Infectious complications, prognostic factors and assessment of anti-infectious management of 212 consecutive patients with acute pancreatitis

Jean-François BOURGAUX (1), Christine DEFEZ (2), Laurent MULLER (3), Julien VIVANCOS (4), Michel PRUDHOMME (5), Francis NAVARRO (6), Philippe POUDEROUX (1), Albert SOTTO (4)

(1) Hepato-Gastroenterology, (2) Epidemiology/Medical Biostatistics, (3) Critical care and emergency, (4) Internal medicine B, (5) Visceral Surgery A, (6) Visceral Surgery B, Nîmes University Hospital.

SUMMARY

Aim — Acute pancreatitis is an important cause of morbidity and mortality, mainly due to sepsis. The aim of this study was to determine the incidence of infectious complications and their impact on mortality in patients hospitalized for acute pancreatitis.

Patients and Methods — Patients admitted for acute pancreatitis were retrospectively included within a period between 1995 and 2000. Incidence of abdominal and extra-abdominal sepsis and specific care were specifically analyzed. Risk factors for death were evaluated by uni- and multivariated analysis.

Results — Two hundred and twelve consecutive patients (128 males, median age 54 years) were included. Mortality was 10.8%. At least one infectious episode was collected in 25% of the patients with an abdominal sepsis (26.8%), bacteriemia (24.4%), respiratory (24.4%) and urinary tract (19.5%) infections. Infection was polymicrobial in 37.5%. An antibiotic prophylaxis was administered in 10.8%, more often in patients with severe pancreatitis. It did not alter mortality or incidence of infections but significantly delayed occurrence of sepsis. Mortality of patients treated with more than one line of antibiotics was higher. However in this study infectious complications were not an independent factor for mortality.

Conclusion — Infections are frequent and polymicrobial but are not an independent prognostic factor during acute pancreatitis.

Introduction

Acute pancreatitis is an important cause of morbidity and mortality, the latter ranging from 6% to 23%. Although premature deaths are mainly linked to visceral failure, infectious complications of pancreatic necrosis observed after the 10th day
of evolution still remain a cause of later death [1-3]. The risk of secondary infection due to pancreatic necrosis appears to be even more important [4]. Systemic prophylactic antibiotic therapy is still discussed by certain authors [2,5]. On the other hand, there is little mention about extra-pancreatic infections or their exact role in the prognosis of acute pancreatitis.

The objectives of this retrospective study were to describe infectious episodes arising in a consecutive series of 212 cases of acute pancreatitis and to analyze the factors associated with mortality.

Materials and methods

Patients

Patients admitted to the Nîmes University Hospital between 1/10/1995 and 30/10/2000, with a diagnosis of acute pancreatitis (typical clinical picture, a serum amylase level and/or serum lipase level over three times higher than the normal rate) were included [6,7]. We established a list of all these patients working from databases provided by the following departments: Emergency, Hepato-Gastroenterology, Intensive Care and Digestive Surgery.

Baseline data collection

For each patient data on age, sex, presence of major dyslipidemia (defined as hypertriglyceridermia over 10 mmol/L), chronic alcoholism (defined as a current daily consumption of over 20 g of alcohol for a woman and 30 g for a man) were collected. The dates of the onset of symptoms, admission into hospital and diagnosis of acute pancreatitis were collected. Ranson’s prognostic signs and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system were used to assess the severity of the pathology [8-10].

The results of abdominal ultrasound, abdominal computed tomography (CT) scan, endoscopic ultrasoundography of the biliary and pancreatic ducts (only after 1999), endoscopic retrograde cholangiopancreatography (ERCP) were recorded. The Balthazar score for abdominal CT scan was performed in 203 patients (95.8%). The Balthazar score for abdominal CT scan was specified [11]. When surgery was performed, the date, type of surgical treatment (early or delayed surgery, nature of the intervention), and the need to re-operate were specified. Infectious events, whatever their localization, were recorded. These were divided into 2 categories: community-acquired infections (which already existed or were under incubation at the time of the patient’s admission) and nosocomial infections diagnosed using the criteria defined by the Centers of Disease Control and Prevention [12]. For the diagnosis for extra-pancreatic infections, we used CDC definitions of nosocomial infections [12].

Antimicrobial treatment

Pre-hospitalization antimicrobial treatment was specified. Antimicrobial treatments given (i) during the hospital period before any infectious event (prophylactic antimicrobial therapy), (ii) following a clinically and/or microbiologically documented infection were analyzed: reason, type, duration, curative antimicrobial therapy. The total duration of hospitalization, as well as the duration of stay in an Intensive Care Unit (ICU) were specified. The number of deaths was recorded.

Statistical analysis

Quantitative parameters were expressed as mean and standard deviation or as median (5th-95th percentiles) according to their distributions in the two groups. We used Spearman’s non-parametric test to look for a correlation between scores. Factors linked to mortality were determined by considering demographical data, patient’s history, severity of the illness, imaging data, microbiological data, anti-infectious and surgical management.

Univariate analysis of factors associated with mortality was performed using Student’s t-test or Kruskal-Wallis tests for comparing quantitative parameters or the Mantel-Haenzel 2 test for comparing qualitative parameters. A multivariate analysis using an unconditional logistic regression model was performed with variables significant at a P value greater or equal 0.20 as assessed by univariate analysis, to control all the confounding factors. Adjusted odds ratios and their 95% confidence intervals were provided. Statistical analyses were performed using SAS software®, version 8.01 (SAS Institute Inc., Cary, NC, USA).

Results

Two hundred and twelve patients were included with 128 men (60.4%) and 84 women, median age 54 years (26-84). Pancreatitis was of alcoholic origin in 82 patients, due to gallstones in 75 patients and undetermined in the acute phase in 55 patients. The median APACHE II score upon admission was 5 (0-17) and the median Ranson score was 1 (0-3). These two scores were correlated (r = 0.666, P < 0.001). The median time between the beginning of symptoms and the date of diagnosis of acute pancreatitis was 1 day (1-8). The median duration of hospitalization was 12 days (3-46). Seventy-one patients required hospitalization in an ICU (33.5%), with a median duration of stay of 6 days (1-39). The mortality rate was 10.8% cases (23 deaths) after a median time of 10 days (3-48). An abdominal CT scan was performed in 203 patients (95.8%). The Balthazar score was divided up as follows: A = 37 cases (18.2%), B = 62 cases (30.5%), C = 40 cases (19.7%), D = 33 cases (16.3%), E = 31 cases (15.3%).

Infectious complications

The evolution of pancreatitis was marked by the occurrence of at least one infectious episode in 53 patients (25.0%): 47 patients had 1 infection, 5 patients had 2 consecutive infections and 1 patient had 3 consecutive infections, i.e. 60 infections. The first infectious episode was hospital-acquired in 44 patients and community-acquired in 9 patients. The median time between the onset of pancreatitis and diagnosis of infection was 4 days (1-31). The most common documented sites of infections were peritoneal fluid (26.8%), bacteriemia (24.4%), respiratory tract (24.4%), and urinary tract (19.5%). Infection was polymicrobial in 37.5% of patients and this represented a predictive factor of death (P < 0.0001). The most commonly isolated germs were Escherichia coli (N = 13), Staphylococcus epidermidis (N = 5), Enterococcus spp. (N = 5), Enterobacter spp. (N = 4), and Pseudomonas aeruginosa (N = 4). For two patients Candida spp. was discovered in the peritoneal fluid. Infectious events were most common among patients with a Balthazar D or E score (32 cases, 60.4%) vs those with an A, B or C score (21 cases, 39.6%), P < 0.001. Infection was a prognostic factor of death using univariate (table I) but not multivariate analysis (table II).

Antimicrobial treatment

In 7 patients (3.3%) antibiotic therapy was prescribed before admission (amoxicillin = 3 patients, azithromycine = 2, norfloxacin = 1, cefixime = 1). Prophylactic antibiotic therapy was carried out in 23 cases (10.8%) (table II). Patients whose pancreatitis was due to gallstones more often underwent prophylactic antibiotic therapy (60.9% vs 32.3%, P = 0.009). As shown in table III, the Ranson score was significantly higher for the prophylactic antibiotic therapy group vs the group without prophylactic antibiotic therapy (P = 0.04), as well as age (P < 0.001) and the APACHE II score (P = 0.07), but not the Balthazar score. The median duration of prophylactic antibiotic therapy was 6 days (3-13). Treatment consisted of monotherapy in 16 cases corresponded in the majority of cases to treatment with ceftriaxone (11 times). In 7 cases, the prophylactic antibiotic therapy consisted of bitherapy. Antibiotherapy did not prevent significantly death and sepsis but delayed the occurrence of infection (16 days vs 4 days, P = 0.03) (table III).
Curative antibiotic therapy was prescribed in 50 patients (23.6%) (figure 1). Three of those had undergone prophylactic antibiotic therapy. A monotherapeutic antibiotic strategy was prescribed for 37 patients (15 monotherapies and 22 bitherapies). A second strategy was elected in addition to the first in 6 patients, and consisted of 2 monotherapies, 2 bitherapies and 2 tritherapies. Further antibiotic treatment was required in 7 patients, in addition to the aforementioned prescriptions. This third strategy was comprised of 1 monotherapy, 5 bitherapies and 1 trithrapy. The frequency of death in the group treated with only one antibiotic therapy strategy was 18.9% (7/37) whereas it was 38.5% (5/13) for the group with more than one strategy (P = 0.25). Likewise, there was no significant difference between these two groups in terms of age, Ranson and APACHE II scores. In the group with a monotherapeutic antibiotic therapy strategy, 4 deaths were counted among the 12 patients (33.3%) treated with antibiotic therapy adapted to their antibiogram. In all cases, antibiotics therapy started on the day of the diagnosis of clinical infection.

Other prognostic factors

The results of the univariate analysis of death-related factors are shown in table I. Classical prognostic factors of death were obtained from univariate analysis: age, Ranson and APACHE II scores, hospitalization in ICU, and sepsis (table I). The multivariate analysis determined the Balthazar D or E score and the APACHE II score as death-related factors (table II).

Surgical and endoscopic treatments

Surgery was performed in 58 patients (27.4%) on an emergency setting for 14 of them (24.1%, 5 for pancreatic necrosectomy, and 9 for cholecystectomy), and on a regular basis for

Table I. – Univariate analysis of factors linked to death.
Analyse univariée des facteurs liés au décès.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dead (N = 23)</th>
<th>Alive (N = 189)</th>
<th>OR [IC95%]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>14 (60.9)</td>
<td>114 (60.3)</td>
<td>1.0 [0.4-2.4]</td>
<td>0.96</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>6 (26.1)</td>
<td>81 (42.9)</td>
<td>0.5 [0.2-1.2]</td>
<td>0.13</td>
</tr>
<tr>
<td>Lithiasis</td>
<td>11 (47.8)</td>
<td>64 (33.9)</td>
<td>1.8 [0.7-4.3]</td>
<td>0.19</td>
</tr>
<tr>
<td>Balthazar D or E</td>
<td>17 (73.9)</td>
<td>47 (24.9)</td>
<td>8.6 [3.2-23.0]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Infections</td>
<td>15 (65.2)</td>
<td>38 (20.1)</td>
<td>7.4 [2.9-18.9]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>4 (17.4)</td>
<td>6 (3.2)</td>
<td>8.5 [2.3-30.5]</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (26.1)</td>
<td>52 (27.5)</td>
<td>0.9 [0.3-2.5]</td>
<td>0.89</td>
</tr>
<tr>
<td>Antibiotics before admission</td>
<td>1 (4.4)</td>
<td>6 (3.2)</td>
<td>1.4 [0.2-12.0]</td>
<td>0.77</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>3 (13.0)</td>
<td>20 (10.6)</td>
<td>1.3 [0.3-4.6]</td>
<td>0.72</td>
</tr>
<tr>
<td>Curative antibiotics</td>
<td>12 (52.2)</td>
<td>38 (20.1)</td>
<td>4.3 [1.8-10.6]</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission in ICU</td>
<td>17 (73.9)</td>
<td>54 (28.6)</td>
<td>7.1 [2.6-18.9]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

| Analysis of risk factors linked to death. |
| Analyse multivariée des facteurs liés au décès. |

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR (a) [ CI 95%]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>4.0 (0.6-25.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Balthazar D or E</td>
<td>6.8 (1.8-25.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>–</td>
<td>0.10</td>
</tr>
<tr>
<td>Apache II</td>
<td>–</td>
<td>0.0002</td>
</tr>
<tr>
<td>Number of bacteria per patient</td>
<td>–</td>
<td>0.13</td>
</tr>
</tbody>
</table>

(a) OR are adjusted on other factors.

(a) CT scan was done in 203 patients: 22 in the group “dead” and 181 in the other;
(b) pc: percentiles.
44 patients (75.9%). Among the surgically treated patients, 21 (36.2%) had a Balthazar D or E score vs 43 (27.9%) for those not surgically treated (P = 0.24). Finally those surgically treated had prophylactic antibiotic therapy more often: 18.9% vs 7.8% in the other group (P = 0.02). Cholecystectomy was performed in 49 cases (84.4%). A second surgical procedure was necessary for 3 patients (5.2%). Secondary surgery was significantly more common (3/14, 21.4%) for cases of emergency surgery versus non-emergency surgery (0/44, 0.0%), P = 0.012. ERCP was performed in 31 patients (one in emergency).

**Discussion**

Most of the studies insist on infected pancreatic necrosis. By contrast, there is little interest for infections at other sites. The role of this study was to assess if extra pancreatic infections have a role in acute pancreatitis. Published data are scarce. In addition, such data do not take into consideration implications of extra pancreatic infection and the mortality or morbidity of patients with acute pancreatitis [1-3]. In 1995, other sites of infection are considered but only in relation to the incidence [4]. In their study, pulmonary infection was the more frequent site (12.5%). The other sites of infections are less than 5%. In our study, we collected all infectious events and observed that occurrence of extra-pancreatic infections was shorter than that of infection of pancreatic necrosis, with a median time of onset of 4 days (1-31). Urinary and pulmonary infections acquired during hospitalization represented only 19.5% and 24.4% of infected sites respectively. Infections of peritoneal fluid and bacteriemia represented 26.8 and 24.4% of infected sites. The microorganisms isolated in this study were mostly gram-negative bacilli, with a modification was indicated N=3 / death=1 appropriate but reduction spectrum possible N=7 / deaths=2 appropriate, no reduction possible N=5 / deaths=2 two strategies N=6 cause of modification no germ identified persistent fever N=2 / deaths=2 1st change no germ identified persistent fever N=1 1st modification other isolated microorganism 2nd modification persistent fever N=3 / death=1 2nd modification persistent fever N=3 / death=1 adaptation to antibiogram other isolated germ N=1 / deaths=1 2nd modification persistent fever N=3 / death=1

Table III. – Univariate analysis of factors related to the use of prophylactic antibiotic therapy. Analyse univariée des facteurs liés à l’utilisation d’une antibiothérapie préventive.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Prophylactic antibiotic therapy (N = 23)</th>
<th>No prophylactic antibiotic therapy (N = 189)</th>
<th>OR [IC95%]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>14 (60.9)</td>
<td>61 (32.3)</td>
<td>3.3 [1.3-7.9]</td>
<td>0.009</td>
</tr>
<tr>
<td>Balthazar D or E score</td>
<td>9 (39.1)</td>
<td>55 (29.1)</td>
<td>1.6 [0.6-3.8]</td>
<td>0.32</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (13.0)</td>
<td>50 (26.5)</td>
<td>0.4 [0.1-1.5]</td>
<td>0.17</td>
</tr>
<tr>
<td>Curative antibiotic therapy</td>
<td>3 (13.0)</td>
<td>47 (24.9)</td>
<td>0.4 [0.1-1.6]</td>
<td>0.22</td>
</tr>
<tr>
<td>Death</td>
<td>3 (13.0)</td>
<td>20 (10.6)</td>
<td>1.3 [0.3-4.6]</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Discussion

Most of the studies insist on infected pancreatic necrosis. By contrast, there is little interest for infections at other sites. The role
E. coli at the top of the list (27.7%). Polymicrobial flora were highlighted in 37.5% of patients, with this rate reaching around 60% in certain series [2, 5]. We found staphylococci (the most common gram-positive bacteria) was in equal quantity with enterococci, which is a normal result. A tendency towards an increase in the number of gram-positive bacteria was observed by several authors [1, 3, 5-7]. This might be explained by the use of prophylactic antibiotic therapy effective against gram-negative bacilli [5]. The role of bacterial translocation from the digestive tract has been cited as a source of pancreatic and peri-pancreatic infection [8, 9]. Other authors observed similarities between microorganisms isolated from pancreatic necrosis and those isolated from other infected sites 2 to 10 days before a pancreatic infection was diagnosed, suggesting that earlier extra-pancreatic infections probably may play a significant role as a source of infection in pancreatic necrosis [5].

Infection of the necrotized pancreatic tissue during acute pancreatitis constitutes a major cause of morbidity and mortality [1, 2, 5, 6, 11], with two thirds of deaths due to septic complications [12-14] occurring usually from the 2nd week onwards and observed in 40 to 70% of patients [1, 15, 16]. Premature mortality during the first two weeks of infection was due to multi-visceral failure [3, 11]. In our study, the overall mortality was 10.8% whereas it was 28.3% in patients with an infectious event. These results were comparable to previous publications [1, 2, 5, 6]. Gloor et al. observed an overall mortality of 9% and 21% of deaths in patients with a pancreatic necrosis infection [5]. In another study, it was noted a comparable overall mortality with this frequency reduced to 3% when there was no infection of the necrotized tissue and 24% when the necrosis was infected (P < 0.01) [2]. The risk of developing infectious complications such as infected pancreatic necrosis or a more distant infection such as a pulmonary or urinary infection has been correlated with the severity of pancreatitis necrosis [16, 17].

This study showed a greater frequency of antibiotic prophylaxis prescription for the most seriously affected patients as well as in those with gallstones (table III). Among these patients, 13% developed a secondary infection compared with 26.5% for those who had not received prophylactic antibiotic therapy, without significant difference between these 2 groups. Prophylactic antibiotic therapy did not influence the duration of stay or the occurrence of death. The use of antibiotic prophylaxis in necrotizing pancreatitis remains controversial. Numerous studies available are contradictory, using various antibiotic drugs with different application schemes and heterogeneous study end points [18]. In 2002, the International Association of Pancreatology (IAP) developed rules for the management of pancreatitis [11]. Their second recommendation (grade A) stated that the use of extended-spectrum prophylactic antibiotic therapy reduced the frequency of infected pancreatic necrosis but did not increase survival. In our study, we did not find reduction of the incidence of infection but they significantly delayed the occurrence of infection from 4 to 16 days. These data are independent of the retrospective characteristics of the study, because it would have been impacted on the frequency of the infectious events but not on the timing of these events.

We found that the patients who had curative antibiotic therapy mainly received only a single antibiotic strategy. In this group, the mortality rate was 33% with 4 deaths among the 12 patients who had received an appropriate antibiotic treatment based on antibiogram, even though there had not been any delay in care. Mortality was higher when the number of antibiotic strategies was greater than 1 (38.5% vs 18.9%, P > 0.05) not significant probably because of the small number of patients.

In conclusion, the implications of early extra-pancreatic infections, which are mostly nosocomial according to our study, must without a doubt be considered. Prior extra-pancreatic infections probably play a significant role in infected pancreatic necrosis. It is therefore important that any treatments of these earlier infections take into consideration their extra-pancreatic location and are absorbed well by pancreatic tissue. However in our study, infectious complications were not an independent factor of mortality.

REFERENCES