Extrapancreatic infections are common in acute pancreatitis and they are related to organ failure: a population-based study

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Background Although the impact of pancreatic infections in acute pancreatitis has been studied extensively, there are no population-based data on extrapancreatic infections and their potential relation to organ failure. We aimed to study the occurrence of pancreatic and extrapancreatic bacterial infections in acute pancreatitis and their relation to patient outcome.
Patients and methods All patients with first-time acute pancreatitis from 2003 to 2012 in a defined area in Sweden were retrospectively evaluated. Data on acute pancreatitis severity, organ failure, infections, and in-hospital mortality were collected.
Results Overall, 304 bacterial infections occurred in 248/1457 patients (17%). Fifteen percent had extrapancreatic and 2% had pancreatic infections. The lungs (35%), the urinary tract (24%), and the bile ducts (18%) were the most common sites of extrapancreatic infections. Organ failure, severe acute pancreatitis, and in-hospital mortality were more common in patients with vs those without (pancreatic/extrapancreatic) infections ($P<0.05$). Organ failure and severe acute pancreatitis occurred more frequently in pancreatic vs extrapancreatic infections (70% vs 34%, $P<0.001$ and 67% vs 28%, $P<0.001$), but in-hospital mortality did not differ between the two groups (7.4% vs 6.8%, $P=1.0$). Both pancreatic and extrapancreatic infections were independent predictors of organ failure ($P<0.05$). Out of culture-positive infections, 18% were due to antibiotic-resistant bacteria, without any significant difference between extrapancreatic vs pancreatic infections ($P>0.05$). About two out of five infections were of nosocomial origin.
Conclusion Extrapancreatic infections occurred in 15% and pancreatic infections in 2% of patients with first-time acute pancreatitis. Both pancreatic and extrapancreatic infections were independent predictors of organ failure, leading to increased mortality. Eur J Gastroenterol Hepatol 32: 1293–1300

Introduction

Acute pancreatitis is a common gastroenterological emergency characterized by reversible inflammation in the pancreas [1]. Although in most cases of acute pancreatitis the inflammatory process is self-limiting [1], in 8–20% of patients persistent organ failure and severe acute pancreatitis may develop [2,3] resulting in both systemic and local complications, such as peripancreatic necrosis [1,4], and increased mortality [5–8]. In particular, infectious complications involving pancreatic necrosis or fluid collections postpancreatitis are of concern as they are related to poor patient outcome with an in-hospital mortality up to 30% [9,10].

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Extrapancreatic infections, most commonly pneumonia and spontaneous bacteremia, are considered to occur frequently in the course of acute pancreatitis [11–16], possibly as a result of bacterial translocation from the gut [17], affecting 15–32% of the patients [11–16]. However, few studies have focused specifically on the occurrence of extrapancreatic infections following acute pancreatitis [11–16], and population-based data on their occurrence are nonexistent, while their potential association with organ failure has not been investigated in a population-based cohort. Furthermore, data on their potential effect on mortality are not unanimous [11–16]. Thus, we hypothesized that extrapancreatic infections are common following acute pancreatitis and that they may be related to organ failure in acute pancreatitis.

The main aims of this study were to investigate the occurrence of extrapancreatic (in comparison to pancreatic) infections in a population-based cohort of patients with first-time acute pancreatitis and their potential relation to patient outcome, in particular organ failure.

Patients and methods

All adult patients (18 years) with first-time acute pancreatitis from 2003 to 2012 in an area of 600 000 inhabitants in Sweden were retrospectively evaluated. The evaluation protocol along with the data collection strategy has been previously described in a paper produced from this cohort investigating the natural course of acute pancreatitis [18].

In short, all patients with acute pancreatitis according to ICD-10 codes in the discharge hospital database and autopsy reports were identified and the diagnosis was confirmed; patients with previous acute pancreatitis or chronic pancreatitis were excluded [18]. Acute hospital care in Sweden is provided only by public hospitals and thus all patients with first-time acute pancreatitis in the primary catchment area of our institution were identified [18]. The local ethics committee approved the study protocol.

Data collection

The electronic medical records of all patients were scrutinized, and relevant data were obtained, including demographics, admission and discharge dates, etiology of acute pancreatitis, comorbidities, and need of ICU care. Data on acute pancreatitis severity, local, and systemic complications as well as the occurrence of organ failure (transient or persistent) according to the revised Atlanta Classification [19] were also registered. The Acute Physiology and Chronic Health Evaluation (APACHE II) score upon admission was calculated [20]. The Charlson Co-morbidity index [21] was calculated as a measure of comorbid illness.

Infection-related data

The occurrence and site of infections were noted and ascertained during medical record scrutinization. The diagnosis of primary bacteremia was based on positive blood cultures in the absence of any other possible cause of bacteremia. Pneumonia, urinary tract infection, skin and soft-tissue infection, bacteremia and other infections were defined according to conventional criteria [22]. Patients were considered to have an infection only when the diagnosis was confirmed and specific diagnostic criteria for each infection were confirmed. For example, for pneumonia, the presence of characteristic imaging (e.g., on chest radiograph) along with clinical signs of airway infection were required [22,23]. Thus, the diagnosis of an infection was not limited to a positive culture result, and this strategy has been followed in several other studies [14,23–25]. In cases of multiple infections, any infection diagnosed after the first infection was considered as a separate infection [26]. Spontaneous bacterial peritonitis was diagnosed as previously described [27] and secondary bacterial peritonitis was diagnosed as previously described [28]. Cholangitis was diagnosed as previously described [29] and as the classical triad of jaundice/raised liver function tests with an obstructive pattern, right upper quadrant pain, and fever. All patients with cholangitis underwent biliary interventions, usually endoscopic retrograde cholangiography, confirming the presence of stones/debris and pus in the bile ducts. Patients with clinical signs of infection suspected of pancreatic infection was diagnosed by imaging confirming gas configuration in the pancreatic necrosis or pseudocyst and by a positive culture with fine needle aspiration, obtained by computed tomography (CT) or MR scan, endoscopic ultrasound or at autopsy [19]. Infections diagnosed at autopsy alone were also included in the study as long as they were described in the autopsy report (including histopathology analysis) and mentioned in the death certificate issued after an autopsy. Nosocomial infections were defined as infections developing at least 2 days after hospitalization [30]. We also noted any antibiotic treatment received by the patients.

Microbiology

In the case of culture-positive infections with available culture results in the medical records, bacteria and their antibiotic susceptibility patterns were registered. Antibiotic-resistant bacterial infections were defined as: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin- or ampicillin-resistant *Enterococcus* species, or extended-spectrum β-lactamase producing Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella pneumonia*), quinolone-resistant gram-negative rods, or isolates not susceptible to at least one agent in three or more antimicrobial categories [31–34]. Coagulase-negative *Staphylococcus epidermidis* was not classified as an antibiotic-resistant organism, because the organism is most likely a contaminant [33].

Statistical analysis

Data are presented as median and interquartile range (IQR) or *n* and percentage, as appropriate. When comparing groups, the Chi-Square test or Fisher's exact test was used for categorical variables and the Mann–Whitney U test for continuous variables. The statistics were performed on the total number of infections when evaluating the bacteria, their antibiotic susceptibility patterns, and possible nosocomial origin following acute pancreatitis similar to other studies [31,35–37], and all other statistics were performed on the total number of patients. All parameters that were independent predictors of organ failure with a P value <0.05 [18] were entered into multivariate logistic regression analysis. All tests were two-tailed and were conducted at a 5% significance level. All statistical analyses were performed by using SPSS Statistics (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 24.0.; IBM Corp, Armonk, New York, USA).

Results

Characteristics of the study population

In all, 1457 patients with a first-time acute pancreatitis during the study period were identified. A total of 304 bacterial infections occurred in 248/1457 (17%) patients with first-time acute pancreatitis. Overall, 277 extrapancreatic infections occurred in 221/1457 (15%) patients and 27/1457 (2%) had pancreatic infections (or a combination of both $n = 12/27 = 44\%$) (Table 1). The lungs, the urinary tract, and the bile ducts were the most common sites of extrapancreatic infections (Table 1). Out of the 248 patients with infections, nine patients had a fungal infection 9/248 (4%): 4/9 patients had combined fungal and bacterial extrapancreatic infections, 4/9 patients had combined fungal and bacterial pancreatic infections, and 1/9 had a fungal extrapancreatic infection. Severe acute pancreatitis developed in 144 patients; 80/144 (56%) patients with severe acute pancreatitis compared to 168/1313 (13%) without severe acute pancreatitis were diagnosed with an infection ($P < 0.001$). In patients with

Table 1. Characteristics of patients with acute pancreatitis without infection, as well as with extrapancreatic and with pancreatic infections

	Patients without infections ($n=1209$)	Patients with extrapancreatic infections ($n=221$)	Patients with pancreatic infections ($n=27$)
Demographics			
Age (years), $n=1457$	61 (47–75)[a]	71 (58–82)	62 (47–74)[b]
Female, $n=1456$	627 (52%)	111 (50%)	13 (48%)
Smoker, $n=915$	173 (14%)	36 (16%)	5 (19%)
BMI (kg/m^2)>30, $n=779$	194 (16%)	41 (19%)	7 (26%)
Charlson comorbidity index score>1, $n=1457$	264 (22%)[a]	77 (35%)	5 (19%)
Etiology of acute pancreatitis			
Biliary, $n=1457$	569 (47%)[a]	127 (57%)	8 (30%)[b]
Alcoholic, $n=1457$	214 (18%)[a]	27 (12%)	8 (30%)[b]
Idiopathic or other etiologies, $n=1457$	426 (35%)	67 (30%)	11 (41%)
Site of infection			
Pneumonia, $n=1457$		78 (35%)	3 (11%)
Urinary tract infection, $n=1457$		54 (24%)	
Cholangitis, $n=1457$		40 (18%)	
Primary bacteremia, $n=1457$		16 (7%)	
Other, $n=1457$		6 (3%)	1 (4%)
Mixed, $n=1457$		27 (12%)	8 (30%)

Data presented as median (interquartile range) or *n* (%), as appropriate. The Chi-Square test or Fisher's exact test was used for categorical variables and the Mann–Whitney U test for continuous variables. There were no significant differences between patients without infections vs patients with pancreatic infections ($P > 0.05$ for all).

[a]$P<0.05$: patients without infection vs those with extrapancreatic infection.

[b]$P<0.05$: patients with extrapancreatic infection vs those with pancreatic infection.

severe acute pancreatitis, extrapancreatic infections were present in 62/144 (43%) and pancreatic infections in 18/144 (13%; $P<0.001$). Sixty-one patients were found to have pancreatic necrosis. In all, 51/61 (84%) patients with pancreatic necrosis had infections compared to 197/1199 (16%) without pancreatic necrosis ($P<0.001$). Among patients with pancreatic necrosis ($n=61$), 27/61 (44%) had a pancreatic infection and 24/61 (39%) had an extrapancreatic infection ($P<0.001$).

Predictors of infections in acute pancreatitis

Patients without infections and with pancreatic infections were significantly younger compared to those with extrapancreatic infections (Table 1). Patients without infections had significantly less comorbidities than those with extrapancreatic infections (Table 1). Extrapancreatic infections were more common in biliary acute pancreatitis mainly due to the occurrence of cholangitis (Table 1). Patients with vs those without infections had higher markers of systemic inflammation, both upon admission and later in the course of acute pancreatitis as well as increased APACHE scores (Table 2).

Infection acquisition type

In total, the exact date of infection diagnosis could be retrieved for 118/248 (48%) patients with an infection, 48/118 (41%, i.e., about two out of five) patients had nosocomial infections and 70/118 (59%) patients had non-nosocomial infections. Thus, 48 out of 1457 patients with a first time acute pancreatitis had a known nosocomial infection (3%). Nosocomial infections were more commonly pancreatic 15/27 (56%) than extrapancreatic 38/277 (14%; $P<0.001$). Patients with non-nosocomial infections had more frequently extrapancreatic 76/277 (27%) than pancreatic foci 3/27 (11%; $P<0.001$). The most common site of nosocomial infections was peripancreatic necrosis, the urinary tract, and the bile ducts (Table 3). Mixed infections were significantly more frequently of nosocomial than non-nosocomial origin (Table 3). The median time from hospital admission to infection diagnosis was 1 day [interquartile range (IQR) 0–4 days]; to extrapancreatic infections 1 day (0–3 days); to pancreatic infections 9 days (2–20 days); and to nosocomial infections 8 days (4–14 days).

Infections with a culture positive result

Data on total numbers of specimens as well as numbers of culture positive results are presented in Supplemental Digital Content 1, *http://links.lww.com/EJGH/A585*. Out of 160 culture positive infections, 117 (73%) had at least one retrievable, bacterial culture with resistance patterns ($n=108$ extrapancreatic infections and $n=9$ pancreatic infections); 65/117 (56%) were caused by gram-negative bacteria, 40/117 (34%) by gram-positive bacteria, and 12/117 (10%) by a mixture of both gram-negative and gram-positive bacteria. Infections with bacteria resistant to at least one kind of antibiotics were present in 70/117 (60%) of culture-positive bacterial infections: 64/108 (59%) of extrapancreatic infections vs 6/9 (67%) of culture-positive pancreatic infections ($P=1.0$). Overall, 29/160 (18%) of culture-positive infections or 29/304 (10%) of all infections were due to antibiotic-resistant bacteria (Table 4). Ampicillin-resistant enterococci were significantly more common in patients with pancreatic vs those with extrapancreatic infections ($P=0.044$) (Table 4).

Overall, 32/53 (60%) of nosocomial and 40/79 (51%) of non-nosocomial infections (i.e., among infections with ascertained exact diagnosis date, $n=132$) had a positive bacterial culture with a retrievable report on resistance patterns (Table 5). Among patients with a positive culture and available results, in 24/32 (75%) of nosocomial and 21/40 (53%) of non-nosocomial infections, bacteria were resistant to at least one antibiotic class ($P=0.013$). Non-nosocomial infections were significantly more frequently caused by gram-negative strains and nosocomial infections trended to have an increased incidence

Table 2. Patient outcome in patients with vs those without infections following first-time acute pancreatitis

	Patients without infections ($n=1209$)	Patients with extrapancreatic infections ($n=221$)	Patients with pancreatic infections ($n=27$)
Severity of acute pancreatitis			
APACHE II score, $n=1443$	6.0 (4.0–8.0)[a,b]	8.0 (6.0–10.0)	8.0 (5.8–10.0)
CRP at admission (mg·l^{-1}), $n=1438$	13.0 (4.0–57.0)[a]	29.5 (7.0–118.5)	24.0 (3.7–134.0)
CRP at 48 h (mg·l^{-1}), $n=1417$	108.0 (35.0–205.0)[a,b]	223.5 (146.8–321.3)	311.0 (192.0–400.0)[c]
SIRS, $n=1446$	485 (40%)[a,b]	177 (80%)	26 (96%)[c]
Severe acute pancreatitis, $n=1457$	64 (5%)[a,b]	62 (28%)	18 (67%)[c]
Organ failure, $n=1457$	83 (7%)[a,b]	74 (34%)	19 (70%)[c]
Persistent organ failure, $n=1457$	64 (5%)[a,b]	62 (28%)	18 (67%)[c]
Systemic complications, $n=1444$	43 (4%)[a,b]	35 (16%)	5 (19%)
Local complications, $n=1448$	170 (14%)[a,b]	86 (39%)	27 (100%)[c]
Pancreatic necrosis, $n=1457$	10 (1%)[a,b]	24 (11%)	27 (100%)[c]
Interventional treatment			
ERCP, $n=1445$	217 (18%)[a]	62 (28%)	3 (11%)
Hospitalization			
Length of hospitalization (days), $n=1455$	6 (3–9)[a,b]	12 (7–20)	61 (21–131)[c]
Admitted to ICU, $n=1447$	22 (2%)[a,b]	51 (23%)	18 (67%)[c]
Length of ICU stay (days), $n=88$[d]	3 (2–6)[a,b]	5 (3–14)	8 (4–24)
In-hospital mortality, $n=1457$	24 (2.0%)[a]	15 (6.8%)	2 (7.4%)

Data presented as median (interquartile range) or *n* (%), as appropriate. The Chi-Square test or the Fisher's exact test was used for categorical variables and the Mann–Whitney U test for continuous variables.
APACHE II score, Acute Physiology and Chronic Health Evaluation II; CRP, C-reacting protein; ERCP, endoscopic retrograde cholangiopancreatography; SIRS, systemic inflammatory response syndrome.
[a]$P<0.05$: patients without infection vs those with extrapancreatic infection.
[b]$P<0.05$: patients without infection vs those with pancreatic infection.
[c]$P<0.05$: patients with extrapancreatic infection vs those with pancreatic infection.
[d]Analyses performed only among patient admitted to ICU.

Table 3. Site of infection in nosocomial vs non-nosocomial infections among 118 patients with a known timepoint of infection diagnosis

Site of infection	Patients with nosocomial infections ($n=48$)	Patients with non-nosocomial infections ($n=70$)	*P* value
Peripancreatic necrosis	10 (21%)	3 (4%)	0.001
Urinary tract	9 (19%)	21 (30%)	0.598
Bile duct	5 (10%)	12 (17%)	0.677
Lung	3 (6%)	10 (14%)	0.530
Bacterial peritonitis	1 (2%)	0	0.337
Skin	1 (2%)	1 (1%)	1.00
Abscess (intra-abdominal)	1 (2%)	0	0.337
Blood (primary bacteremia)	0	12 (17%)	0.007
Mixed	18 (38%)	11 (16%)	0.023

Data presented as n (%). The Chi-Square test or Fisher's exact test was used for categorical variables.

of gram-positive strains, but this did not reach statistical significance (Table 5). Carbapenem-resistant strains were significantly more common in nosocomial infections compared to non-nosocomial infections, but nosocomial infections did not significantly differ regarding other resistance patterns of isolated bacteria, despite trends of increased incidence of antibiotic resistance in the former (Table 5).

Antibiotic treatment

In all, 240/248 (97%) patients with infections received antibiotic treatment: 214/221 (97%) patients with extrapancreatic infections and 26/27 (96%) patients with pancreatic infections. In 8/248 (3%) of patients with infections, antibiotic treatment was not specified: five patients had acute uncomplicated cystitis, two patients had pneumonia, and one patient was diagnosed with infected pancreatic necrosis postmortem (at autopsy). In total, two patients had an infection confirmed with an autopsy with histopathology out of 248 patients with infection. Out of 1209 patients without infection diagnosis, 391 (32%) received antibiotic treatment (Supplemental Digital Content 2, *http://links.lww.com/EJGH/A586*, which demonstrates characteristics of these patients and Supplemental Digital Content 3 *http://links.lww.com/EJGH/A587*, which demonstrates the antibiotics administered).

Relation of infections with organ failure and patient outcome

Organ failure, systemic complications, severe acute pancreatitis, and need for intensive care were more common and length of hospital stay (LOS) prolonged among patients with extrapancreatic and pancreatic infections vs those without infections (Table 2). Local complications, organ failure, and severe acute pancreatitis occurred more often in pancreatic compared to extrapancreatic infections (Table 2). We have previously shown that organ failure is the only independent predictor of in-hospital mortality at first-time acute pancreatitis [18]. After adjustment for confounders (age, extrapancreatic infections, pancreatic infections, and pancreatic necrosis) by means of multivariate logistic regression analysis, both extrapancreatic infections [Odds ratio (OR) 4.8, (95% confidence interval (CI) 3.27–7.035), $P < 0.001$] and pancreatic infections [OR 7.03, (CI 2.156–22.895), p=0.001] were independent predictors of organ failure. Organ failure, but not persistent organ failure, and ICU admission were significantly

Table 4. Microbiologic findings in culture-positive bacterial extrapancreatic and pancreatic infections

	Extrapancreatic infections ($n=108$)	Pancreatic infections ($n=9$)	*P* value
Gram-negative bacilli	60 (56%)	5 (56%)	1.00
QRGNR	9 (8%)	0	1.00
Enterobacteriaceae resistant to at least one β-lactam[a]	31 (29%)	2 (22%)	-
ESBL	2 (2%)	0	-
Gram-positive cocci	37 (34%)	3 (33%)	1.00
Enterococcus[b]	19 (18%)	3 (33%)	-
Ampicilin-resistant *Enterococcus*	2 (2%)	2 (22%)	0.044
Vancomycin-resistant *Enterococcus*	0	0	-
MRSA	0	0	-
Gram-negative and gram-positive strains	11 (10%)	1 (11%)	1.00
Third-generation cephalosporin-resistant strains	14 (13%)	2 (22%)	0.632
Carbapenem-resistant strains	10 (9%)	3 (33%)	0.357
Piperacillin-tazobactam-resistant strains	10 (9%)	3 (33%)	0.173
Quinolone-resistant strains	11 (10%)	0	1.00
Bacteria resistant to three or more antibiotic classes	23 (21%)	3 (33%)	1.00
Bacteria causing antibiotic-resistant infections[c]	26 (24%)	3 (33%)	0.700

Data presented as *n* (%). The Chi-Square test or Fisher's exact test was used for categorical variables.
QRGNR, Quinolone resistant gram-negative rods; ESBL, extended-spectrum β-lactamase producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]All extrapancreatic and pancreatic culture-positive Enterobacteriaceae infections were resistant to at least one β-lactam.
[b]All extrapancreatic and pancreatic infections with culture-positive Enterococci infections.
[c]MRSA, vancomycin- or ampicillin-resistant Enterococcus species, ESBL, QRGNR or isolates not susceptible to at least one agent in three or more antimicrobial categories.

Table 5. Microbiologic findings in culture-positive bacterial non-nosocomial infections and nosocomial infections

	Non-nosocomial infections ($n=40$)	Nosocomial infections ($n=32$)	*P* value
Gram-negative bacilli	31 (78%)	15 (47%)	0.007
QRGNR	4 (10%)	2 (6%)	1.00
Enterobacteriaceae resistant to at least one β-lactam[a]	12 (30%)	9 (28%)	-
ESBL	1 (3%)	0	-
Gram-positive cocci	8 (20%)	13 (41%)	0.056
Enterococcus[b]	3 (8%)	9 (28%)	-
Ampicilin-resistant Enterococcus	0	1 (3%)	1.00
Vancomycin-resistant Enterococcus	0	0	-
MRSA	0	0	-
Gram-negative and gram-positive strains	1 (3%)	4 (13%)	0.164
Third-generation cephalosporin-resistant strains	4 (10%)	3 (9%)	0.646
Carbapenem-resistant strains	1 (3%)	4 (13%)	0.042
Piperacillin-tazobactam–resistant strains	1 (3%)	3 (9%)	0.089
Quinolone-resistant strains	3 (8%)	4 (13%)	0.412
Bacteria resistant to three or more antibiotic classes	3 (8%)	9 (28%)	0.308
Bacteria causing antibiotic-resistant infections[c]	5 (13%)	9 (28%)	0.052

Data presented as *n* (%). The Chi-Square test or Fisher's exact test was used for categorical variables.
QRGNR, Quinolone resistant gram-negative rods; ESBL, extended-spectrum β-lactamase producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]All non-nosocomial and nosocomial culture-positive Enterobacteriaceae infections were resistant to at least one β-lactam.
[b]All non-nosocomial and nosocomial infections with culture-positive Enterococci infections.
[c]MRSA, vancomycin- or ampicillin-resistant Enterococcus species, ESBL, QRGNR or isolates not susceptible to at least one agent in three or more antimicrobial categories.

more common in combined extrapancreatic and pancreatic infections vs pancreatic infections alone and vs extrapancreatic infections alone ($P<0.05$ for both; data not shown). Among patients with fungal infections severe acute pancreatitis occurred significantly more frequently when compared to patients with pancreatic infections alone ($P<0.05$; data not shown).

In total, 41/1457 (3%) patients with first-time acute pancreatitis died during admission. Unsurprisingly, more patients with infections died during their first-time acute pancreatitis compared to those without infections [17/248 (7%) vs 24/1209 (2%), $P<0.001$; Table 2]. No patients with necrotizing acute pancreatitis without infections died during hospitalization. In-hospital mortality in patients with necrotizing acute pancreatitis and any bacterial infection was 6/51 (12%); 2/27 (7%) in those with pancreatic and 4/24 (17%) in those with extrapancreatic infections ($P=0.402$). In-hospital mortality did not differ between patients with pancreatic compared to those with extrapancreatic infections (7.4% vs 6.8%, $P=1.0$). There were no significant differences in in-hospital mortality among patients with different infection acquisition types or etiologies, that is, biliary vs alcohol vs other ($P>0.05$ for all; data not shown). There was no significant difference in in-hospital mortality between the group of combined extrapancreatic and pancreatic infections or fungal infections vs the other groups of patients ($P>0.05$ for all; data not shown).

When analyses were restricted to patients with a culture confirmed infection and those with negative cultures and no clinical signs of infection, the main findings of our study regarding the relation of infections with patient outcome remained unchanged (data not shown). Furthermore, when dividing our cohort to patients diagnosed with acute pancreatitis early (2003–2007) vs late (2008–2012) in the study period, urinary tract infection and infected

pancreatic necrosis were significantly less common in the former ($P<0.05$ for both; data not shown). The occurrence of other infections and their effect on patient outcome did not differ significantly between the two groups ($P>0.05$ for all; data not shown).

Discussion

Based on a population-based cohort of 1457 patients with first-time acute pancreatitis, 15% experienced extrapancreatic infections, mainly from the respiratory and urinary systems and the biliary tract, while about 2% had pancreatic infections. Both extrapancreatic and pancreatic infections were found to be independent predictors of organ failure. Eighteen percent of culture-positive infections were due to antibiotic-resistant bacteria. Although antibiotic resistance was more common in pancreatic infections, differences from extrapancreatic infections did not reach statistical significance. To our knowledge, this is the first population-based study evaluating both extrapancreatic and pancreatic bacterial infections, along with resistance to antibiotics and patient outcome in a large cohort of patients with first-time acute pancreatitis.

Infections and patient outcome

A recent meta-analysis of 19 studies (with 1741 patients included) reported higher occurrence of both extrapancreatic (32%) and pancreatic (12%) infections [11]. This may possibly be attributed to differences in design between the current study which was population-based and previous reports [11] which were mainly based on tertiary care institution cohorts. In line with previously published data, the occurrence of infections was related to severe pancreatitis, longer LOS, and increased in-hospital mortality [11].

Although it has been previously reported that the occurrence of a pancreatic infection in the course of acute pancreatitis is related to a worse patient outcome in terms of organ failure, longer LOS, and in-hospital mortality [9,11,38,39], we found that this is also the case for extrapancreatic infections. This is in line with a previous Dutch study showing that infections have an impact on mortality [13], although a recent meta-analysis reported that extrapancreatic infections are not associated with the predicted severity or mortality of acute pancreatitis [11]. Discrepancies between the findings of the current and previous studies may be due to, at least in part, patient selection; our cohort is population-based and consists only of cases of incident acute pancreatitis, while previous studies were usually conducted in tertiary centers accepting referrals of patients from other institutions, including patients with relapsing acute pancreatitis [11]. According to our results, both infection types are independent predictors of organ failure, which is a novel finding. Thus, although pancreatic infections appear to have a heavier impact on outcome, patients with extrapancreatic infections may also suffer a poor prognosis. Importantly, in-hospital mortality did not differ significantly between the two groups (7.4% vs 6.8%). It should be noted that our findings may not be interpreted as evidence of causality. Although it is conceivable that bacterial infections may contribute to systemic inflammation, increased acute pancreatitis severity, and worse patient outcome, it is also likely that, at least in some patients with severe acute pancreatitis, a compensatory anti-inflammatory response syndrome, resulting in immunosuppression, may lead to increased susceptibility to bacterial infections [40]. In any case, appropriate diagnostic work-up should be performed in all patients with acute pancreatitis and a suspected infection, so that antibiotic treatment may be initiated in a timely manner in positive cases.

The relatively low mortality observed among patients with pancreatic infections, compared to previous reports, could possibly be attributed to the population-based design of our study. Previously published data show a mortality up to 30% among patients with pancreatic infections following acute pancreatitis [9,10,41] but they were performed in tertiary care centers with patients referred from other institutions. Thus, patients with pancreatic infections in our cohort required ICU care in 67% compared to 87% in a previous report [42], while in most previous studies all patients with infected pancreatic necrosis were under ICU care [24,43–46]. The results from this study show that extrapancreatic infections also are an independent predictor of organ failure. Furthermore, extrapancreatic infections are more common following acute pancreatitis than pancreatic infections. Thus, it could be argued to treat extrapancreatic infections with the same caution as pancreatic infections. Further prospective studies investigating mortality in patients with acute pancreatitis in general and persistent organ failure due to acute pancreatitis are clearly warranted.

Predictors of infections

Factors related to extrapancreatic infections were biliary acute pancreatitis (mainly due to cholangitis) as well as comorbid illness. Alcohol is known to result in impaired host defense to invading pathogens [47], but we did not find any association between alcohol etiology and infections, neither did we find an association between alcohol etiology and bacterial resistance patterns (data not shown). Patients with non-nosocomial infections had more frequently extrapancreatic infections, which is not surprising because pancreatic infections are rare during the first days of hospitalization due to acute pancreatitis. At least two out of five infections in our cohort were nosocomial, and thus may be related to interventional procedures, insertion of tubes, lines, and catheters which is often the case in patients admitted due to acute pancreatitis. The predominance of gram-negative strains among patients with non-nosocomial infections and gram-positive strains among patients with nosocomial infections lends support to this hypothesis. Another possibility for the increased gram-positive strains among nosocomial infections is the larger proportion of bacteria resistant to at least one kind of antibiotics in nosocomial infections compared to non-nosocomial infections. A recent Cochrane review found that prophylactic antibiotics did not reduce the occurrence of infections in acute pancreatitis [48], but, to our knowledge, the specific issue of prophylactic antibiotics in acute pancreatitis patients undergoing interventional procedures (such as line and catheter insertions) has not been investigated.

Infection acquisition type

Interestingly, at least 3% of all patients included in our cohort suffered a nosocomial infection. This is much

higher than the 0.7% previously reported in a single multicenter study from the USA, in which registry data were used [30]. The occurrence of infections in general was related with increased in-hospital mortality, but infection acquisition type *per se* was not related to a significant difference in-hospital mortality, despite that nosocomial infections accounted for about two out of five infections with an ascertained infection diagnosis date in our cohort. This finding is not in line with the aforementioned report from the USA [30], which showed increased mortality among acute pancreatitis patients with nosocomial infections. However, our study was not specifically aimed (or powered) to investigate the potential effect of infection acquisition type on in-hospital mortality. Nosocomial infections are known to have a negative impact on patient outcome in general [30,35] and thus the high proportion of nosocomial infections in our cohort is of concern.

Antibiotic treatment

Sweden is in general considered a country with low antibiotic use and thus low bacterial resistance [49], which is in line with the findings of the bacterial resistance patterns in our study. A recent report from a tertiary care center in Korea showed that 63% of pancreatic infections in patients with severe acute pancreatitis were due to multidrug resistant bacteria, frequently MRSA [32]. In contrast, we found that 33% of culture positive pancreatic infections in our population-based cohort of first-time acute pancreatitis were due to antibiotic-resistant bacteria, with no MRSA cases among them. Carbapenem and piperacillin-tazobactam are commonly used antibiotics as an empirical therapy in hospitalized patients with presumed infections in Scandinavia with good results [50,51]. However, we found that 33% of the pancreatic infections were due to bacteria resistant to carbapenem and 33% due to bacteria resistant to piperacillin-tazobactam. Despite that differences from extrapancreatic infections in the occurrence of resistance to carbapenem (9%) and piperacillin-tazobactam (9%) did not reach statistical significance, possibly due to a lack of power, it seems prudent to suggest that modification of the empiric antibiotic treatment in patients with acute pancreatitis and sepsis due to pancreatic infection or infection with an unknown focus could be considered.

Strengths and limitations

The main strength of the current study is its population-based design as it was carried out in a well defined geographic area served exclusively by one medical institution. This made it possible to identify all incident cases of acute pancreatitis in the catchment area of the hospital. However, certain limitations should also be taken into consideration when interpreting the results of the current study. First, it is retrospective in nature. Imaging and laboratory evaluations, such as bacterial cultures, were performed as per the clinical judgment of the physician in charge and were not part of a standardized procedure. Thus, although medical records were carefully scrutinized to confirm the diagnosis of acute pancreatitis and infections as well as patient outcomes, such as mortality and organ failure, it is conceivable that, for instance, the occurrence of antibiotic resistance in our cohort may have been under or overestimated. Also, the study period was 10 years during which changes in patient management with a potential impact on our results may have occurred.

Conclusion

In conclusion, extrapancreatic infections (mainly pneumonia and urinary tract infections) occurred in about 15% and pancreatic infections in about 2% of patients with incident acute pancreatitis. Although significantly more patients with pancreatic infections experienced organ failure and severe acute pancreatitis, both extrapancreatic and pancreatic infections were independent predictors of organ failure. Unsurprisingly, patients with infections had increased in-hospital mortality. Almost one out of 10 bacterial infections was caused by antibiotic-resistant strains and about two out of five infections were of nosocomial origin. Larger prospective studies, including patients from different institutions and geographical areas, are warranted to fully elucidate the role of bacterial infections in the course of acute pancreatitis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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