENCE STUDY

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Key words: intestinal failure, acute, epidemiology, parenteral nutrition, mortality, abdominal surgery

ABSTRACT

Background & Aims

Intestinal failure (IF) is defined from as requirement ~~o~~for intravenous supplementation due to failing capacity to absorb nutrients and fluids. Acute IF is an acute, potentially reversible form of IF. We aimed to identify the prevalence, underlying causes and outcomes of acute IF.

Methods

This point-of-prevalence study included all adult patients hospitalized in acute care hospitals and receiving parenteral nutrition (PN) on a study day. The reason for PN and the mechanism of IF (if present) were documented by local investigators and reviewed by an expert panel.

Results

Twenty-three hospitals (19 university, 4 regional) with a total capacity of 16,356 acute care beds and 1,237 intensive care unit (ICU) beds participated in this study. On the study day, 338 patients received PN (21 patients/1000 acute care beds) and 206 (13/1000) were categorized as acute IF. The categorization of reason for PN was revised in 64 cases (18.9% of total) in consensus between the expert panel and investigators. Hospital mortality of all study patients was 21.5%; the median hospital stay was 36 days. Patients with acute IF had a hospital mortality of 20.5% and median hospital stay of 38 days (P>0.05 for both outcomes). Disordered gut motility (e.g. ileus) was the most common mechanism of acute IF, and 71.5% of patients with acute IF had undergone abdominal surgery. Duration of PN of ≥42 days was identified as being the best cut-off predicting hospital mortality within 90 days. PN ≥42 days was independently associated with 90-day hospital mortality, age, sepsis, and ICU admission.

Conclusions

Around 2% of adult patients in acute care hospitals received PN, 60% of them due to acute IF. High 90-day hospital mortality and long hospital stay were observed in patients receiving PN, whereas presence of acute IF did not additionally influence these outcomes. Duration of PN was associated with increased 90-day hospital mortality.

INTRODUCTION

A definition of intestinal failure (IF) was first proposed in 1981 by Fleming and Remington (1). Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed the following definition: 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 (2,3). Along with this definition, three types of IF are described: types I to III IF. Type I acute IF (AIF) is an acute, short-term and usually self-limiting condition, commonly occurring in the perioperative setting and/or in association with critical illnesses, and requiring IVS from a few days to a few weeks. Type II AIF is a prolonged acute condition, often in metabolically unstable patients such as those with complicated intra-abdominal infection or acute mesenteric ischemia, often needing multiple surgeries and/or developing enterocutaneous fistulae, requiring complex multi-disciplinary care and IVS over periods of weeks or months. Type III IF (chronic IF = CIF) is a chronic condition, in metabolically stable patients, who require IVS over months or years.

Since the first definition, further reviews and studies have analyzed the causes, outcomes and quality of life in chronic IF (4,5,6,7). One recent paper describes the underlying pathologies causing acute IF and the outcome of patients with acute IF (8). However, the actual prevalence of acute IF is still unknown. Based on data from the National Health Service (NHS) in the United Kingdom, ~~type I IF is thought to occur in about 15% of hospitalized patients, whereas~~ the annual incidence of type II IF has been estimated to be around 9-18 patients per million inhabitants, depending on the method used (9). It has been estimated that about 50% of type II IF may develop into type III IF (3).

The etiology of acute IF has also not been studied in detail. The most likely underlying conditions for acute IF are perioperative complications, or those associated with critical illness, such as bowel paralysis or acute pancreatitis (5).

This study was conducted: 1) to identify the prevalence of acute IF; 2) to identify the mechanisms and diseases underlying IF; 3) to describe the 90 day outcome for patients with acute IF.

MATERIALS AND METHODS

Study design

This was a multicenter point-of-prevalence study amongst acute care hospitals worldwide.

There were two points of data collection: 1) study day (a weekday between November 2016 and March 2017 defined by each hospital); 2) outcome day 90 days after the study day.

Data was collected regarding the category of the hospital (university, regional, local), total numbers of acute care beds (excluding psychiatric beds) for adult patients in the hospital, as well as the number of beds in intensive care units (ICU), in specialist IF units and in intermediate care/high-dependency unit(s) (IMC/HDU) if applicable.

All patients receiving PN on the study day independent of their location (ward) in the acute care hospital were identified and included in the study. The following variables were collected on the study day: 1) admission variables (age, gender, reason for admission, location in the hospital); 2) data on PN (the reason for PN, method of administration, total or supplemental PN) and 3) data on IF (mechanism leading to IF, underlying disease/condition, abdominal surgeries, details of stomas and fistulas if present).

On the outcome day, the following variables were collected: hospital survival, discharge destination, total number of days on PN, total number of abdominal surgeries, presence of fistula and stoma at discharge and total duration of ICU and hospital stay.

Objectives

The primary objective was to identify the prevalence of acute IF among patients treated in acute care hospitals.

Secondary objectives were to identify prevalence, indications and duration of PN, mechanisms and outcome of IF, and to compare the hospital length of stay and 90-day hospital mortality of patients with and without acute IF.

Definitions

Parenteral nutrition was defined as IVS of macronutrients (glucose, amino acids, lipids). Administration of only glucose solutions in low concentration (<10%), only electrolytes or only isolated amino acids were not considered as PN in this context.

Intestinal failure was defined based on investigators' judgment using the definition provided by ESPEN (2,3). Investigators were asked to separate acute (Type I or II, or not differentiated) and chronic IF (Type III).

Categorization for pathophysiological mechanisms and underlying diseases of AIF was provided to investigators (10). Disordered motility was used as an all-encompassing term for impaired motility in any level of GI tract.

Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, according the definition of Singer et al. (11). Septic shock was defined as a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial blood

pressure (MAP) ≥65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation (11).

Data collection and review

Data were collected by local investigators at the individual sites and entered into a web-based electronic file in de-identified form.

The experts (from the ESPEN Acute Intestinal Failure Special Interest Group (AIF-SIG) reviewed all cases. Two experts independently performed the review of collected data and suggested changes on the reasons for PN, and the pathophysiological mechanism and underlying disease/condition for acute IF when appropriate. Cases where the two experts had different opinions were reviewed during the AIF-SIG Winter meeting in January 2018. After the AIF-SIG members agreed on the possible need to change the initial categorizations, queries were sent to the respective local investigators with a request to review the cases and agree or not with changes suggested by the experts.

Statistics

IBM Statistics SPSS version 25.0 was used for data analysis.

Data are presented as number of patients (percentage) and median [interquartile range] if not stated otherwise. The Shapiro-Wilk test was used to test normality of distribution. To compare groups, Student's t-test (normal distribution) and Mann-Whitney U test (non-Gaussian distribution) were used for continuous variables and the Chi-square test for categorical variables.

ROC curve analysis was used to identify the cut-off for duration of PN in predicting 90-day hospital mortality.

The variables with P≤0.2 on bivariate analysis were tested in stepwise multiple regression analysis for associations with hospital mortality within 90 days. Competing variables (e.g. total number of ICU days vs. ICU admission ever) were added and removed stepwise. The final model represents the best prediction of 90-day hospital mortality with collected data.

Ethics

Ethical approval was obtained by all participating hospitals. Waiver of informed consent was granted.

RESULTS

Participating hospitals

A total of 25 sites (in 17 countries) participated in this study (Table 1). Two sites were excluded from analysis due to failure to include all patients in the whole hospital receiving PN on the study day. Of the remaining 23 sites, 19 were university hospitals and 4 were regional hospitals. In total, these hospitals had a capacity of 16,356 acute care beds and 1237 ICU beds. Fifteen hospitals had an IMCU or HDCU, with a total of 447 beds. Seven hospitals had a specialist IF unit, with a total of 49 beds. One site was a small hospital specializing only in abdominal surgery (Site number 10 in Table 1).

Table 1. Overview of study sites

Site	Type of hospital	Acute care beds	ICU beds	IMC/ HDU beds	Specialist IF unit beds	Patients on PN	Patients with AIF	Patients with CIF
1	University	876	40	61	0	13 (1.5)	8 (0.9)	0
2	*University*	*1200*	*28*	*15*	*10*			
3	University	745	28	0	10	22 (3.0)	9 (1.2)	6 (0.8)
4	University	900	180	0	0	21 (2.3)	17 (1.9)	1 (0.1)
5	University	948	18	10	0	5 (0.5)	3 (0.3)	0
6	University	508	27	33	0	11 (2.2)	9 (1.8)	2 (0.4)
7	University	227	5	12	0	3 (1.3)	3 (1.3)	0
8	University	300	10	8	2	2 (0.7)	2 (0.7)	0
9	University	1000	52	0	2	4 (0.4)	1 (0.1)	0
10	Regional	21	4	0	4	6 (28.6)	2 (9.5)	4 (19.0)
11	Regional	350	10	0	0	5 (1.4)	4 (1.1)	0
12	University	1200	50	20	0	19 (1.6)	10 (0.8)	3 (0.3)
13	*University*	*960*	*21*	*0*	*20*			
14	University	387	85	49	0	10 (2.6)	7 (1.8)	3 (0.8)
15	Regional	529	45	133	0	10 (1.9)	5 (0.9)	2 (0.4)
16	University	762	114	12	0	25 (3.3)	13 (1.7)	5 (0.7)
17	University	933	50	30	0	17 (1.8)	11 (1.2)	0
18	Regional	523	19	0	0	7 (1.3)	6 (1.1)	0
19	University	1142	228	0	0	44 (3.9)	24 (2.1)	17 (1.5)
20	University	342	18	17	0	13 (3.8)	11 (3.2)	1 (0.3)
21	University	745	50	28	2	14 (1.9)	13 (1.7)	0
22	University	1346	93	24	2	41 (3.0)	20 (1.5)	2 (0.1)
23	University	1127	38	0	0	23 (2.0)	13 (1.2)	3 (0.3)
24	University	648	27	0	27	13 (2.0)	9 (1.4)	0
25	University	797	46	10	0	10 (1.3)	6 (0.8)	0
TOTAL		16’356	1237	447	49	338 (2.1)	206 (1.3)	49 (0.3)
CI 95% for prevalence						1.58-2.53	1.00 - 1.61	0.11 - 0.41
TOTAL without Site 10		16’335	1233	447	45	332 (2.0)	204 (1.2)	45 (0.3)
CI 95% for prevalence without Site 10						1.55 - 2.41	0.99 - 1.58	0.11 - 0.37

ICU – intensive care unit; IMC/HDU – intermediate care/high-dependency unit; IF – intestinal failure; PN – parenteral nutrition; AIF –acute intestinal failure; CIF – chronic intestinal failure; CI – confidence interval

Data on study day

On the study day, 338 patients received parenteral nutrition (21/1000 acute care beds). One site (Site number 10 in Table 1) reported a very high prevalence of PN and AIF compared to the others. Therefore, total prevalence was also recalculated without this site and was 20/1000 acute care beds.

The characteristics of patients receiving PN are presented in Table 2.

In 253/338 (74.9%) patients PN was the only route for administration of nutrients. In patients with supplemental PN (25.1%) the amount of energy intake through PN varied between 10% and 90% of total energy intake, with a median of 60%.

Table 2. Characteristics of all patients with PN. Data presented as number of patients (percentage) or median [interquartile range] if not stated otherwise.

	All patients N=338	CIF N=49	AIF N=206	Non-IF N=83	p-value AIF vs non-IF
Male	170	15	114	56	0.021
Age, median [range]	64 [19-85]	54 [20-83]	63 [19-92]	66 [25-94]	0.081
Hospital unit					<0.001
Surgical ward	109	20 (40.8%)	71 (34.5%)	18 (21.7%)	
ICU	102	6 (12.2%)	70 (34.0%)	26 (31.3%)	
Gastroenterology ward	24	5 (10.2%)	13 (6.3%)	6 (7.2%)	
IMC/HDU	22	1 (2.0%)	14 (6.8%)	7 (8.4%)	
Specialized IF Unit	5	4 (8.2%)	1 (0.5%)	0	
Any other acute care ward	76	13 (26.5%)	37 (18.0%)	26 (31.3%)	
Oncology ward	12	1 (2.0%)	4 (1.9%)	7 (8.4%)	
Hematology ward	9	0	6 (2.9%)	3 (3.6%)	
Transplant unit	9	6 (12.2%)	2 (1.0%)	1 (1.2%)	
Days on PN before study day during current hospitalization	9 [3-21]	19 [7-71]	8 [3-16]	9 [3-20]	0.949
Days of hospitalization before study day	16 [8-33]	15 [7-37]	16 [9-33]	16 [10-32]	0.815
Admission diagnosis category					<0.001
Gastrointestinal pathology	225	43 (87.7%)	145 (70.4%)	37 (44.6%)	
Cardiac pathology	24	2 (4.1%)	10 (4.9%)	12 (14.5%)	
Pulmonary pathology	20	-	10 (4.9%)	10 (12%)	
Neurological pathology	11	-	2 (1.0%)	9 (10.8%)	
Trauma	3	1 (2.0%)	1 (0.5%)	1 (1.2%)	
Other	55	3 (6.1%)	38 (18.4%)	14 (16.9%)	
Venous access for PN†					<0.001
Multi-lumen CVC	144	3 (6.1%)	100 (48.5%)	41 (49.4%)	
Multi-lumen PICC	68	13 (26.5%)	43 (20.9%)	12 (14.5%)	
Tunneled CVC	42	23 (46.9%)	18 (8.7%)	1 (1.2%)	
Single-lumen CVC	29	1 (2.0%)	19 (9.2%)	9 (10.8%)	
Single-lumen PICC	28	7 (14.3%)	13 (6.3%)	8 (9.6%)	
Peripheral	18	1 (2.0%)	8 (3.9%)	9 (10.8%)	
Not sure/other	9	1 (2.0%)	5 (2.4%)	3 (3.6%)	

ICU – intensive care unit; IMC/HDU – intermediate care/high-dependency unit; IF – intestinal failure; PN – parenteral nutrition; AIF –acute intestinal failure; CIF – chronic intestinal failure; CVC - central venous catheter, PICC - peripherally inserted central catheter

Originally, 159 patients were categorized as AIF patients. During case-by-case evaluation of data, experts suggested and investigators agreed to correct the reason for PN in 64 cases (18.9%). Corrections were performed in 51/236 of patients (21%) enrolled from study sites without specialized IF unit and in 13/102 (13%) of patients hospitalized in sites having an IF unit. Reasons for PN (primarily documented and after revision by expert panel) are presented in Table 3.

Acute IF was primarily documented as a reason for PN in 159 patients; after expert review and re-evaluation by local investigators 206 patients were categorized as acute IF. This gives a prevalence of acute IF of 13/1000 acute care beds (12/1000 beds with site number 10 excluded).

Table 3. Reasons for PN, original data and expert revision

	Original data		Expert Revision	
	Number	**%**	**Number**	**%**
Acute IF	159	47.0	206	60.9
Chronic IF	56	16.6	49	14.5
No access for EN	25	7.4	27	8.0
Perceived danger from EN	22	6.5	21	6.2
Dysphagia	14	4.1	13	3.8
Severe condition	20	5.9	6	1.8
Other	35	10.4	16	4.7
Not sure	7	2.1	-	-
TOTAL	338	100	338	100

IF – intestinal failure; EN: enteral nutrition

During case-by-case evaluation of the data, experts suggested and investigators agreed to correct the pathophysiological mechanisms of IF in 17 cases (6.7% of total revised 255 cases of IF); 15 of them were enrolled from sites without a specialized IF unit. The underlying disease was corrected in 22 cases (8.6%), 18 of them from sites without an IF unit. For all further analyses, corrected categorizations were used and respective results are presented in Table 4.

Table 4. Pathophysiology and underlying diseases in AIF

	Number of patients N=206	**%**
Mechanism of AIF		
Disordered motility	106	51.5
Obstruction	29	14.1
Fistula	23	11.2
Short bowel	12	5.8
Extensive mucosal disease	12	5.8
Other	24	11.7
Underlying disease		
Surgical complication	76	36.9
Active malignancy	31	15.0
Crohn's disease/IBD	16	7.8
Shock	10	4.9
Pancreatitis	10	4.9
Mesenteric vascular pathology	8	3.9
Primary motility disorder	2	1.0
Other abdominal pathology	23	11.2

Other pathology	30	14.6

AIF – acute intestinal failure; IBD - inflammatory bowel disease

Of the 106 patients where the mechanism of AIF was considered to be disordered motility, 53 patients had AIF due to a surgical complication, 9 active malignancy, 8 pancreatitis, 6 shock, 3 Crohn's/inflammatory bowel disease, 1 mesenteric vascular pathology, 1 primary motility disorder, 10 other abdominal pathology (including e.g. cholecystitis/cholangitis, adhesions, abdominal trauma), and 15 other pathology not of primarily abdominal origin. This other pathology was mainly hematological malignancy, graft versus host disease or multiple organ failure, resulting in paralytic ileus or enterocolitis in ICU or IMC/HDU patients (11/15).

In the 24 patients where the mechanism underlying AIF was not considered to be a defined gastrointestinal problem or dysmotility, the pathophysiological mechanisms of AIF included four cases of suspected or confirmed bowel ischemia. The remaining 20 patients had graft versus host reactions, pancreatitis, peritonitis or recent GI surgery. On balance the most probable mechanism in these cases was disordered motility, however, extensive mucosal injury and fear of development or worsening of AIF due to the administration of EN could not be excluded from the data collected.

Surgical data on 9 patients of the total of 206 patients with AIF were missing.

Of the remaining 197 patients with AIF, 134 patients (68%) had undergone abdominal surgery before the study day, most patients had undergone a lower (49%) or upper (26%) gastrointestinal (GI tract procedure. Elective surgery was performed in 85 patients, semi-elective surgery (e.g. change of VAC-dressing) in 25 patients, and emergency surgery in 77 patients. A total of 55 patients had more than one surgery.

A total of 54 patients had sepsis on the study day, of whom 14 patients had septic shock. The most common presumed origin of sepsis was an abdominal cause (70%), followed by a pulmonary cause (13%).

On the study day, 14 patients had an open abdomen, 56 patients had a stoma and 23 had an enterocutaneous fistula.

Data on outcome day

90 day outcome data were obtained in 330/338 (98%) patients. For the 8 patients with missing data, 2 did not have AIF and 6 had AIF. The hospital outcome at 90 days is shown in Table 5.

Table 5. Outcome data at day 90. Data presented as number of patients (percentage) or median [interquartile range] if not stated otherwise.

	All patients N=330	**CIF N=49**	**AIF N=200**	**Non-IF N=81**	**p-value AIF vs non-IF**
Outcome					0.257
Discharged	239 (72.4)	39 (79.6)	147 (73.5)	53 (65.4)	
Deceased	71 (21.5)	6 (12.2)	41 (20.5)	24 (28.9)	
Still in hospital	20 (6.1)	4 (8.2)	12 (6.0)	4 (4.8)	
Abdominal surgery	196 (59.4)	27 (55.1)	147 (73.5)	22 (27.1)	<0.001
Two or more abdominal surgeries	77 (22.8)	12 (24.5)	57 (28.5)	8 (9.9)	0.001

Presence of a stoma during the study	110 (33.3)	32 (65.3)	70 (35.0)	8 (9.9)	<0.001
Presence of fistula during the study	58 (17.6)	16 (32.7)	38 (19.0)	4 (4.9)	0.003
Total duration of PN, days	19 [10-37]	26 [11-79]	19 [10-37]	17 [10-29]	0.269
Total patients in the ICU	174 (52,7)	19 (38,8)	118 (59.0)	37 (45.7)	0.014
Total ICU stay, days	29 [16-50]	27 [16-42]	30 [16-46]	26 [16-75]	0.647
Total hospital stay, days	36 [21-61]	26 [14-54]	38 [21-61]	35 [23-71]	0.950

ICU – intensive care unit; IF – intestinal failure; PN – parenteral nutrition; AIF –acute intestinal failure; CIF – chronic intestinal failure

The total 90-day hospital mortality in patients with PN was 21.5%, and in patients with AIF 20.5%. Of the patients without IF, 41 patients (77%) were discharged home, 8 patients transferred to another hospital and 4 patients discharged to a rehabilitation center. Of the patients with AIF, 100 patients (68%) were discharged home, 29 patients transferred to another hospital, 12 patients to a rehabilitation center, 3 patients to a hospice and 3 patients to another institution. Of the patients with CIF, 33 patients (67%) were discharged home, 4 patients to another hospital and 2 patients to a rehabilitation center.

At 90 days after the study day 5/70 AIF patients, 3/32 CIF patients and 1/8 no IF patients no longer had a stoma. At 90 days 17/38 AIF patients no longer had a fistula (11 were closed surgically, 6 closed without surgery). In 6/16 CIF patients with a fistula were successfully treated surgically. Four patients categorized as no IF on the study day developed a fistula during their hospital stay, in 2/4 the fistula closed within 90 days, one of these with surgery. In two of these patients “perceived danger from EN” and in two “no access for EN” was documented as a reason for PN on the study day.

The outcomes (mortality, ICU admission, duration of PN and hospital stay) of AIF patients without abdominal surgery were not different from surgical patients (data not shown).

Associations of PN and AIF with 90-day hospital outcome

There was a significant association between active sepsis on the study day and the risk of death. Prolonged PN was also associated with higher mortality, ROC curve analysis identified that a total duration of PN of ≥42 days as the most informative threshold for hospital mortality within 90 days. Older patients, those who had an intestinal stoma, and those who had required an ICU stay during the current admission were also more likely to die (Table 6).

Multivariate analysis yielded the final regression model presented in Table 7. Age, sepsis on the study day, ICU admission during the current hospitalization, and duration of PN ≥42 days were independently associated with 90-day hospital mortality, the strongest of these being for the long duration of PN, but sepsis and ICU admission were also associated with more than double the risk of death.

Table 6. Comparison of survivors and non-survivors. Data presented as number of patients (percentage) or median [interquartile range] if not stated otherwise.

	All (330)	Survivors (N=259)	Nonsurvivors (N=71)	-value
Age, median [range]	64 [19-85]	58 [19-85]	69 [25-83]	0.001
Male gender	166 (50.3)	133 (51.4)	33 (46.5)	.276
Home PN before hospitalization	44 (13.3)	38 (14.7)	6 (8.5)	.119
IF as the reason for PN on study day				.056
No IF	81 (24.5)	57 (22.0)	24 (33.8)	
AIF	200 (60.6)	159 (61.4)	41 (57.7)	
CIF	49 (14.8)	43 (16.6)	6 (8.5)	
Sepsis on study day	66 (20.0)	45 (17.4)	21 (29.6)	.002
Number of abdominal surgeries	1 [0-1]	1 [0-1]	1 [0-1]	.983
Abdominal surgery ever	196 (59.4)	157 (60.6)	39 (54.9)	.233
Stoma ever	110 (33.3)	93 (35.9)	17 (23.9)	.038
Fistula ever	58 (17.6)	47 (18.1)	11 (15.5)	.373
Total duration of PN	28 [15-65]	30 [15-72]	27 [17-50]	.130
PN for >=14 d	209 (63.3)	161 (62.2)	48 (67.6)	.242
PN for >=42 d	74 (22.4)	52 (20.1)	22 (31.0)	.039
Total ICU days	29 [16-50]	25 [15-44]	33 [18-73]	.200
ICU admission ever	174 (52.7)	127 (49.0)	47 (66.2)	.007
Total hospital stay, days	36 [21-61]	35 [22-59]	40 [19-78]	.309

ICU – intensive care unit; IF – intestinal failure; PN – parenteral nutrition; AIF –acute intestinal failure; CIF – chronic intestinal failure

Table 7. Stepwise multiple regression analysis identifying variables associated with hospital mortality within 90 days.

Variable	P-value	Odds ratio	95% CI lower	95% CI upper
Intestinal failure				
No IF	0.988			
Acute IF	0.956	1.053	0.166	6.689
Chronic IF	0.886	1.107	0.276	4.428
Age	**0.013**	**1.029**	**1.006**	**1.052**
Sepsis on study day	**0.024**	**2.349**	**1.120**	**4.925**
Home PN before	0.731	0.775	0.180	3.325
Stoma ever	0.230	0.624	0.289	1.347
ICU admission ever	**0.023**	**2.459**	**1.133**	**5.336**
3 or more abdominal surgeries	0.105	0.405	0.136	1.206
PN ≥42 days	**0.008**	**2.868**	**1.319**	**6.235**

IF – intestinal failure; PN – parenteral nutrition; CI – confidence interval

DISCUSSION

Our study has estimated the prevalence of PN to be 2.1% in adult patients hospitalized in acute care hospitals. Acute IF was the main reason for usage of PN (in 61% of patients), and the prevalence of

acute IF in adult patients in acute care hospitals was 1.3%. Patients receiving PN had high hospital mortality (20.5%), and a long hospital stay (36 days), whereas outcomes of acute IF patients did not differ significantly from those in other patients receiving PN.

Our pragmatic study aimed to obtain the very first results on overall prevalence and description of acute IF to form the basis for future studies.

Prevalence of PN and IF

We did not identify any earlier studies identifying the prevalence of PN in hospitalized patients. Our study suggests rather low total number of patients receiving PN, although considerable variability between different countries and institutions exists. This was exemplified by our partial exclusion of center 10 which has a specialist practice concentrated on patients at high risk of PN and AIF, as compared to the larger multidisciplinary hospitals that included many acute services (such as respiratory medicine for example, where AIF would be much less common than in the surgical units of those hospitals). Our results on prevalence should therefore be interpreted with caution.

Additional small errors may also result from the point-of-prevalence design and because we counted prevalence for acute care beds instead of the exact number of patients. The precise number of patients being treated during one day in entire hospitals is difficult to identify due to multiple discharges and admissions, therefore number of beds was taken into account instead. Furthermore, the methodology behind this study called only for patients actually treated with PN, although there must be ~~an~~ awareness that the time to initiate parenteral nutrition in comparable conditions may be different between settings. More precise results would require a prospective observational study with a relatively long screening period.

The prevalence of acute IF in our study is lower than was estimated by the NHS in the UK (9). The actual overall prevalence could be even lower taking into account that most hospitals participating in this study are university hospitals and therefore tertiary referral centers. Moreover, several participating sites had specialized IF units which are still uncommon worldwide.

This study showed that there was some discrepancy between the opinion of local investigators and the expert panel for the reasons for PN. Compared to local investigators, the experts categorized more patients as having acute IF (206 instead of 159). Such discrepancy suggests that the concepts and definitions of intestinal failure – only very recently reviewed - require further time and experience so they can be more widely understood and applied (12).

There was a considerable proportion of patients receiving PN without having acute or chronic IF (Table 3). Of note, these patients often had GI pathology without IF, meaning that ability of the bowel to absorb was at least thought to be maintained. This group includes patients with GI pathology resulting in or accompanied by dysphagia or obstruction, and those without established access for EN (e.g. esophageal pathology) or perceived danger of EN (e.g. pancreatitis, anastomosis). Respective decisions to administer PN in these cases were taken at each site and not influenced centrally.

In acute IF patients, whenever possible, treatment of the origin of the condition is of utmost importance and PN then just provides a “bridge” until restoration of intestinal function. Many patients with severe illness require IVS with fluids and electrolytes due to increased requirements in the acute phase which are unrelated to acute IF. At the same time, acute intestinal insufficiency is

initially managed with trophic enteral nutrition without supplementary PN, as in other severely ill patients (2).

Mechanisms of acute IF

Disordered motility was considered to be the mechanism of acute IF in more than half of the cases (Table 3). It should be noted that this categorization does not imply that these patients were considered to have an underlying chronic motility disorder (primary dysmotility). Identification of the pathophysiological mechanism leading to AIF as well as identification of this acute dysmotility was difficult; in more than 10% of cases 'other' pathophysiological mechanisms were documented (Table 4), and expert review of collected data did not always allow clear categorization into predefined groups either. The main reason for this is the lack of appropriate objective tools to identify the presence of dysmotility or of progression to gastrointestinal mucosal injury. Development of diagnostic markers to identify both intestinal dysmotility and mucosal injury at the bedside is required.

The most frequently documented underlying disease causing development of acute IF was a surgical complication followed by active malignancy, in line with previous results from Lal et al. (13). Most of the patients with acute IF were abdominal surgery patients (73.5% underwent abdominal surgery, 13.1% of them twice, and 27.7% more than twice during the index hospitalization). In a recent study addressing patients with AIF, the median number of surgeries per patient was as high as four (8). Possibly only the most complicated surgical patients were identified in this previous study, supported by the fact that two thirds of patients had fistula(s) (8). In our study, we will also have captured less complicated surgical patients (including Type I IF).

However, a quarter of patients in our study had not undergone surgery and still developed AIF with outcomes comparable to patients undergoing abdominal surgery. These patients may be the most challenging subgroup of patients, as AIF in these cases is usually not caused by anatomical abnormalities (short bowel, fistula), but is purely functional. Laboratory or other markers to identify disordered intestinal function and subsequent insufficient absorption of nutrients in anatomically intact bowel would be useful indicators for future studies (14).

Outcome

The mortality of patients with AIF in this study was 20.5%, whereas Atema et al. (8) reported hospital mortality of AIF patients to be 16%. Patients in the above-mentioned study were referred to an IF specialized center and had already been on PN for a median of 2 months before referral. Our current study, in contrast, could also identify patients in the early phase of acute IF. One third of our AIF patients were in the ICU on the study day and two thirds needed intensive care during their hospital stay, whereas only 23% of patients in the study by Atema et al had an unplanned admission to ICU postoperatively. These differences need to be taken into account when interpreting mortality. However, we believe that referral of patients with Type II IF to a specialized center should be a standard strategy and can improve survival. The mortality in established IF units is estimated to have fallen from over 10% in the 1980s to less than 5% in the last 10 years (unpublished data from Salford and St Marks hospitals, UK).

Sepsis is undoubtedly an important component in the course of acute IF leading to impaired outcome. In current study, presence of sepsis on the study day was associated with increased

hospital mortality. This is important, as it is the only one of the four risk factors identified by multivariate analysis, which is directly amenable to intervention - either by better treatment or by anticipation and prevention. However, the point-of-prevalence design does not allow more detailed interpretation of the role of sepsis with our data.

Other variables associated with 90-day hospital mortality in patients receiving PN were age and admission to ICU during the current hospitalization. Duration of PN as a continuous variable did not add to prediction of mortality, whereas PN ≥42 days as a categorical variable based on a cut-off identified with current data did. Whether this cut-off may add to a future definition needs to be clarified. However, possible previously proposed empiric cut-offs for defining acute IF such as 28 days (8) did not allow the identification of patients with impaired survival, and a definition that can be realized only after 42 days is of limited clinical value.

Other patient outcomes beyond hospital stay were not assessed in our study. Earlier studies in chronic IF patients have demonstrated that home PN is associated with sarcopenia (6) and osteoporosis (7).

Due to the above-mentioned limitations of our study design, our final model of multiple regression analysis serves as a basis for future studies and cannot itself be interpreted as an identification of risk factors for mortality in patients on PN.

Strengths and limitations

The main strength of our study is that it is the first study to screen all adult hospitalized patients receiving PN to identify the overall prevalence of acute IF. A multicenter worldwide design adds to the achievement of representative results.

Limitations, as already discussed above, include the point-of-prevalence design, that the number of acute care beds was used to describe prevalence and that 90 day outcome was limited to data available in the hospital. However, considering a long hospital stay among study patients, the expected number of patients where death might have occurred after discharge from the hospital but within 90 days of study day is low. All these limitations were foreseen but unavoidable in this pragmatic study.

An additional limitation to the interpretation of our results is the difficulty in identifying acute IF. However, our study can be seen as the first step towards improvement in this regard.

~~**Future studies**~~

~~Based on our study, we suggest that future prospective studies that could support development in this area and facilitate the diagnosis of acute IF should address:~~

~~1) criteria for anatomical abnormality of the intestine associated with acute IF;~~

~~2) identification and development of tools and markers for GI dysmotility and mucosal injury;~~

~~3) the role of sepsis in the course of acute IF.~~

Conclusions

In this point-of-prevalence study, 21 patients per 1000 adult acute care beds received PN, and in more than half of them (13 patients/1000 beds) the reason for PN was acute IF. The majority of patients (68%) categorized to have acute IF had previously undergone abdominal surgery and the main mechanism of AIF was an acute motility issue. Patients receiving PN had high 90-day hospital mortality, whereas the presence of AIF did not additionally influence this outcome. Patients who had

sepsis on the study day, those of older age and those who were admitted to ICU had significantly higher mortality. The duration of PN most associated with increased 90-day hospital mortality in this study was 42 days or longer. All four factors were independently associated with 90-day hospital mortality.

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STATEMENT OF AUTHORSHIP

All the co-authors participated in designing and preparing the study. IP and ARB performed all analyses and drafted the manuscript. LP, JS, SG and OI performed as experts independently evaluating categorization of patients. MH, HHR, RB, AF, RT, ARB, MSP, MvdP, LP, JS, SG and OI participated in revision of cases during the AIF-SIG Meeting. All the co-authors reviewed the manuscript and agreed the final version.

CONFLICT OF INTEREST STATEMENT

ARB received honoraria for advisory board meeting participation and/or speakers fees from Nestlé, Fresenius and Nutricia and a study grant (for the University of Tartu) from Fresenius. MH received honoraria for advisory board meeting participation and/or speakers fees from Nestlé, Fresenius and Nutricia. HHR received honoraria for advisory board meeting participation and/or speakers fees from Nestlé, Fresenius, Baxter and Nutricia. RB received honoraria for advisory board meeting participation and /or speakers fee from Abbott and SHS. AF received speaker fees from BBraun, Baxter and Fresenius Kabi. RT received consulting fees and/or congress invitations from: Aguettant, Astra-Zeneca, Baxter, BBraun, Fresenius-Kabi, Lactalis, Nestlé, Nutricia, Shire. JS received speaker and consultancy fees from Fresenius Kabi. SG received speaker fees from Shire. LP received consulting fees from Baxter, Fresenius-Kabi and Shire, and educational fee from BBraun.

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