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ORIGINAL

Patients with faecal peritonitis admitted to European intensive care units: an epidemiological survey of the GenOSept cohort

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Take-home message: This is the largest cohort of patients admitted to ICU with faecal peritonitis reported to date. Six-month mortality was 32 %; age, acute renal dysfunction, hypothermia and lower haematocrit were consistently associated with an increased risk of death.

Electronic supplementary material
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Abstract *Introduction:* Faecal peritonitis (FP) is a common cause of sepsis and admission to the intensive care unit (ICU). The Genetics of Sepsis and Septic Shock in Europe (GenOSept) project is investigating the influence of genetic variation on the host response and outcomes in a large cohort of patients with sepsis admitted to ICUs across Europe. Here we report an epidemiological survey of the subset of patients with FP. *Objectives:* To define the clinical characteristics, outcomes and risk factors for mortality in patients with FP admitted to ICUs across Europe. *Methods:* Data was extracted from electronic case report forms. Phenotypic data was recorded using a detailed, quality-assured clinical database. The primary outcome measure was 6-month mortality. Patients were followed for 6 months. Kaplan–Meier analysis was used to determine mortality rates. Cox proportional hazards regression analysis was employed to identify independent risk factors for mortality. *Results:* Data for 977 FP patients admitted to 102 centres across 16 countries between 29 September 2005 and 5 January 2011 was extracted. The median age was 69.2 years (IQR 58.3–77.1), with a male preponderance (54.3 %). The most common causes of FP were perforated diverticular disease (32.1 %) and surgical anastomotic breakdown (31.1 %). The ICU mortality rate at 28 days was 19.1 %, increasing to 31.6 % at 6 months. The cause of FP, pre-existing co-morbidities and time from estimated onset of symptoms to surgery did not impact on survival. The strongest independent risk factors associated with an increased rate of death at 6 months included age, higher APACHE II score, acute renal and cardiovascular dysfunction within 1 week of admission to ICU, hypothermia, lower haematocrit and bradycardia on day 1 of ICU stay.

Conclusions: In this large cohort of patients admitted to European ICUs with FP the 6 month mortality was 31.6 %. The most consistent predictors of mortality across all time points were increased age, development of acute renal dysfunction during the first week of admission, lower haematocrit and hypothermia on day 1 of ICU admission.

Keywords Faecal peritonitis · ICU outcome · GenOSept · Sepsis · Septic shock · Genetic epidemiology

Introduction

Peritonitis is characterized by inflammation of the serosal membrane lining the abdominal wall and the intra-abdominal organs, often associated with infection within the peritoneal cavity, bacteraemia and severe sepsis/septic shock [1, 2]. Faecal peritonitis (FP) is a common cause of secondary peritonitis caused by spillage of faecal material from the large bowel into the peritoneum.

A previous pan-European study of 1,177 ICU patients with sepsis published in 2006 included 263 in whom the abdomen was the primary source of infection, but outcomes for this sub-population were not reported [3]. Other studies of patients with peritonitis were retrospective [4, 5] and described heterogeneous populations, without focusing specifically on FP [4–10]. Consequently, reported mortality rates from all-cause secondary peritonitis vary widely from as low as 5.8 % to as high as 63 %, reflecting differences in causation, source of infection, severity and treatment [11]. Only one of these studies [4] documented the organisms isolated (the commonest organisms were *E. coli*, streptococci and bacteroides), none reported any influence of microbiological isolates on mortality (Supplementary Table 1) [4–11] and none documented the antimicrobial regimes used or their relationship to outcomes.

Two relatively small single-centre retrospective cohort studies, published as abstracts, have specifically investigated FP outcomes after ICU admission [12, 13]. Pawa and coworkers [12] evaluated the effects of evolving sepsis management strategies (in particular the introduction of structured care bundles) on mortality in 360 patients, finding no evidence of a significant improvement in outcome. Sayer et al. [13] investigated 133 FP patients and identified the presence of underlying malignancy as a factor associated with increased survival, shorter ICU stay, lower inotropic requirements and decreased inflammatory markers, findings that the authors attributed to a less aggressive inflammatory response as a consequence of the malignancy.

A multiplicity of disease-specific and generic severity of illness scoring systems have been devised and tested, aimed at risk stratifying critically ill patients. The APACHE II (Acute Physiology and Chronic Health Evaluation II) score [14] correlates closely with outcome for patients with peritonitis, but does not take into account factors related to surgical intervention, which in turn can potentially alter many of the key physiological variables. Peritonitis-specific scores, such as the Mannheim Peritonitis Index (MPI), the Peritonitis Index Altona II (PIA-II), and the Elebute and Stoner score have also been developed [15–17] and evaluated [4, 6–10] (Supplementary Table 1). A number of other factors, including age, markers of nutritional state, co-morbidities, development of sepsis, extent of organ failures, time from onset of peritonitis to surgical intervention and effectiveness of source control, have also been reported to influence outcome [4–9].

GenOSept (Genetics of Sepsis and Septic Shock in Europe) is a pan-European part-FP7-funded study conceived by the European Critical Care Research Network of the European Society for Intensive Care Medicine to investigate the potential impact of genetic variation on the host response and outcomes in sepsis (https://www.genosept.eu/). To date the GenOSept cohort includes the largest and diagnostically most homogeneous collection of critically ill patients with FP. Analysis of this large, prospectively collected, quality-controlled data set provides a unique opportunity to characterise FP patients admitted to ICUs across Europe, including short- and long-term outcomes and to identify important prognostic indicators [18].

Methods

Recruitment

Ethics approval was granted either nationally or locally (for individual centres), or both. Written, informed consent for inclusion in the GenOSept study was obtained from all patients or a legal representative. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients were recruited from 102 centres across 16 countries (see electronic supplement for contributors) between September 2005 and January 2011.

The diagnosis of sepsis was based on the International Consensus Criteria which define sepsis as "the clinical syndrome defined by the presence of both infection and a systemic inflammatory response" [19]. Patients were followed for up to 6 months from enrolment, or until death.

Inclusion criteria: adult patients (>18 years) admitted to a high dependency unit or intensive care unit (ICU) with FP. FP was defined as inflammation of the serosal membrane that lines the abdominal cavity, secondary to contamination by faeces, as diagnosed at laparotomy.

Exclusion criteria: peritonitis due to gastric or upper GI-tract perforation (e.g., gastric or duodenal ulcer perforation, terminal ileum perforation), patient or legal representative unwilling or unable to give consent; patient pregnant; advanced directive to withhold or withdraw life-sustaining treatment or admitted for palliative care only; patient immunocompromised.

Database and quality assurance

See electronic supplement.

Statistical analysis

Clinical data of FP patients recruited to GenOSept were collected on days 1, 2, 3, 5 and 7 of ICU stay. Data extracted from the electronic case report form (eCRF) for the purposes of this analysis pertained to the first 24 h of ICU admission (including the total Sequential Organ Failure Assessment (SOFA) score), apart from organ-specific SOFA scores, which were derived from data for the whole of week 1 [20]. We used investigator-coded presence (or absence) of acute renal failure (ARF), corroborated by the renal SOFA score, as an objective measure of acute renal dysfunction, while the cardiovascular SOFA was used to indicate the presence and severity of shock. Calculation of APACHE II scores was based on ICU day 1 data.

Patients were right censored at 6-month follow-up. The primary study outcome was 6-month mortality. Secondary end points were ICU, hospital and 28-day mortality. Time from estimated FP onset to diagnosis was calculated using the date of symptoms' onset and date of confirmatory laparotomy.

Kaplan–Meier survival analysis was performed to determine mortality rates.

To determine risk factors for mortality, we analysed all of the 50 clinical variables that were available in the GenOSept database. For each variable, Cox proportional hazards (PH) regression analyses adjusted for age and gender were performed for association with each end point. Variables found to be significant in these single-variable analyses after Bonferroni correction for multiple testing ($p < 0.001 = 0.05/50$ to take account of the 50 variables tested) were entered into a multivariate Cox PH model. Stepwise regression in the multivariate Cox PH regression models was performed to determine independent predictors of mortality with adjustment for potential confounding factors. The full list of variables tested is provided in the electronic supplement.

A test for PH using the Schoenfeld residuals was performed and, for covariates indicating evidence of non-proportionality, spline smooth estimates of time-dependent hazard ratios (HRs) with pointwise confidence bands were calculated [21].

Schoenfeld residuals for the Cox PH regression model can be regressed against time to test for independence between residuals and time and test the PH assumption. The PH assumption is supported by a non-significant relationship between residuals and time, and refuted by a significant relationship.

Where the PH assumption is not supported, smooth estimates of HRs can be calculated using the method of Therneau and Grambsch [22].

Post hoc analyses were performed to evaluate the influence on outcome of the various antibiotic combinations, the use of antifungal agents and whether or not the antibiotics administered were considered to be "appropriate". Combinations of antibiotics given up to 10 days before and including the day of admission to the ICU were recorded. Antibiotic combinations given to less than 10 patients were recorded as "other". The adequacy of the administered antibiotics and the use of antifungal agents were also recorded. Cox PH regression models with adjustment for age and gender were performed to assess the effect of each antibiotic combination, whether or not they were considered appropriate, and the use of antifungal agents on outcome.

Statistical analysis was performed using R version 2.11.1 (The R Project for Statistical Computing. http://www.r-project.org/) and STATA statistical software version 10.1 (STATA 10.1, StataCorp, Lakeway Drive, College Station, Texas 77845 USA. http://www.stata.com).

Results

Patient characteristics and mortality

Table 1 provides details of the patients' baseline (day 1) and other characteristics (additional baseline characteristics are presented in Supplementary Table 2).

Nine hundred and seventy seven patients with FP, recruited between 29 September 2005 and 5 January 2011, were included in the analysis; 462 (47.3 %) patients were enrolled in the UK, the remainder in mainland Europe (Supplementary Table 2).

The median age was 69.2 (IQR 58.3–77.1) years; 54.3 % were male; 98.6 % of patients were Caucasian. The median ICU length of stay (LOS) was 10 days (IQR 5–21, range 1–160 days); the median hospital LOS was 28 days (IQR 15–51). The median APACHE II score was 16 (IQR 12–21) and the median day 1 SOFA score was 7 (IQR 5–10). Seven hundred and forty two patients (76.2 %) were mechanically ventilated, 959 (98.2 %) had severe sepsis, 835 (85.7 %) had a cardiovascular SOFA score $\geq$1 and 29 % had acute renal dysfunction (based on investigators' opinion), 271 (27.7 %) patients had a renal

Table 1 Patients' baseline characteristics recorded on day 1

Characteristics	*N*	N or Median[a]	% or IQR[b]
Medical co-morbidities			
Heart and vascular disease	976	390	40.0
Respiratory disease	976	244	25.0
Neurological disease	976	106	10.9
Severe renal disease	941	96	10.2
Gastrointestinal disease	976	230	23.6
Malignancy	976	295	30.2
Diabetes	976	163	16.7
Previous serious infection[c]	976	33	3.4
Other illness	976	339	34.7
Severe exercise restriction	976	9	0.9
Chronic dialysis	971	13	1.3
Chronic steroids use[d]	976	10	1.0
Cause of FP	972		
Perforated diverticular disease		312	32.1
Anastomotic breakdown		302	31.1
Malignancy		129	13.3
Trauma		67	6.9
Other		162	16.7
Time to surgery (days)	936		
		1	1–3
Acute physiology	977		
APACHE II score		16[a]	12–21[b]
SOFA score		7[a]	5–10[b]

APACHE Acute Physiology and Chronic Health Evaluation, *IQR* interquartile range, *N* number of non-missing observations, *SOFA* Sequential Organ Failure Assessment

[a] Median is shown instead of count

[b] IQR is shown instead of percentage

[c] Serious infection was defined as a serious, prolonged or recurrent infection

[d] Chronic steroid use was defined as taking corticosteroids below the immunosuppressive dose (>7 mg/kg/day hydrocortisone), which would exclude a patient from inclusion in the study

SOFA score ≥2 on day 1 (indicative of moderate to severe renal dysfunction), 11.8 % required renal replacement therapy (RRT) on day 1 and 208 (21.3 %) of patients received RRT during the first week.

The most common co-morbidities were cardiovascular, malignant and respiratory diseases. Perforated diverticular disease and anastomotic breakdowns together accounted for 63.2 % of causes of FP. Surgical source control had been attempted in all patients, prior to admission to intensive care.

Of the 977 patients admitted to ICU with a confirmed diagnosis of FP, 187 (19.1 %) had died at 28 days, 204 (20.9 %) died during their ICU stay, 283 (28.7 %) died in hospital and 309 (31.6 %) had died at 6 month follow-up (Table 2).

Individual variable analyses

Supplementary Table 3 shows the estimated HRs for the primary end point (6-month mortality) for variables that were significant after adjusting for multiple testing ($p < 0.001$) in individual variable analyses (results from the individual variable analyses for other secondary outcomes are shown in Supplementary Tables 4–6). Supplementary Fig. 1 shows Kaplan–Meier estimates of survival over 6 months for selected associations. The most significant associations with 6-month mortality were the APACHE II, total SOFA score on day 1, and the highest renal SOFA score during the first 7 days of ICU admission (used as a cumulative proxy marker of severity of renal dysfunction during this period) [20]. Other variables indicative of acute renal dysfunction were also significantly associated with 6-month mortality. These included investigator-recorded presence of ARF, need for RRT, pH, highest and lowest recorded creatinine and highest recorded urea on day 1. The next most significant association with 6-month mortality was for the highest cardiovascular SOFA score during the first week of ICU stay. Many of the variables associated with 6-month mortality were also significantly associated with the other outcome measures in single-variable analyses.

Table 2 Outcomes: mortality at the four time points for the 977 patients in the FP cohort; ICU and hospital length of stay

Outcome time point	Status	*N*	Deaths (%)	Exposure time (person-days)	Crude morality rate (95 % CI) (events/1,000 person-days)
6 months	Alive	668	31.6	121,498	2.54 (2.27–2.84)
	Dead	309			
ICU	Alive	773	20.9	16,549	12.3 (10.8–14.1)
	Dead	204			
Hospital	Alive	698	28.7	37,644	7.44 (6.62–8.36)
	Dead	283			
28 days	Alive	790	19.1	23,707	7.89 (6.83–9.10)
	Dead	187			

	Median	IQR
ICU length of stay (days)	10	5–21
Hospital length of stay (days)	28	15–51

CI confidence interval, *IQR* interquartile range, *N* number of non-missing observations

The cause of FP, the presence of co-morbidities, the time from estimated FP onset to surgical intervention and the finding of bilateral infiltrates on chest radiography (seen in 220 patients and suggestive of acute lung injury/acute respiratory distress syndrome) had no influence on survival at any time point.

The antimicrobial combinations administered on admission to ICU varied widely (Table 3) but were deemed by the local investigators to be appropriate in 91.8 % of cases. The most common combinations were piperacillin–tazobactam (12.1 %), cefuroxime/metronidazole (5.4 %) and amoxicillin–clavulanate (5.3 %). Antifungal agents were included in 5.8 % of initial antimicrobial combinations. In a post hoc analysis, no specific antimicrobial combination was associated with improved survival for the primary outcome (6-month mortality), although in a small subgroup the combination of amoxicillin–clavulanate/metronidazole appeared to be associated with significantly increased mortality at hospital discharge and 28 days, and in another the administration of metronidazole alone appeared to be associated with a significant increase in ICU mortality. Neither the co-administration of antifungals nor the appropriateness of the antimicrobial combinations was significantly associated with mortality (Supplementary Tables 7–10).

Table 3 Initial anti-microbial regimes

	N	%
Initial antimicrobial regimes[a]	761	
Ceftriaxone/metronidazole	15	2
Cefuroxime/gentamicin/metronidazole	15	2
Cefuroxime/metronidazole	41	5.4
Fluconazole/piperacillin–tazobactam	11	1.5
Gentamicin	28	3.7
Imipenem/cilastatine	25	3.3
Amoxicillin–clavulanate	40	5.3
Amoxicillin–clavulanate/metronidazole	17	2.2
Meropenem	27	3.6
Metronidazole	17	2.2
Metronidazole/piperacillin–tazobactam	35	4.6
Piperacillin–tazobactam	92	12.1
Other combinations	291	38.2
No antimicrobials given on day 1	107	14.1
Co-administration of antifungal agent	654	
Fluconazole	35	5.4
Caspofungin	1	0.2
Clotrimazole	1	0.2
Amphotericin B	1	0.2
No antifungal agent used	616	94.2
Appropriateness of antimicrobial treatment[b]	734	
Appropriate	674	91.8
Not appropriate	60	8.2

[a] Data was available for 761 patients. Antimicrobial combinations administered on day 1 of ICU admission to 10 or more patients are shown, less common combinations are included in the "other combinations" category; for 107 patients no antimicrobial treatment was recorded as having been given in the first 24 h

[b] Appropriateness of antimicrobial treatment during first 24 h ICU admission was based on local investigator opinion

HRs for the pH value on ICU admission showed evidence of non-proportionality of hazards for 6-month mortality ($p < 0.01$). Figure 2 (electronic supplement) shows the estimated non-proportional time-dependent HRs for this variable and suggests that the effect of pH on mortality over 6 months is greatest at admission to ICU and typically decreases to little or no effect over a 6-month period.

Multivariate analysis

Table 4 shows the results of a multivariate Cox PH regression model retaining the variables independently predictive of mortality at each end point. At all time points, age, highest recorded renal SOFA score over the first week of ICU stay and lowest recorded temperature on day 1 remained independently associated with mortality. For each unit increase in the highest renal SOFA score recorded during the first week of ICU stay, the hazard of death at 6 months increased by 26.4 % (HR = 1.26, 95 % CI 1.16–1.38), and similar increases were seen for ICU and hospital mortality (25.4 and 24.8 % respectively). This effect was more marked for 28-day mortality, where for each unit increase in renal SOFA score there was an increase in hazard of 34 % (HR = 1.34, 95 % CI 1.21–1.49).

The other consistent and independent predictor of outcome across all time points was hypothermia during day 1 of admission to ICU. Every degree centigrade increase in the lowest recorded temperature on day 1 reduced the mortality hazard at 6 months by 14.6 % (HR = 0.85, 95 % CI 0.76–0.96). This effect was also present for ICU, hospital and 28-day mortality (17.1, 12.5 and 18.4 % respectively).

The highest cardiovascular SOFA score, bradycardia, haematocrit and APACHE II score remained predictive of mortality at 6 months after adjustment for other variables in the multivariate model.

Whereas the SOFA score was not retained as an independent predictor for outcome at any time point, the APACHE II score was an independent predictor of 6 months and hospital mortality. For each unit increase in APACHE II score the 6 months and hospital mortality risks increased by 3.5 % (HR 1.035, 95 % CI 1.015–1.056) and 3.1 % (HR 1.031, 95 % CI 1.011–1.052) respectively.

The presence of acidosis affected shorter-term outcomes: lower values for pH on day 1 being predictive of mortality at 28 days and in ICU. The lowest recorded heart rate was independently associated with mortality at 6 months only.

Thrombocytopaenia was an independent predictor of 28-day and hospital mortality.

Table 4 Independent predictors of outcome, after inclusion in multivariate (stepwise regression) analysis

Variable	Unit	HR	95 % CI	*p* value
6-month mortality				
Age	1 year	1.04	1.03–1.05	3.0×10^{-10}
Female gender		1.27	1.0–1.6	0.05
Highest renal SOFA week 1	1 point	1.26	1.16–1.38	9.5×10^{-8}
Highest CVS SOFA week 1	1 point	1.17	1.04–1.32	0.01
Haematocrit	1 %	0.97	0.95–0.99	2.9×10^{-3}
Lowest temperature day 1	1 °C	0.85	0.78–0.96	9.3×10^{-3}
Lowest heart rate day 1	10 bpm	1.08	1.02–1.16	0.01
APACHE II	1 point	1.04	1.02–1.06	7.8×10^{-4}
ICU mortality				
Age	1 year	1.04	1.02–1.05	2.8×10^{-7}
Female gender		1.29	0.97–1.72	0.08
Highest renal SOFA week 1	1 point	1.25	1.14–1.38	3.0×10^{-6}
Lowest temperature day 1	1 °C	0.83	0.73–0.94	3.9×10^{-3}
pH day 1	1 point	0.90	0.82–0.99	0.03
Hospital mortality				
Age	1 year	1.04	1.03–1.05	6.1×10^{-10}
Female gender		1.23	0.96–1.58	0.1
Highest renal SOFA week 1	1 point	1.25	1.14–1.36	6.7×10^{-7}
Haematocrit day 1	1 %	0.98	0.96–1.0	0.02
APACHE II	1 point	1.03	1.01–1.05	2.0×10^{-3}
Lowest temperature day 1	1 °C	0.88	0.78–0.99	0.03
Lowest platelets day 1	10^{-9}/l	0.99	0.98–1.0	0.03
28 days-mortality				
Age	1 year	1.04	1.03–1.06	3.0×10^{-8}
Female gender		1.09	0.81–1.48	0.57
Highest renal SOFA week 1	1 point	1.34	1.21–1.49	4.1×10^{-8}
Haematocrit day 1	1 %	0.97	0.94–0.99	0.01
Lowest platelets day 1	10^{-9}/l	0.98	0.97–1.0	0.01
Lowest temperature day 1	1 °C	0.82	0.70–0.95	0.01
pH day 1	1 point	0.89	0.79–1.0	0.04
Highest heart rate day 1	10 bpm	1.08	1.01–1.15	0.02

Results are adjusted for age and gender
bpm beats per minute, *CVS* cardiovascular, *HR* hazard ratio, *CI* confidence interval

A higher haematocrit decreased the risk of death at 6 months (HR 0.97, 95 % CI 0.95–0.99), 28 days (HR 0.97, 95 % CI 0.94–0.99) and in hospital (HR 0.98 95 % CI 0.96–0.99).

Discussion

This large, prospectively collected cohort provides a contemporary pan-European view of the clinical characteristics, outcomes and independent risk factors for mortality for patients admitted to ICU with FP. Mortality in this cohort was 19.1 % at 28 days, 20.9 % in the ICU, 28.7 % at hospital discharge and 31.6 % at 6 months. The ICU mortality is similar to that observed in the APACHE II 2011 model (23.4 %) and that found in a recently reported, smaller single-centre study specifically investigating FP outcome in ICU [13], although much higher mortality rates were reported in an earlier study [12].

The GenOSept FP cohort was characterized by an elderly population, with a high prevalence of cardiovascular, malignant and respiratory co-morbidities. Populations across Western countries are aging, with an inevitable impact on the use and availability of critical care resources [23]. Our cohort reflects this trend; more than 60 % of patients included were aged above 65 years and almost one-third were more than 75 years old. In keeping with previous studies we found older age to be significantly and consistently associated with an increased risk of death [24, 25].

Unexpectedly, neither the presence of co-morbidities nor time from presumed onset of symptoms to surgery, nor the underlying cause of FP appeared to influence survival. Increased age, severity of renal and cardiovascular dysfunction within the first week of ICU stay, anaemia, hypothermia, bradycardia and APACHE II score were found to be independent predictors of 6-month mortality. Some of these factors (age, renal dysfunction during the first week, hypothermia and anaemia) were also found to be independent predictors of mortality at other time points. Acute renal dysfunction has been shown in previous large series of critically ill patients to be independently associated with higher ICU and hospital

mortality rates [26–29]. In the GenOSept FP cohort, the presence of acute renal dysfunction during the first week of ICU stay was strongly associated with mortality, the effect being more marked for the shorter-term outcomes (ICU and 28-day mortality), but remaining significant at 6 months. Raised creatinine and urea, acute renal dysfunction and the need for RRT on day 1 of admission to ICU were also all associated with worse outcomes in the single-variable analyses. Debate continues as to whether the excess mortality associated with renal dysfunction is simply a reflection of the severity of the underlying illness, or whether the worse outcomes are directly attributable to the effects of renal dysfunction. While renal impairment tends to accompany other organ dysfunctions in the critically ill, there is evidence to suggest that acute kidney injury contributes independently to poor outcomes [29].

The adverse effect of hypothermia, measured within 24 h of admission to ICU, on outcome in the critically ill has also been previously reported [30, 31], as has an association between severe hypothermia and the risk of ICU acquired infections [32]. Recently a large multicentre cohort study, including over 10,000 patients (not undergoing therapeutic hypothermia), suggested that after controlling for confounding variables, hypothermia was a strong and independent predictor of mortality [30]. At present it is not known whether active re-warming to correct hypothermia improves outcomes [31].

A low haematocrit on day 1 was associated with worse short- and long-term outcomes in this study. The explanation for this observation is unclear, but anaemia in patients undergoing both cardiac and non-cardiac surgery has previously been shown to be associated with worse outcomes [33–37], although the effects of blood transfusion have not been fully clarified [38, 39]. All of the patients with FP in the GenOSept study underwent laparotomy (a requirement for making the diagnosis). In addition, a significant proportion of patients (40 %) were documented to have cardiovascular co-morbidity, a group in which anaemia has been shown to be associated with increased mortality and major adverse cardiovascular events. A previously reported large observational study showed a higher 30-day survival rate in patients who received a blood transfusion compared to those who did not receive a transfusion [40]. The contribution of dilutional anaemia as a result of fluid resuscitation is unclear, but this could also be postulated to have had an adverse effect by compromising tissue oxygen delivery during early (<6 h) fluid resuscitation [41].

The observation that acidosis influenced short-term outcomes (ICU and 28-day mortality) suggests a possible association with renal dysfunction. This association is unlikely to reflect acid–base disturbance secondary to respiratory acidosis, as none of the respiratory variables seemed to have an effect on any mortality end point. Alternatively metabolic acidosis may reflect impaired tissue perfusion and inadequate resuscitation.

Thrombocytopaenia was amongst the independent predictors of hospital and 28-day mortality. A link between thrombocytopaenia and the outcome of critical illness has been previously reported. Thrombocytopenia is often a marker of illness severity, administration of blood products and an increased risk of death [42–46]. Our findings suggest that thrombocytopaenia is a marker of severity of illness in patients admitted to ICU with FP, perhaps in association with the development of consumption coagulopathy.

In the present study there appeared to be no effect of co-morbidities on mortality at any time point. This finding is in agreement with most [5, 6, 8–10] but not all [4, 7] of the previously published studies of patients with secondary peritonitis. Differences in the populations studied and their internal heterogeneity may explain such discrepancies. Interestingly, neither the cause of FP nor the time from onset of symptoms to surgery influenced survival in this cohort. This finding contrasts with previously published studies of secondary peritonitis in which time to reoperation, source control and indices of physiological derangement have been the strongest outcome predictors [4–10]. It is possible that in the GenOSept cohort the degree of acute physiological derangement overwhelmed the influence of the time to operative intervention, or that significant delay was unusual. In the cohort reported here the median time delay between onset of symptoms and surgery was 1 day (IQR 1–3), which is comparable with previously published data [10].

As might be expected in a pan-European study involving a large number of centres from 16 countries, a wide variety of initial antibiotic combinations were administered to these patients with FP. Consequently it was not possible to draw firm conclusions from this observational study as to whether the initial choice of antibiotic (which was considered by the local investigator to be appropriate in more than 90 % of cases) might influence outcome. These observations are in keeping with a recent Cochrane review that studied 16 different antibiotic regimes but was unable to make any specific recommendations for the first-line treatment of secondary peritonitis as all showed equivalent efficacy [47]. We are not aware of any other epidemiological studies of peritonitis that have documented antibiotic regimes or identified any associations with outcome.

Although larger than any previous series of patients admitted to ICU with FP, this study has a number of important limitations. Firstly recruitment was based on a clinical diagnosis of FP, but participating centres were at liberty to decide which patients they would recruit; subjects were not, therefore, enrolled consecutively, thereby introducing a potential for selection bias. Secondly there was considerable variation in the numbers of patients recruited in each country and some centres contributed only small numbers of patients. Nevertheless there were a wide range of ages, severity of physiological derangement

and co-morbidities, suggesting that a significant systematic selection bias is unlikely. Thirdly, the use of the Bonferroni correction to address multiplicity of testing could be viewed as a conservative method, although such an approach can be justified given the large number of tests performed and the importance of avoiding false positive results. Finally, in common with all but one of the previous epidemiological studies of peritonitis (which found no relationship between microbial isolates and outcome) [4] (Supplementary Table 1) we did not collect microbiological data.

Conclusions

This is the largest cohort of patients admitted to ICU with FP reported to date, providing a contemporary European view of their clinical characteristics, outcomes and prognostic features. The ICU mortality rate was 20.9 %, increasing to 31.6 % at 6 months. Age, acute renal dysfunction during the first week of admission to ICU, hypothermia and lower haematocrit were consistently associated with an increased risk of death.

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