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

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- 63

**64 ABSTRACT****65 Background & Aims**

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

**69 Methods**

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

**73 Results**

74 Twenty-three hospitals (19 university, 4 regional) with a total capacity of 16,356 acute care beds and  
75 1,237 intensive care unit (ICU) beds participated in this study. On the study day, 338 patients  
76 received PN (21 patients/1000 acute care beds) and 206 (13/1000) were categorized as acute IF. The  
77 categorization of reason for PN was revised in 64 cases (18.9% of total) in consensus between the  
78 expert panel and investigators. Hospital mortality of all study patients was 21.5%; the median  
79 hospital stay was 36 days. Patients with acute IF had a hospital mortality of 20.5% and median  
80 hospital stay of 38 days ( $P>0.05$  for both outcomes). Disordered gut motility (e.g. ileus) was the most  
81 common mechanism of acute IF, and 71.5% of patients with acute IF had undergone abdominal  
82 surgery. Duration of PN of  $\geq 42$  days was identified as being the best cut-off predicting hospital  
83 mortality within 90 days.  $PN \geq 42$  days was independently associated with 90-day hospital mortality,  
84 age, sepsis, and ICU admission.

**85 Conclusions**

86 Around 2% of adult patients in acute care hospitals received PN, 60% of them due to acute IF. High  
87 90-day hospital mortality and long hospital stay were observed in patients receiving PN, whereas  
88 presence of acute IF did not additionally influence these outcomes. Duration of PN was associated  
89 with increased 90-day hospital mortality.

90 **INTRODUCTION**

91 A definition of intestinal failure (IF) was first proposed in 1981 by Fleming and Remington (1).  
92 Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed the following  
93 definition: the reduction of gut function below the minimum necessary for the absorption of  
94 macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is  
95 required to maintain health and/or growth (2,3). Along with this definition, three types of IF are  
96 described: types I to III IF. Type I acute IF (AIF) is an acute, short-term and usually self-limiting  
97 condition, commonly occurring in the perioperative setting and/or in association with critical  
98 illnesses, and requiring IVS from a few days to a few weeks. Type II AIF is a prolonged acute  
99 condition, often in metabolically unstable patients such as those with complicated intra-abdominal  
100 infection or acute mesenteric ischemia, often needing multiple surgeries and/or developing  
101 enterocutaneous fistulae, requiring complex multi-disciplinary care and IVS over periods of weeks or  
102 months. Type III IF (chronic IF = CIF) is a chronic condition, in metabolically stable patients, who  
103 require IVS over months or years.

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

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

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

116

117

**118 MATERIALS AND METHODS****119 Study design**

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

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

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

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

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

**136 Objectives**

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

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

**142 Definitions**

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

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

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

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

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

157

### 158 **Data collection and review**

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

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

### 169 **Statistics**

170 IBM Statistics SPSS version 25.0 was used for data analysis.

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

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

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

### 181 **Ethics**

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

183

184 **RESULTS**185 **Participating hospitals**

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

192 *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
<b>TOTAL</b>		16'356	1237	447	49	338 (2.1)	206 (1.3)	49 (0.3)
<b>CI 95% for prevalence</b>						1.58-2.53	1.00 - 1.61	0.11 - 0.41
<b>TOTAL without Site 10</b>		16'335	1233	447	45	332 (2.0)	204 (1.2)	45 (0.3)
<b>CI 95% for prevalence without Site 10</b>						1.55 - 2.41	0.99 - 1.58	0.11 - 0.37

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

195



196 **Data on study day**

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

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

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

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

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

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

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

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

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

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

218 IF – intestinal failure; EN: enteral nutrition

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

224 *Table 4. Pathophysiology and underlying diseases in AIF*

	Number of patients N=206	%
<b>Mechanism of AIF</b>		
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
<b>Underlying disease</b>		
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

225 AIF – acute intestinal failure; IBD - inflammatory bowel disease

226 Of the 106 patients where the mechanism of AIF was considered to be disordered motility, 53  
 227 patients had AIF due to a surgical complication, 9 active malignancy, 8 pancreatitis, 6 shock, 3  
 228 Crohn's/inflammatory bowel disease, 1 mesenteric vascular pathology, 1 primary motility disorder,  
 229 10 other abdominal pathology (including e.g. cholecystitis/cholangitis, adhesions, abdominal  
 230 trauma), and 15 other pathology not of primarily abdominal origin. This other pathology was mainly  
 231 hematological malignancy, graft versus host disease or multiple organ failure, resulting in paralytic  
 232 ileus or enterocolitis in ICU or IMC/HDU patients (11/15).

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

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

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

245 A total of 54 patients had sepsis on the study day, of whom 14 patients had septic shock. The most  
 246 common presumed origin of sepsis was an abdominal cause (70%), followed by a pulmonary cause  
 247 (13%).

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

#### 250 Data on outcome day

251 90 day outcome data were obtained in 330/338 (98%) patients. For the 8 patients with missing data,  
 252 2 did not have AIF and 6 had AIF. The hospital outcome at 90 days is shown in Table 5.

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

	All patients N=330	CIF N=49	AIF N=200	Non-IF N=81	p-value AIF vs non- IF
<b>Outcome</b>					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)	
<b>Abdominal surgery</b>	196 (59.4)	27 (55.1)	147 (73.5)	22 (27.1)	<0.001
<b>Two or more abdominal surgeries</b>	77 (22.8)	12 (24.5)	57 (28.5)	8 (9.9)	0.001
<b>Presence of a stoma during the study</b>	110 (33.3)	32 (65.3)	70 (35.0)	8 (9.9)	<0.001
<b>Presence of fistula during the study</b>	58 (17.6)	16 (32.7)	38 (19.0)	4 (4.9)	0.003

<b>Total duration of PN, days</b>	19 [10-37]	26 [11-79]	19 [10-37]	17 [10-29]	0.269
<b>Total patients in the ICU</b>	174 (52,7)	19 (38,8)	118 (59.0)	37 (45.7)	0.014
<b>Total ICU stay, days</b>	29 [16-50]	27 [16-42]	30 [16-46]	26 [16-75]	0.647
<b>Total hospital stay, days</b>	36 [21-61]	26 [14-54]	38 [21-61]	35 [23-71]	0.950

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

257 The total 90-day hospital mortality in patients with PN was 21.5%, and in patients with AIF 20.5%. Of  
 258 the patients without IF, 41 patients (77%) were discharged home, 8 patients transferred to another  
 259 hospital and 4 patients discharged to a rehabilitation center. Of the patients with AIF, 100 patients  
 260 (68%) were discharged home, 29 patients transferred to another hospital, 12 patients to a  
 261 rehabilitation center, 3 patients to a hospice and 3 patients to another institution. Of the patients  
 262 with CIF, 33 patients (67%) were discharged home, 4 patients to another hospital and 2 patients to a  
 263 rehabilitation center.

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

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

#### 272 **Associations of PN and AIF with 90-day hospital outcome**

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

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

283

284 Table 6. Comparison of survivors and non-survivors. Data presented as number of patients (percentage) or median  
 285 [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 $\geq 14$ d	209 (63.3)	161 (62.2)	48 (67.6)	.242
PN for $\geq 42$ 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

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

288 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
<b>Intestinal failure</b>				
No IF	0.988			
Acute IF	0.956	1.053	0.166	6.689
Chronic IF	0.886	1.107	0.276	4.428
<b>Age</b>	<b>0.013</b>	<b>1.029</b>	<b>1.006</b>	<b>1.052</b>
<b>Sepsis on study day</b>	<b>0.024</b>	<b>2.349</b>	<b>1.120</b>	<b>4.925</b>
Home PN before	0.731	0.775	0.180	3.325
Stoma ever	0.230	0.624	0.289	1.347
ICU admission ever	<b>0.023</b>	<b>2.459</b>	<b>1.133</b>	<b>5.336</b>
<b>3 or more abdominal surgeries</b>	0.105	0.405	0.136	1.206
<b>PN <math>\geq 42</math> days</b>	<b>0.008</b>	<b>2.868</b>	<b>1.319</b>	<b>6.235</b>

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

## 290 DISCUSSION

291 Our study has estimated the prevalence of PN to be 2.1% in adult patients hospitalized in acute care  
 292 hospitals. Acute IF was the main reason for usage of PN (in 61% of patients), and the prevalence of  
 293 acute IF in adult patients in acute care hospitals was 1.3%. Patients receiving PN had high hospital

294 mortality (20.5%), and a long hospital stay (36 days), whereas outcomes of acute IF patients did not  
295 differ significantly from those in other patients receiving PN.

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

### 298 **Prevalence of PN and IF**

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

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

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

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

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

330 In acute IF patients, whenever possible, treatment of the origin of the condition is of utmost  
331 importance and PN then just provides a “bridge” until restoration of intestinal function. Many  
332 patients with severe illness require IVS with fluids and electrolytes due to increased requirements in  
333 the acute phase which are unrelated to acute IF. At the same time, acute intestinal insufficiency is  
334 initially managed with trophic enteral nutrition without supplementary PN, as in other severely ill  
335 patients (2).

**336 Mechanisms of acute IF**

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

347 The most frequently documented underlying disease causing development of acute IF was a surgical  
348 complication followed by active malignancy, in line with previous results from Lal et al. (13). Most of  
349 the patients with acute IF were abdominal surgery patients (73.5% underwent abdominal surgery,  
350 13.1% of them twice, and 27.7% more than twice during the index hospitalization). In a recent study  
351 addressing patients with AIF, the median number of surgeries per patient was as high as four (8).  
352 Possibly only the most complicated surgical patients were identified in this previous study, supported  
353 by the fact that two thirds of patients had fistula(s) (8). In our study, we will also have captured less  
354 complicated surgical patients (including Type I IF).

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

**361 Outcome**

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

373

374 Sepsis is undoubtedly an important component in the course of acute IF leading to impaired  
375 outcome. In current study, presence of sepsis on the study day was associated with increased  
376 hospital mortality. This is important, as it is the only one of the four risk factors identified by  
377 multivariate analysis, which is directly amenable to intervention - either by better treatment or by  
378 anticipation and prevention. However, the point-of-prevalence design does not allow more detailed  
379 interpretation of the role of sepsis with our data.

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

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

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

393

#### 394 **Strengths and limitations**

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

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

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

406

#### 407 **Conclusions**

408 In this point-of-prevalence study, 21 patients per 1000 adult acute care beds received PN, and in  
409 more than half of them (13 patients/1000 beds) the reason for PN was acute IF. The majority of  
410 patients (68%) categorized to have acute IF had previously undergone abdominal surgery and the  
411 main mechanism of AIF was an acute motility issue. Patients receiving PN had high 90-day hospital  
412 mortality, whereas the presence of AIF did not additionally influence this outcome. Patients who had  
413 sepsis on the study day, those of older age and those who were admitted to ICU had significantly  
414 higher mortality. The duration of PN most associated with increased 90-day hospital mortality in this  
415 study was 42 days or longer. All four factors were independently associated with 90-day hospital  
416 mortality.

417

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#### 419 **STATEMENT OF AUTHORSHIP**

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



425 **CONFLICT OF INTEREST STATEMENT**

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

436 The other co-authors do not have any conflicts of interest to disclose.

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440

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