What is the outcome for patients presenting with severe acute pancreatitis requiring a hospital stay of more than one month?

Quel est le devenir des patients présentant une pancréatite aiguë grave nécessitant une hospitalisation supérieure à un mois ?

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Summary

Objective. — The aim of this study was to investigate the clinical progression of patients who had severe acute pancreatitis (AP) and a stay in hospital of more than a month.

Methods. — A total of 24 patients (median age: 57 years) were included in this eight-year retrospective study. Cure was defined as the restoration of the pancreatic parenchyma, and the disappearance of all pseudocysts and pancreatic fistulae. Data including the duration of hospital stay, disease severity and pancreatic sequelae were also collected.

Results. — The median total duration of the hospital stay was 67 days. The overall mortality rate was 20.8%, whereas the mortality rate due to AP was 12.5%. The average healing period was 7.7 months. On univariate analysis, patients who also had respiratory diseases, chronic alcoholism, necrotizing superinfection, pseudocyst, food intolerance and/or hospital-acquired infection took significantly longer to heal. After cure, we observed pancreatic and/or hepatic duct stenoses in 50% of cases, and the onset or aggravation of diabetes in 25%.

Conclusion. — In patients hospitalized for more than one month because of necrotizing AP, the rate of mortality is around 20%, with a final hospital stay of two months and a healing period of more than seven months. In addition, half of the patients presented with pancreatic or biliary sequelae.

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Introduction

Restitutio ad integrum was the leitmotif of the first French symposium devoted to pancreatitis held in Marseilles in 1963 [1]. Later, at the 1984 symposium on the classification of pancreatitis that was also held in Marseilles [2], the experts recognized that acute pancreatitis (AP) comprises different degrees of lesions — ranging from benign or edematous to severe or necrotizing — and that, indeed, the prognosis is completely different across this range of lesions. Approximately 10–20% of patients with AP will develop pancreatic necrosis with a rate of mortality in the 15–20% range [3], whereas patients who have edematous AP have a mortality rate of 1–3%.

Since the 1984 symposium, it has been generally agreed that alterations in exocrine and endocrine functions are variable in terms of both intensity and duration after an acute episode. As for necrotizing forms, attention has focused mainly on serious acute episodes, with little investigation into the long-term functional consequences. A consensus workshop held in 2001 examined the full range of sequelae observed after an acute episode of pancreatitis, and identified studies reporting specific consequences for endocrine function, exocrine function, pancreatic morphology, extra-pancreatic structures and quality of life [4]. The majority of these studies analyzed the outcomes of severe AP in patients who had undergone necrosectomy or pancreatectomy for superinfection of necrotic tissues. This is probably related to the fact that surgery is generally considered to be the standard treatment. More recently, given the development of new drainage techniques using ultrasound and radiological guidance, alternatives have become available [5]. However, little is known of the long-term outcome of AP severe enough to require a prolonged stay in hospital (≥ 1 month).

The purpose of our study was to carry out a retrospective analysis of a series of patients hospitalized for at least one month because of an acute episode of severe pancreatitis. The objective was to ascertain the type of complications observed and their consequences, the time needed to achieve cure, the proportion of patients with sequelae (biliary and pancreatic duct anomalies, endocrine and exocrine pancreatic insufficiency) and rate of mortality. Identifying any predictive factors (duration of hospital stay, healing time, pancreatic/biliary duct lesions and/or exocrine dysfunction) was a secondary objective.

Material and methods

Patients

Patients hospitalized in our unit with AP from December 1997 through to June 2005 were identified retrospectively using the database of the Department of Medical Information. Inclusion criteria were AP with at least one zone of peripancreatic necrosis and AP-related hospitalization for at least one month. Twenty-four patients — nine men and 15 women — were selected. Median age was 57 years (range 35–80). Nearly all (23/24) had one or several comorbid conditions, predominantly cardiovascular disease and excess body weight. Median body mass index (BMI) was 26 (range 19–31). The AP was related to biliary disease in 12 patients, surgery in four cases (aneurysm of the abdominal aorta, nephrectomy for cancer, L4–L5 fusion, cholecystectomy with choledocotomy), alcoholism in three, hypertriglyceridemia in two and idiopathic chronic pancreatitis in two. One patient had postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

Duration of the overall hospital stay and duration of care in the intensive care unit were used to estimate the severity of the initial episode of AP. The most significant clinical findings and results of complementary tests recorded during the first week were noted, as were the modified Glasgow score [6] and the presence of organ failure(s). A computed tomography (CT) scan of the abdomen with contrast injection obtained 48 to 72h after symptom onset was available for all patients. The Balthazar score [7] and the percentage of pancreatic necrosis were also noted.

Complications

Complications were recorded as ‘early’ (occurring during the first month), ‘persistent’ (persisting for more than one month) or ‘late’ (developing more than one month after admission). They were
The diagnosis of pancreatic fistula was noted for patients with guided percutaneous bacteriology samples provided confirmation. Emission of pus during endoscopic cystotomy. When available, radiographic percutaneous bacteriology samples provided confirmation. The diagnosis of pancreatic fistula was noted for patients with pancreatic ascites or when the ERCP revealed a breach in a duct repaired during exploration.

Outcome

Patients attended regular follow-up visits for at least two years to undergo physical examination, routine blood tests (serum glucose, liver tests) and abdominal CT, which were performed every three months for one year, then every six months for two years. Magnetic resonance cholangiopancreatography (MRCP) was performed to monitor pancreatic fistulae and lesions of the pancreatic or biliary ducts. Cure was defined as restitutio ad integrum of the pancreatic parenchyma and total resolution of any pseudocysts (confirmed by CT) or pancreatic fistulae (confirmed by MRCP or ERCP). For the three patients who were not followed-up beyond two years posture, the outcomes of pancreatic sequelae were ascertained from their primary-care physician. Overall, mortality was determined by follow-up and death attributable to AP. For each patient, we noted: presence of pancreatic morphological sequelae (duetal stenosis); presence of biliary stenosis; development or aggravation of diabetes mellitus; initiation of treatment with pancreas extracts; and presence of residual pain. The presence of persistent pancreatic or biliary duct lesions or impaired endocrine function was considered objective evidence of sequelae.

Univariate analysis was applied to the following variables to identify factors predictive of duration of hospital stay, healing time and long-term sequelae: patient characteristics; characteristics of the AP; and early and late complications.

Statistical analysis

Data were processed using Excel worksheets (Microsoft, USA) and StatView software (1992; Abacus Concepts, Berkeley, CA, USA). Discrete variables are expressed as medians and range. Student’s t test and the Mann–Whitney non-parametric test were used as deemed appropriate to search for statistically significant differences between discrete variables. Comparisons were made using the Kruskal–Wallis non-parametric test. The chi-square test, or Fisher’s exact test when needed, were applied to compare non-discrete variables. A p value less than or equal to 0.05 was considered statistically significant.

Results

Duration of hospital stay and initial patients’ characteristics

Median hospital stay was 67 days (range 30–244 days) (Table 1). Univariate analyses identified several factors significantly associated with a long hospital stay (Table 2): elevated BMI; excess body weight; late necrotizing superinfection; late development of pseudocyst; portal hypertension; early or late thrombosis of the portosplenomesenteric system; late-onset food intolerance; and late development of hospital-acquired infection. No other significant correlations with any other patient characteristics, AP features or other complications could be found.

Ten patients (41.7%) required intensive care. Median duration of stay in the intensive care unit was 21 days (range 0–75 days). The median modified Glasgow score was 4 (range 2–7); it was greater than three in 11 of 47 patients (64.7%). Organ failure (of one or more organs) occurred in 15/24 patients, neurological failure developed in three patients, hemodynamic failure in six and respiratory failure in 13, including seven patients who required intubation for ventilatory assistance and three who developed acute respiratory failure. Kidney failure was noted in 10 patients, three of whom required dialysis. All patients developed at least one peripancreatic fluid collection or phlegmon; the Balthazar score was D (one collection or phlegmon) in four patients and E (at least two collections) in 20. The percentage of necrotic pancreatic parenchyma was noted: initially zero in three patients; less than one-third in eight patients; between one-third and one-half in five patients; and more than one-half in five patients (5/21).

Complications

The observed complications are presented in Table 3. Pseudocyst, seen in 19 patients, was the most frequent early complication, and led to gastrointestinal compression in seven patients and to a phlegmon in a further seven. Early pancreatic fistula occurred in eight patients. The most common late complications were phlegmon (n=6 patients) and CT-determined segmental portal hypertension (n=5 patients).
### Table 2 Factors predictive of duration of hospital stay, healing time, and development of pancreatic sequelae, identified among patient characteristics and late complications ($p \leq 0.05$).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Duration of hospital stay (days)</th>
<th>Healing time (months)</th>
<th>Sequelae (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>$p = 0.03^*$ ($r = 0.37$)</td>
<td>$p = 0.30$</td>
<td>$p = 0.74$</td>
</tr>
<tr>
<td>Body mass index</td>
<td>$p = 0.07^*$ ($r = 0.45$)</td>
<td>$p = 0.3$</td>
<td>$p = 0.76$</td>
</tr>
<tr>
<td>Past history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>$p = 0.48$</td>
<td>$p = 0.01^*$ (8 vs 2)</td>
<td>$p = 0.64$</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>$p = 0.89$</td>
<td>$p = 0.05^*$ (11.5 vs 5)</td>
<td>$p = 0.99$</td>
</tr>
<tr>
<td>Necrotic superinfection</td>
<td>$p = 0.003^*$ (114 vs 57)</td>
<td>$p = 0.04^*$ (10 vs 5)</td>
<td>$p = 0.03^*$ (8/12 vs 4/12)</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>$p = 0.004^*$ (106 vs 51)</td>
<td>$p = 0.04^*$ (10 vs 5)</td>
<td>$p = 0.01^*$ (10/12 vs 2/12)</td>
</tr>
<tr>
<td>Phlegmon</td>
<td>$p = 0.003^*$ (114 vs 58)</td>
<td>$p = 0.04^*$ (10 vs 5)</td>
<td>$p = 0.03^*$ (8/12 vs 4/12)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>$p = 0.007^*$ (127 vs 66)</td>
<td>$p = 0.75$</td>
<td>$p = 0.63$</td>
</tr>
<tr>
<td>Porto-splênomesaraic thrombosis</td>
<td>$p = 0.004^*$ (154 vs 71)</td>
<td>$p = 0.94$</td>
<td>$p = 0.99$</td>
</tr>
<tr>
<td>Food intolerance</td>
<td>$p = 0.01^*$ (147 vs 72)</td>
<td>$p = 0.05^*$ (12 vs 6)</td>
<td>$p = 0.99$</td>
</tr>
<tr>
<td>Hospital-acquired infections</td>
<td>$p = 0.009^*$ (121 vs 65)</td>
<td>$p = 0.007^*$ (13 vs 5)</td>
<td>$p = 0.02^*$ (10/12 vs 1/12)</td>
</tr>
</tbody>
</table>

### Table 3 Complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Early $^a$</th>
<th>Persistent $^b$</th>
<th>Late $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>79.2% (19)</td>
<td>45.8% (11)</td>
<td>8.3% (2)</td>
</tr>
<tr>
<td>Gastrointestinal compression</td>
<td>29.2% (7)</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Biliary compression</td>
<td>8.3% (2)</td>
<td>0</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Phlegmon</td>
<td>29.2% (7)</td>
<td>16.7% (4)</td>
<td>25% (6)</td>
</tr>
<tr>
<td>Necrotic superinfection</td>
<td>33.3% (8)</td>
<td>16.7% (4)</td>
<td>8.3% (2)</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>33.3% (8)</td>
<td>16.7% (4)</td>
<td>8.3% (2)</td>
</tr>
<tr>
<td>Food intolerance</td>
<td>16.7% (4)</td>
<td>12.5% (3)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>12.5% (3)</td>
<td>4.2% (1)</td>
<td>20.8% (5)</td>
</tr>
<tr>
<td>Porto-splênomesaraic thrombosis</td>
<td>8.3% (2)</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Pseudo-aneurysm</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
<td>0</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>8.3% (2)</td>
<td>0</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Persistent necrotic collection</td>
<td>0</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>0</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Recurrent acute pancreatitis</td>
<td>0</td>
<td>8.3% (2)</td>
<td>4.2% (1)</td>
</tr>
<tr>
<td>Bilioma</td>
<td>0</td>
<td>0</td>
<td>4.2% (1)</td>
</tr>
</tbody>
</table>

$^a$ Early: complication occurring during the first month of hospitalization.

$^b$ Persistent: early complication persisting beyond one month.

$^c$ Late: complication occurring after the first month of hospitalization.

### Outcome

Median overall postcure survival was 36 months (range 31–56).

### Mortality

Overall mortality was 20.8% (5/24) and death due to AP was 12.5% (3/24). Median time to AP-attributable death was 1.7 months (range 1–2). Three patients died during their hospital stay while in the study. The first was a 62-year-old woman with serious concomitant disorders, including morbid obesity, insulin-dependent diabetes, hypertension and atrioventricular block (requiring a pacemaker). The second death was a 39-year-old woman with a history of alcohol and tobacco consumption who had chronic calcifying pancreatitis. The third was an 80-year-old man with no known comorbidity. Two patients died of causes unrelated to AP: cancer of the colon 11 months...
after AP cure; and myocardial infarction 22 months after AP cure.

Healing time
Median healing time was six months (range 1–24 months). On univariate analysis, healing time was significantly longer for patients with respiratory disease and chronic alcoholism (Table 2). Several late complications were also significantly associated with longer healing time: necrotizing superinfection; pseudocyst; food intolerance; and hospital-acquired infection. There was no significant correlation with the other variables studied.

Sequelaes
Among the 20 survivors, eight were free of any objective morphological or endocrine sequelae. In contrast, nine patients developed pancreatic sequelae: stenosis of the main pancreatic duct (n = 7) associated with upstream dilatation in two cases; and distal pancreatic atrophy in two others. One-third of the patients with pancreatic sequelae also had impaired endocrine function, and one-third had residual pain that warranted endoscopic treatment (detailed below).

Three patients had biliary sequelae. Two developed intrapancreatic biliary stenosis which was not treated endoscopically or surgically. In the third patient, healing of a pancreaticobiliary fistula led to stenosis, which required intubation for one year. All three patients with biliary morphological sequelae remained free of clinical symptoms; their liver tests also remained normal.

Five survivors experienced impaired endocrine function. Insulin-dependent (type 1) diabetes developed in two patients, and preexisting non-insulin-dependent (type 2) diabetes became insulin-dependent in three cases.

On univariate analysis, several late complications were significantly linked with objective sequelae (Table 2) — namely, necrotizing superinfection, pseudocyst and hospital-acquired infection. It was noted, however, that morphological sequelae of the pancreatic ducts did not develop in any of the patients who initially had pancreatic intubation (management protocol not included here). There was no significant correlation with the other variables studied.

Among survivors, eight complained of abdominal pain long after their AP cure. In three of these patients, the pain was clearly attributable to pancreatic duct sequelae. These three patients underwent successful endoscopic pancreatic duct intubation. The five remaining patients were given a long-term regimen of pancreatic extracts because of clinical steatorrhea.

Discussion
For this study, we defined AP as causing pancreatic necrosis that warranted hospitalization for more than one month. Our objective was to analyze the outcome among patients receiving prolonged care. This means that we excluded patients who had serious disease and died early — within less than one month after admission. In the study population, prolonged care was required because of the initial gravity of the AP or because of serious comorbidity. AP-related mortality was 12.5%, excluding early deaths (before one month). This rate was not representative of the overall mortality due to AP. In the literature, overall AP-attributable mortality is around 15–20%, with about half the reported deaths occurring during the first two weeks due to multiple-organ failure, and the other half due to later necrosis-related complications, especially superinfection [3]. In our study, all deaths occurred during the first two months of hospitalization. After that time, all of the patients survived.

Prolonged hospital care is commonly required for patients with necrotizing AP. In a prospective study of 53 patients on the usefulness of several bioclinical and CT variables as prognostic factors, Uomo et al. used duration of hospital stay as a criterion of disease severity [9]. These authors defined severe AP as warranting hospitalization for more than three months or leading to death. In the literature, the mean duration of hospital stay required for severe AP has ranged from 21.8 to 102 days [10–13]. We chose to study the outcome among patients requiring hospitalization for more than one month. Thus, our median hospital stay was 67 days — about two months — with a maximum stay of 244 days — slightly more than eight months.

To our knowledge, no other study has looked for factors that might be predictive of a prolonged hospital stay. Malangoni and Martin noted that the duration of the hospital stay was significantly longer among patients who required surgery [13]. In our study, we searched for predictive factors. Not surprisingly, BMI and excess body weight were significantly associated with longer hospitalization (Table 2). A recent meta-analysis has already shown that obesity in AP is a definite risk factor for disease severity and mortality [14]. No other patient factor was found to be associated with longer hospitalization. It would, however, be interesting to examine this hypothesis among a larger group of patients without using duration of hospital stay as an inclusion criterion.

Pancreatic necrosis also has an effect on the local course and prognosis of AP. In addition, superinfection, which is expected to develop in 30–50% of cases within 1–3 weeks of symptom onset, has a major impact on the local course of disease [15]. In our study, we had a similar rate of necrotizing superinfection, involving one-third of our patients and occurring late in one-fourth of them. Nevertheless, beyond the fourth week, the necrosis progressively resolved in more than half the patients and, in 30–50% of cases, the usual outcome is the development of a pseudocyst [16]. In our study, the rate was considerably higher, with early formation of a pseudocyst in 79.2% of patients and late formation in 54.2%.

While clinicians generally agree that it takes several months for the pancreas to regenerate, no one — to our knowledge — has investigated the time needed to achieve cure or the factors affecting the healing process in AP. In our series, the median time to cure was six months, with a range of 1–24 months. Excessive alcohol intake, which was one of the main causes of AP in our patients, is also known to delay pancreas healing (Table 2). This may, however, be explained by the presence of underlying chronic pancreatitis. In addition, we found other factors predictive of a slow healing time (Table 2). Food intolerance and infection can also have a deleterious effect on the healing process in general. However, we have no explanation for the negative impact of respiratory failure.
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Few studies have investigated anomalies of the pancreatic ducts after necrotizing pancreatitis. Morphological sequelae (stenosis or irregular duct caliber) have been reported less than one year after AP in 46.8–76% of patients [17–21]. These anomalies are therefore frequent, but are likely to have little clinical relevance as their presence has no clear correlation with subsequent episodes of AP, onset of severe abdominal pain, or the development of clinically significant exocrine insufficiency or diabetes [4]. In our study, 45% of patients developed morphological sequelae of the pancreas, about one-third of which led to abdominal pain while another third impaired endocrine function. Biliary stenosis was also seen in 15% of patients, but had no clinical impact. According to the literature, these duct anomalies are more frequent in necrotizing AP and alcoholic AP [4].

Caperan et al. found that the risk of pancreatic seque-

lae is greater in patients who develop vascular thrombosis as a complication of pseudocyst formation due to extrinsic vessel compression [21]. Hyperglycemia is an early complication of AP, whereas diabetes can arise early, immediately after the acute episode, or several months or even years later [4]. Newly diagnosed diabetes or aggravation of existing diabetes was noted in one-fourth of the patients in our study. Surgery is also known to affect the risk of developing diabetes. After necrosectomy, the risk is in the 0–40% range at 1–6 years [4,10,22–24]. In our series, only two patients underwent early surgery for conservative necrosectomy, and neither developed diabetes. Alcoholism as the cause of AP may also be correlated with a significant increase in the prevalence of diabetes compared with biliary AP [9].

In our series, the only factors predictive of objective sequelae (duct lesions and diabetes) were the presence of late complications. The cause of AP, particularly alcohol, was not predictive of sequelae. There was, however, a certain bias in our series due to the retrospective selection of a small number of patients. This issue is nonetheless of clinical importance as, in routine practice, the problem is to distinguish between the role of AP per se and that of the underlying disease in the development of pancreatic seque-

lae.

AP also has an impact on pancreatic exocrine func-

tion [17,18,20,22,25,26]. Exocrine insufficiency is a common finding shortly after an acute episode of pancreatitis in both necrotic and edematous forms. Exocrine function tests are abnormal in 10–75% of patients one month after an episode of AP, and full recovery is not the general rule [27]. Esti-

mates of exocrine insufficiency after AP have varied greatly from 18 to 95%. This variability is probably due to the diverse methods used to assess exocrine function, including function tests, degree of steatorrhea and treatment by pancreatic extracts. Our patients did not undergo function tests or any measurements of steatorrhea, but all of the patients given pancreatic extracts had clinical steatorrhea.

Conclusion

Necrotizing AP is a serious disease with a high risk of early death. Patients who survive this early period require long and costly care. In contrast with earlier ideas, it is now recognized that pancreatic sequelae often persist well after cure of the acute episode, requiring prolonged, well-adapted surveillance. It is important to identify patients at risk of developing such sequelae to better target surveil-

lance tests. The long-term clinical outcome is nevertheless limited, thus demanding optimal early management.

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