Incidence and Reversibility of Organ Failure in the Course of Sterile or Infected Necrotizing Pancreatitis

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Background: Multiple organ failure (MOF) and infected necrosis are both considered severe adverse events during the course of necrotizing pancreatitis.

Hypothesis: The incidence of MOF and its reversibility in patients with necrotizing pancreatitis are influenced by the presence or absence of infected necrosis.

Design: Case series.

Setting: Intensive care, university teaching hospital.

Patients: Forty-three patients with necrotizing pancreatitis and failure of at least 1 organ were prospectively included.

Main Outcome Measures: Organ failure defined according to the Goris classification; MOF defined by the simultaneous occurrence of 3 organ failures and graded with an MOF score. Microbial status of necrosis was assessed by percutaneous or intraoperative sampling. Surgical drainage was performed in patients with infected necrosis, whereas sterile necrosis was managed conservatively.

Results: Infected necrosis occurred in 27 patients (63%). The mean (±SEM) number of organ failures was greater in cases of infection (3.6±1.1 vs 2.6±1.5; \( P = .02 \)). Multiple organ failure occurred more frequently in cases of infected necrosis (23/27 vs 7/16; \( P = .01 \)) and was responsible for an increased mortality in this subgroup (33% vs 6%; \( P = .1 \)). The severity of MOF graded by the MOF score was related to the bacteriologic status of necrosis.

Conclusions: The higher mortality commonly attributed to MOF in patients with infected necrosis appears to be due to a higher frequency and an increased severity of MOF. Conservative management in patients with severe necrotizing pancreatitis and sterile necrosis complicated by MOF is supported by the high reversibility rate of MOF and the low mortality rate observed in this series.

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The mortality rate in patients with acute pancreatitis is high (7% to 15%), and this figure has remained unchanged during the past 20 years. The major adverse events in the course of necrotizing pancreatitis (NP) are the occurrence of infected necrosis and organ failure (OF). The importance of necrosis superinfection as an adverse prognostic factor was described by Beger et al, who reported a mortality rate of 37% in patients with infected necrosis vs 9% in sterile necrosis. Even though mortality rates secondary to multiple OF (MOF) have markedly decreased during the past 10 years irrespective of the underlying disease, the prevalence of OF complicating NP results in high morbidity and remains the leading cause of death in patients with NP. Currently, the relationship between OF and infected necrosis remains controversial. Organ failure was more frequently observed in Beger and coworkers’ series in cases of infected necrosis, whereas Tenner et al found no significant relationship between the occurrence of OF and infection of necrosis. This prospective study aimed, therefore, at assessing the incidence, severity, and reversibility of OF in patients with severe NP as a function of the bacteriologic status of necrosis. Results of management of both sterile and infected necrosis are also reported.

RESULTS

STERILE NECROSIS

In 16 patients (37%), pancreatic necrosis remained sterile, and all cases but 2 were managed conservatively. Reasons for surgical treatment included intra-abdominal hemorrhage in 1 patient and suspi-
PATIENTS AND METHODS

From January 1, 1986, to December 31, 1998, 43 patients with a median age of 56 years (range, 37–84 years), admitted to the digestive surgical intensive care unit (ICU) in a single center with an established diagnosis of severe NP associated with 1 or more OFs, were prospectively included in this study. The causes of pancreatitis included gallstones (n=19), alcohol (n=16), previous cholangiography (n=5), previous surgery (n=1), and idiopathic (n=2). All patients studied fulfilled the following criteria: dysfunction of at least 1 organ, documented grade D or E pancreatic necrosis according to Balthazar and coworkers’ classification on computed tomography (CT), and pancreatic necrosis confirmed intraoperatively or diagnosed by partial or complete nonenhancement of pancreatic parenchyma on CT after intravenous contrast enhancement. All CTs were reviewed at completion of the study. The preoperative diagnosis of infected necrosis was made in the presence of gas in peripancreatic collections or by percutaneous aspiration sampling of necrosis by means of CT or ultrasound guidance (routinely used since 1989). In addition, infected necrosis was strongly suspected in the presence of generalized sepsis with positive blood cultures in the absence of another identifiable cause of infection, or in patients with NP complicating endoscopic retrograde cholangiopancreatography, which is believed to induce mostly infected pancreatitis. The bacteriologic result of intraoperative sampling of necrosis in patients operated on defined the final status of pancreatic necrosis (sterile or infected). Patients not undergoing surgery were considered to have sterile necrosis when percutaneous aspirations were sterile.

A policy of conservative treatment was adopted in patients with sterile necrosis, whatever the patients’ clinical status. All patients in this series received prophylactic intravenous antibiotics for at least 15 days. This consisted of intravenous piperacillin sodium, 4 g, 3 times daily, until 1992, and thereafter either piperacillin sodium, 4 g, plus tazobactam sodium, 500 mg, 3 times daily, or ciprofloxacin, 200 mg, in 100 mL of 5% dextrose, 4 times daily. All patients received total parenteral nutrition exclusively.

All patients with sterile necrosis, which was confirmed by surgery. The last 5 patients had NP complicating endoscopic retrograde cholangiopancreatography and were operated on because of both severe OF and the strong suspicion of infection associated with this procedure. In these 5 patients, infection was confirmed by surgery. Bacteria from the intestinal flora were found in all 27 patients, and staphylococcal species were found in 6. Nine of 27 patients had polymicrobial infection. No fungal infection occurred. Postoperative continuous irrigation of necrotic sites was performed for a mean (±SEM) duration of 26±9 days (range, 20–40 days).

INFECTED NECROSIS

Twenty-seven patients (63%) developed infection of pancreatic necrosis and underwent surgery, of whom 9 (33%) died of MOF. Four patients (15%) needed 1 to 8 courses of hemodialysis, and 23 patients (85%) underwent mechanical ventilation. The preoperative diagnosis of infection of necrosis was made by percutaneous aspiration in 15 cases and by CT findings in 3. One patient with postoperative pancreatitis and 3 patients with positive blood cultures in the absence of another identifiable cause of infection were supposed preoperatively to have infected necrosis, which was confirmed by surgery. The last 5 patients had NP complicating endoscopic retrograde cholangiopancreatography and were operated on because of both severe OF and the strong suspicion of infection associated with this procedure. In these 5 patients, infection was confirmed by surgery. Bacteria from the intestinal flora were found in all 27 patients, and staphylococcal species were found in 6. Nine of 27 patients had polymicrobial infection. No fungal infection occurred. Postoperative continuous irrigation of necrotic sites was performed for a mean (±SEM) duration of 26±9 days (range, 20–40 days).

ORGAN DYSFUNCTION, CLINICAL OUTCOME, AND MICROBIOLOGICAL STATUS OF NECROSIS

All patients developed at least 1 OF. The incidence of OF (including single and multiple) as well as clinical out-
comes with respect to microbiological status of necrosis is presented in Table 2. Five patients had single OF. A total of 141 OFs occurred in the entire group of 27 patients. Respiratory dysfunction was the most frequent OF. All OFs were more frequently observed when infected necrosis was present, but the difference between sterile and infected necrosis was statistically significant only for hemodynamic failure, adult respiratory distress syndrome, the mean number of OFs, and MOF syndrome.

Table 1. Scoring Method Based on the Modified Goris Classification†‡

<table>
<thead>
<tr>
<th>Organ Dysfunction</th>
<th>Score</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>1</td>
<td>Mechanical ventilation with positive end-expiratory pressure &lt;8 cm H2O and FIO2 ≤0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Mechanical ventilation with positive end-expiratory pressure ≥8 mm Hg and/or FIO2 &gt;0.5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1</td>
<td>Hypotension requiring volume loading or dopamine infusion of ≤10 µg/kg per minute</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hypotension requiring use of &gt;10 µg/kg per minute, or adding other vasoactive agents</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>Serum creatinine ≥2.0 mg/dL (≥175 µmol/L)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
<td>PT&gt;70</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>PT≤70</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>PT&lt;50</td>
</tr>
<tr>
<td>Hematologic</td>
<td>1</td>
<td>Thrombocyte count &lt;50.0×10⁹/µL and/or leukocyte count ≥30 000/µL</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hemorrhagic diathesis or leukocyte count &lt;2500/µL</td>
</tr>
<tr>
<td>Neurologic</td>
<td>1</td>
<td>Diminished responsiveness</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Severely disturbed responsiveness</td>
</tr>
</tbody>
</table>

*FIO2 indicates fraction of inspired oxygen; PT, prothrombin time.
†Modified from the original Goris classification.

Table 2. Organ Failure and Mortality as a Function of Bacteriologic Status of Necrosis*

<table>
<thead>
<tr>
<th>Organ Failure</th>
<th>Sterile Necrosis (n = 16)</th>
<th>Infected Necrosis (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic failure</td>
<td>7 (44)</td>
<td>22 (81)</td>
<td>.03</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>11 (69)</td>
<td>23 (85)</td>
<td>.37</td>
</tr>
<tr>
<td>ARDS</td>
<td>6 (37)</td>
<td>20 (74)</td>
<td>.04</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7 (44)</td>
<td>16 (59)</td>
<td>.50</td>
</tr>
<tr>
<td>Neurologic failure</td>
<td>4 (25)</td>
<td>10 (37)</td>
<td>.63</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>10 (63)</td>
<td>20 (74)</td>
<td>.65</td>
</tr>
<tr>
<td>Hematologic failure</td>
<td>2 (13)</td>
<td>9 (33)</td>
<td>.25</td>
</tr>
<tr>
<td>No. of organs failed, mean ± SEM</td>
<td>2.6 ± 1.5</td>
<td>3.6 ± 1.1</td>
<td>.02</td>
</tr>
<tr>
<td>MOF score</td>
<td>7 (44)</td>
<td>23 (85)</td>
<td>.01</td>
</tr>
<tr>
<td>MOF score, mean ± SEM</td>
<td>3.7 ± 2.8</td>
<td>5.4 ± 2.4</td>
<td>.02</td>
</tr>
<tr>
<td>Reversible MOF†</td>
<td>6 (86)</td>
<td>14 (61)</td>
<td>.44</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (6)</td>
<td>9 (33)</td>
<td>.10</td>
</tr>
</tbody>
</table>

*ARDS indicates adult respiratory distress syndrome; MOF, multiple organ failure (sustained occurrence of at least 3 organ dysfunctions). Data are given as number (percentage) of patients unless otherwise specified.†Reversible MOF is the ratio of patients who recovered from MOF divided by the number of patients who developed MOF.

Table 3. Severity of Illness According to Microbial Status of Necrosis*  Summary of Results

<table>
<thead>
<tr>
<th>Criteria of Severity</th>
<th>Sterile Necrosis (n = 16)</th>
<th>Infected Necrosis (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranson score</td>
<td>4.4 ± 1.7</td>
<td>4.3 ± 1.7</td>
<td>.88</td>
</tr>
<tr>
<td>Peak APACHE II score</td>
<td>11.2 ± 4.8</td>
<td>10.8 ± 4.8</td>
<td>.75</td>
</tr>
<tr>
<td>MOF score</td>
<td>3.7 ± 2.8</td>
<td>5.4 ± 2.4</td>
<td>.02</td>
</tr>
<tr>
<td>Reversibility of MOF, No. (%)</td>
<td>6 (86)</td>
<td>14 (61)</td>
<td>.44</td>
</tr>
<tr>
<td>Surgical treatment, No. (%)</td>
<td>2 (12)</td>
<td>26 (96)</td>
<td>.01</td>
</tr>
<tr>
<td>Subsequent operations, No. (%)</td>
<td>0</td>
<td>10 (37)</td>
<td>.02</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>25 ± 13</td>
<td>52 ± 32</td>
<td>.01</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>1 (6)</td>
<td>9 (33)</td>
<td>.10</td>
</tr>
</tbody>
</table>

*APACHE II indicates Acute Physiology and Chronic Health Evaluation II; MOF, multiple organ failure; and ICU, intensive care unit. Values are mean ± SEM unless otherwise specified.

**SEVERITY OF ILLNESS AND TREATMENT ACCORDING TO MICROBIOLOGICAL STATUS OF NECROSIS**

Criteria used to estimate the severity of illness according to the microbiological status of necrosis are listed in Table 3. Mean Ranson score and mean peak APACHE II score were similar in the 2 groups of patients. The severity of MOF, reflected by the MOF score, was correlated with the infection of necrosis, but MOF was reversible in both groups without a statistically significant difference. In case of infection, surgical treatment was the rule (P = .01). The only patient with infected necrosis not operated on was treated by percutaneous drainage inserted under CT guidance. After initial debridement, 10 (37%) of 27 patients had to undergo a mean of 1.9 subsequent operations (range, 1-4). The length of stay in the ICU was statistically different in the 2 groups, with a 2-fold longer duration in case of infection. Mortality rate was higher in the group of infected patients, but the difference was not significant.

**CLINICAL OUTCOME AND ONSET OF MOF**

Thirteen patients did not develop MOF, including 9 with sterile necrosis and 4 with infected necrosis. All of these patients recovered after a mean duration of 21 days in the ICU (range, 8-60 days). Deterioration of at least 3 organ functions occurred in 30 patients (Table 4), leading to death in 10 (33%) of them, after a mean duration in the ICU of 42 days (range, 7-140 days). Twenty patients recovered from MOF after a mean stay in the ICU of 52 days (range, 8-120 days). The outcome of MOF was not correlated with age, bacteriologic status of necrosis, or Ranson or APACHE II scores (Table 4). Factors predictive of an adverse outcome included a high MOF score and the need for vasoactive medications (P = .01 and P = .02, respectively).

**COMMENT**

All patients included in this series developed at least 1 OF, justifying management in the ICU, and thus were considered to have severe pancreatitis according to the...
posed by the Atlanta conference differ from those used. Thus, the definitions of organ dysfunction proposed by the Atlanta conference differ from those used in most studies devoted to MOF and do not allow assessment of the severity of individual OF. Since the first scoring system proposed by Knaus et al as a prognostic indicator of mortality in OF, several other scoring systems have been validated, some of which have been used to assess the severity of acute pancreatitis. The scoring system of Goris et al was chosen in the present series and proved easy to use, offering assessments of dysfunction in 6 organs and also providing a score to quantify the severity of each OF and MOF. To study the relationship between the presence of inflammatory markers and the onset of subsequent OF in NP, de Beaux et al in 1996 used the same scoring system and reported OF in 36% of 28 patients treated in a surgical unit.

In the present study, the higher frequency of MOF observed in the presence of infected necrosis yielded a higher mortality than in cases of sterile necrosis (33% vs 6%). Although not statistically significant in this study, increased mortality secondary to infected necrosis in NP is in accordance with previous reports and represents a strong argument to prevent occurrence of secondary infection. A single recent study found no correlation between OF and infected necrosis in the course of NP, but this latter series included patients with less severe NP (prevalence of OF of 50%, with an overall mortality of 7.8%) and did not use the same criteria to define OF. Another recent study including 86 patients showed that MOF was significantly more frequent in cases of infected necrosis than of sterile necrosis (69% vs 18%). In the present study, too, MOF was more frequent and its intensity assessed by the MOF score was higher in cases of infected necrosis. Meanwhile, the rate of MOF reversibility was comparable whether or not necrosis was infected. Thus, infection of necrosis favors the occurrence of MOF but, as previously described, does not necessarily induce the inflammatory process implicated in the pathogenesis of MOF.

The onset of OF during the course of NP should prompt an active search for infected necrosis, which is currently easily diagnosed by percutaneous aspiration with CT or ultrasound guidance. Treatment of infected necrosis by surgical debridement is currently considered the standard approach and should be combined with systemic antibiotic therapy targeted toward identified microorganisms. Conversely, if necrosis remains sterile in the absence of extrapancreatic complications, there is currently no consensus with respect to the therapeutic strategy. Advocates of systemic surgical debridement underscore a 10% risk of false-negative results of percutaneous bacteriologic aspiration. Recently, early surgical debridement has been advocated in patients with sterile necrosis and evidence of clinical deterioration and was found to result in a remarkably low mortality rate of 7.1%. However, the incidence of OF, the definition of which was not clearly defined, in the latter study was only 31%. An intermediate strategy was proposed by Rau et al, who reported on 172 patients with sterile necrosis studied retrospectively. In their study, conservative treatment was recommended when pancreatic necrosis involved less than 50% of the gland, and surgical debridement was recommended in cases of more extensive necrosis in patients who exhibited clinical deterioration after 72 hours of supportive therapy. However, a delay of only 72 hours seems too short to allow improvement of failure of most organs, and both the retrospective design of this study and the lack of statistical significance of their data weaken these guidelines.

Strict conservative treatment in patients with sterile necrosis was advocated initially in 1991 by Bradley and Allen and in 1994 by Bradley. In their first study of 11 patients with sterile NP treated conservatively, no patients died despite pulmonary failure in 4 patients and renal failure in 2 (requiring dialysis). Their study raised criticism, however, because of the 11% mortality rate observed in patients who did not exhibit necrosis on CT. More recently, Buchler et al reported a 1.8% mortality rate in 56 patients with sterile necrosis—including 35 (62%) with OF—who underwent nonsurgical management with early antibiotic treatment; in an intent-to-treat analysis, the death rate was 5% in the patients who had nonsurgical treatment, because of 2 patients in whom infection could not be diagnosed in a timely fashion and who ultimately died. These results and our own do support this conservative strategy when necrosis remains sterile on repeated percutaneous aspiration analysis. Considering our results, clinical deterioration despite optimal intensive medical management does not appear to be an absolute indication for operative treatment in cases of sterile necrosis. Management, then, largely consists of carefully controlling the consequences of the severe inflammatory response to pancreatitis and its deleterious effects on organ functions. Indeed, in the present study, intensive supportive therapy, including mechanical ven-
tilation, hemodynamic support, and hemodialysis, reversed MOF in 86% of patients with sterile necrosis. The mortality rate of 6% in the subgroup of patients with sterile necrosis compares favorably with the recently reported series of surgically treated patients.\textsuperscript{23,27} The benefit of antagonists of inflammatory mediators in the treatment of such patients has not been demonstrated yet by clinical controlled studies.\textsuperscript{26,30}

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**REFERENCES**