# Acute intestinal failure International multicenter point-of-prevalence study

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

2  Annika Reintam Blaser [1,2]; Ilse Ploegmakers[3], Michael Benoit[2], Mette Holst[4], Henrik Hojgaard

3  Rasmussen[4], Rosa Burgos[5], Alastair Forbes[6], Jon Shaffer[7], Simon Gabe[8], Oivind Irtun[9], Ronan

4  Thibault[10], Stanislaw Klek[11], Steven Olde Damink[3], Marcel van de Poll[3], Marina Panisic-Sekeljic[12],

5  Geert Wanten[13], Loris Pironi[14]; AIF study group: Vladislav Mihnovits[1], Antonina Britenkova[1], Kadri

6  Lind[1], Ivan Pertsev[1], Gregor Lansche[2], Anna Simona Sasdelli[14], Zsolt Bodnar [15], Francisco Pracca[16],

7  Italo Bioni[16], Gintautas Kekstas[17], Karolina Venlavicute[17], Pietro Vecchiarelli[18], Zeljko Krznaric[19], Ana

8  Kunovic[19], Ramiro Manzano Nunez[20], Carlos A Ordonez[20], Hanna-Liis Lepp[21], Charlene Compher[22],

9  Marianne Aloupis[22], Nizar Senussi[23], Ana Zugasti Murillo[24], María Maíz-Jiménez[25], Pilar Matia[26],

10  Carmina Wanden-Berghe[27], Wojciech Dabrowski[28]

11  [1] Department of Anaesthesiology and Intensive Care, University of Tartu, Puusepa 8, 51014 Tartu,
12  Estonia. E-mail: annika.reintam.blaser@ut.ee

13  [2] Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Spitalstrasse, 6000 Lucerne,
14  Switzerland. E-mail: michael.benoit9@gmail.com

15  [3] Department of Surgery, Maastricht University Medical Center, P. Debyelaan 25, 6221 HX
16  Maastricht, The Netherlands. E-mail: ibm.ploegmakers@gmail.com

17  [4] Centre for Nutrition and Bowel Disease, Department of Gastroenterology, Aalborg University
18  Hospital,Faculty of Health, Aalborg University, 9000 Aalborg, Denmark. E-mail: hhr@rn.dk

19  [5] Nutritional Support Unit. University Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035
20  Barcelona, Spain. E-mail: rburgos@vhebron.net

21  [6] Norwich Medical School and Norfolk and Norwich University Hospital, Norwich, United Kingdom. E-
22  mail: alastair.forbes@uea.ac.uk

23  [7] Intestinal Failure Unit, Salford Royal Hospital, UK. E-mail: jon.shaffer@srft.nhs.uk

24  [8] Lennard Jones Intestinal Failure Unit, St Marks Hospital ,Northwick Park, Watford road, Harrow
25  Middlesex HA1 3UJ,UK. E-mail: simon.gabe@nhs.net

26  [9] University Hospital North-Norway, Tromso, Norway. E-mail: oivind.irtun@unn.no

27  [10] Nutrition Metabolisms and Cancer institute, NuMeCan, INRA, INSERM, Univ Rennes, Nutrition unit,
28  CHU Rennes, 35000 Rennes, France. E-mail: ronan.thibault@chu-rennes.fr

29  [11] Stanley Dudrick's Memorial Hospital, Skawina, Poland. E-mail: klek@poczta.onet.pl

30  [12] Department for perioperative nutrition, Clinic for General Surgery, Military Medical Academy
31  Belgrade, Serbia. E-mail: panisicm@gmail.com

32  [13] Intestinal Failure Unit, Department of Gastroenterology and Hepatology, Radboud University
33  Nijmegen Medical Centre, Geert Grooteplein Zuid 10, 6525 GA, Nijmegen, The Netherlands. E-mail:
34  geert.wanten@radboudumc.nl

35  [14] Department of Digestive System, Center for Chronic Intestinal Failure, St Orsola-Malpighi Hospital,
36  University of Bologna, Via Massarenti, 9 – 40138 Bologna, Italy. E-mail: loris.pironi@unibo.it

37  [15] Department of Surgery, Letterkenny University Hospital, Letterkenny, Co. Donegal, Ireland,
38  F92AE81. E-mail: drbozsolt@gmail.com

39  [16] Department  of Intensive Care Medicine – Hospital de Clínicas- Universidad de la República. Av.
40  Italia S/N, 11600 Montevideo, Uruguay. E-mail: fpracca@gmail.com

41  [17] 1st ICU Vilnius University Hospital Santaros Clinics, Vilnius University Hospital Santariskiu Clinics,
42  Vilnius, Lithuania. E-mail: gintautas.kekstas@santa.lt

43  [18] Intensive Care Unit, Belcolle Hospital, Viterbo, Italy. E-mail: pietro.vecchiarelli@asl.vt.it

44  [19] Department of Gastroenterology, Hepatology and Nutrition, University Hospital Center Zagreb,
45  Zagreb, Croatia. E-mail: zeljko.krznaric1@zg.t-com.hr

46 [20] Trauma and Acute Care Surgery - Surgical Critical Care Department, Fundación Valle del Lili -
47 Universidad del Valle, Cali Colombia. E-mail: ordonezcarlosa@gmail.com

48 [21] North Estonia Regional Hospital, Tallinn, Estonia. E-mail: liis.lepp@gmail.com

49 [22] Clinical Nutrition Support Services, Hospital of the University of Pennsylvania, 3400 Spruce Street,
50 Philadelphia, PA 19104. E-mail: Marianne.aloupis@uphs.upenn.edu

51 [23] Digestive Disease and Surgery Institute, Cleveland Clinic, 9500 Euclid Avenue/A51 Cleveland, OH
52 44159, USA. E-mail: nsenussi@gmail.com

53 [24] Complejo Hospitalario de Navarra (Sección Nutrición) c/Irunlarrea 3, 31008 Pamplona (Navarra). E-
54 mail: ana.zugasti.murillo@cfnavarra.es

55 [25] University Hospital 12 de Octubre. Madrid, Spain. E-mail: mariairene.maiz@salud.madrid.org

56 [26] Hospital Clinico San Carlos, Madrid, Spain. E-mail: pilar.matia@gmail.com

57 [27] Home Hospital Department, General University Hospital Alicante. Pintor Baeza sn. 03010 Alicante,
58 Spain. E-mail: carminaw@telefonica.net

59 [28] Department of Anaesthesiology and Intensive Therapy Medical University of Lublin, Poland. E-mail:
60 w.dabrowski5@yahoo.com

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

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 ≥42 days was identified as being the best cut-off predicting hospital
83 mortality within 90 days. PN ≥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

5

155  pressure (MAP) ≥65mmHg and having a serum lactate level >2 mmol/L (18mg/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≤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 |
| **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 |

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.

| | 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%) | |

**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** | **%** |
| **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 |

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** | **%** |
| --- | --- | --- |
| **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 |

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.

**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 |
|---|---|---|---|---|---|
| **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 |

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 ≥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 ≥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

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

12

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).

**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.

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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 ≥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**

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