Surgical management of severe pancreatitis including sterile necrosis

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Abstract

Background/Purpose. Severe pancreatitis develops in 15% to 20% of patients with acute pancreatitis, morphologically characterized by extra- and intrapancreatic necrosis and associated with single or multiple organ failure. It is well accepted that surgery is indicated in patients with infected pancreatic necrosis. However, management of sterile necrosis is still controversial. In a prospective study, we evaluated the effect of maximal intensive care unit (ICU) treatment combined with prophylactic antibiotics in patients with necrotizing pancreatitis.

Methods. A total of 306 consecutive patients with acute pancreatitis were hospitalized between November 1993 and August 2001. All patients with necrotizing pancreatitis diagnosed by computed tomography received ICU treatment, including antibiotics (imipenem/cilastin). Fine-needle aspiration of pancreatic necrosis was performed in patients with clinical signs of sepsis, and necrosectomy combined with continuous postoperative lavage was indicated when bacterial testing demonstrated infection. In the presence of sterile necrosis, surgery was only performed when there was no clinical improvement despite maximal ICU treatment.

Results. Necrotizing pancreatitis was found in 121 patients. Infected necrosis was verified in 41 patients (34%) at a mean of 26 days. Four percent of patients with sterile necrosis and 95% of patients with infected necrosis were operated on. The surgical procedure was successful in 83% of patients as a single intervention; relaparotomy had to be performed in only 7 patients (17%). Pancreatic abscesses were found in 7 patients; four of these were drained interventionally. The overall mortality of the patients with necrotizing pancreatitis was 9.9%. The mortality of patients with sterile and infected necrosis was 2.5% and 24%, respectively (sterile vs infected; $P < 0.01$).

Conclusions. Due to improved intensive care treatment, including prophylactic antibiotics, surgical intervention is usually not indicated in the early course of severe acute pancreatitis. Surgery is clearly indicated in patients with proven infected necrosis. Patients with sterile necrosis should undergo surgery when there is no clinical improvement within 4 weeks of intensive care treatment. In the majority of patients a single intervention is sufficient. Reinterventions are rare and even in patients with abscess formation are not needed, because these can easily be drained interventionally.

Key words Acute pancreatitis · Surgery · Necrosis

Introduction

The clinical course of acute pancreatitis varies from a mild transitory form to a severe necrotizing disease. Patients with mild pancreatitis respond well to medical treatment, and morbidity and mortality rates are below 1%. Therefore, the majority of cases can be managed successfully in a regular ward. Severe pancreatitis with pancreatic or peripancreatic necrosis and development of single or multiple organ failure is found in about 15% to 20% of cases, and these patients need maximal supportive therapy in an intensive care unit (ICU). Identification of patients who are at risk of developing complications is essential in the early course of the disease. Unfortunately, no reliable parameters or scoring systems exist to predict severe courses of acute pancreatitis. Even optimal treatment, including the administration of prophylactic antibiotics, cannot stop the progression of the disease in some patients. Surgery may then become the treatment of choice in clearly defined subsets of patients, e.g., those with infected necrosis. Surgical intervention in sterile necrosis, however, is controversial.

The present article gives an overview of the surgical management of severe acute pancreatitis by reviewing the principal indications (see Table 1), the timing, and the techniques of surgical intervention. The review

Table 1. Indications for surgery in acute necrotizing pancreatitis

Characteristics of patients	Surgery requirement
Sterile necrosis, no organ failure	No surgery
Sterile necrosis with single/multiple organ failure	No surgery
Sterile necrosis, with nonresponding or progressing MOF despite maximal ICU therapy	Surgery may be indicated (>4 weeks), more trials required
Infected necrosis	Indication for surgery

MOF, Multiple organ failure; ICU, intensive care unit

includes our own experience of the past 8 years, during which we treated 121 patients suffering from necrotizing pancreatitis who were recorded prospectively.

Clinical course of acute pancreatitis

Severe necrotizing pancreatitis is a challenging disease which progresses in two phases. The first 2 weeks after the onset of symptoms are characterized by the systemic inflammatory response syndrome (SIRS). The release of proinflammatory mediators is thought to contribute to the pathogenesis of SIRS-associated pulmonary, cardiovascular, and renal insufficiency. Mediators include pancreatic proteases, cytokines, reactive oxygen species, and many more.[1–3] It is important to note that SIRS in the early phase of severe pancreatitis is frequently found in the absence of pancreatic infection. Today, only few patients with severe acute pancreatitis die of SIRS-associated complications, because diagnostics and intensive care therapy have been improved progressively.[4] However, randomized trials have failed to establish specific drugs for the early treatment of acute pancreatitis.[5–7]

Prior to the introduction of prophylactic antibiotic treatment, infection of pancreatic necrosis developed in the second and third week after onset of the disease, and was reported in 40% to 70% of patients with necrotizing pancreatitis.[8–10] Today, infection of pancreatic necrosis is still the most important risk factor in severe pancreatitis, and sepsis-related multiple organ failure is the main life-threatening complication, with a mortality rate of up to 50%.[11,12] Evidence has been provided that there is a positive correlation between the frequency of infection and the extent of pancreatic and peripancreatic necrosis,[8,13] and that most microorganisms found in infected necrosis are of enteric origin.[8,9] However, despite all the advances in ICU therapy, infected pancreatic necrosis with consecutive septic multiple organ failure still bears an extremely high mortality rate.[11,14] In this respect, several surgical approaches have been advocated to improve the outcome of patients with necrotizing pancreatitis.

Management of infected necrosis

When pancreatic necrosis has developed, the differentiation between sterile and infected necrosis is essential for the management of patients. Proven infected necrosis, as well as septic complications resulting from pancreatic infection, are well accepted indications for surgical treatment.[4,15,16] The mortality rate for these patients is higher than 30%, and more than 80% of fatal outcomes in acute pancreatitis are due to septic complications.[8,11,17] When treated nonsurgically, mortality rates of up to 100% have been reported for infected necrosis associated with multiple organ failure.[18] With surgical treatment, the mortality rate for patients with infected pancreatic necrosis was lowered to about 20% to 30% in various specialized centers.[11,19,20]

For the differentiation of sterile and infected necrosis, fine-needle aspiration (FNA) of pancreatic or peripancreatic necrosis has been established as an accurate, safe, and reliable technique.[9,21,22] FNA can be guided by either computed tomography (CT) or ultrasonography, and should be performed in patients who present with clinical signs of sepsis. The complication rate of this procedure is low, with only very few serious complications, such as bleeding or aggravation of acute pancreatitis.[23,24] Bacterial tests, including Gram staining and culture of the aspiration material, have a diagnostic sensitivity and specificity of 88% and 90%, respectively.[25] It is important that only those patients who present clinical signs of sepsis should undergo FNA, because FNA bears a potential risk of secondary infection.

At our institution, prophylactic antibiotics (imipenem/cilastin 3–4 × 0.5 g) are administered early in the course of necrotizing pancreatitis. In a series of 121 patients with necrotizing pancreatitis, CT guided FNA verified infected necrosis in 34% of patients at a mean of 26 days (range, 10–49 days) after onset of symptoms. No complications were associated with FNA in this series.

Management of sterile necrosis

Sterile necrosis, in general, is no indication for surgery, because several reports have demonstrated that patients with sterile necrosis can be managed well non-operatively.[4,19] In a series of 38 patients with necrotizing pancreatitis, Bradley and Allen[19] reported an overall survival rate of 100% in patients with sterile necrosis treated conservatively. However, when sterile necrosis is associated with organ failure, the role of surgery remains controversial.[26–30] It is still unclear why some patients with sterile necrosis can be treated nonsurgically while others die without timely intervention.

The manifestation of single or multiple organ failure in acute pancreatitis is associated with mortality rates of 23% to 75%, no matter whether the pancreatic necrosis is infected or sterile.[26,29–31] Therefore, some authors have favored surgical therapy in extended pancreatic necrosis. Theoretically, necrosectomy eliminates the risk of the necrosis getting infected. Furthermore, removal of the necrosis is thought to prevent or reduce the risk of inflammatory mediators and toxic substances being released into the systemic circulation, thereby ameliorating the systemic inflammatory response. However, because proinflammatory mediators are released very early in the course of the disease,[32] surgery is not the tool to interfere with the stimulation of the various cascade systems contributing to SIRS. Another drawback of early surgery is the risk of secondary infection of preoperative sterile necrosis, which has been shown in about 30% of patients.[28,33,34] Thus, surgical intervention in sterile necrosis even seems harmful, with worsening of the prognosis of patients. ICU therapy, including prophylactic antibiotic treatment in the early phase, has been shown to generate better survival.[4,35–37]

Nevertheless, some patients do not improve despite maximal therapy in the ICU. In this subset of patients, some authors advocate surgery. In a large retrospective series of 172 patients with sterile necrosis published by Beger's group (Rau et al.[28]), 62% of patients were managed surgically, whereas the remainder were treated conservatively. The surgical group was characterized by higher Ranson and Acute Physiology and Chronic Health Evaluation (APACHE) II scores and higher C-reactive protein serum levels on admission. Mortality rates were not significantly different between the two groups, at 13.1% for the surgically treated patients and 6.2% for those treated nonsurgically. It was concluded that the presence of persistent or progressive organ complications despite maximal ICU treatment is an indication for surgery in patients with sterile necrosis. However, there is no established uniform definition of when a patient should be considered a "nonresponder" to ICU therapy. Also, in the rare event of rapidly progressive multiple organ failure in
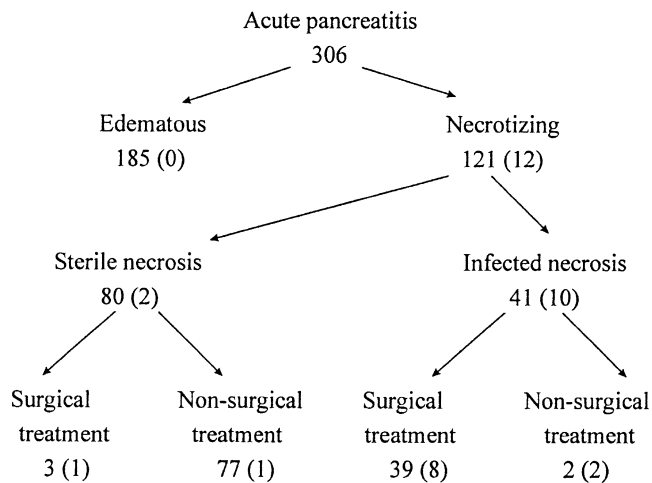

Fig. 1. Three hundred and six consecutive patients with acute pancreatitis grouped according to the status of infection and treatment modality — the authors' experience. Values in parentheses indicate the number of patients in each group who died

the first days of acute pancreatitis despite ICU therapy, so-called "fulminant acute pancreatitis", surgery may be indicated. Given the poor outcome with both surgical and conservative therapy and the lack of published data, the optimal therapy for this subset of patients remains unclear.[36,38]

Our experience is in agreement with the widely established approach of managing sterile necrosis initially nonsurgically. In a series of 121 consecutive patients with acute necrotizing pancreatitis (between 1993 and 2001), only 2 of 80 patients with sterile necrosis died, giving a mortality rate of 2.5%. Of these 2 patients, 1 patient died of severe respiratory distress syndrome, not responding to resuscitation. Autopsy revealed massive retroperitoneal necrosis and severe lung injury. The other patient developed early multiple organ failure which did not respond to intensive care treatment, and surgery was performed. One week after surgical debridement of sterile necrosis, infection with methicillin-resistant *Staphylococcus aureus* and *Candida albicans* was found, and the patient died of septic multiple organ failure a few days later. Two more patients with sterile necrosis who were operated on because of persistent multiple organ failure despite maximum ICU treatment survived (Fig. 1).

Timing of surgery

Patients with severe necrotizing pancreatitis can progress to a critical condition within a few hours or days after the onset of symptoms. In the early course of the disease, patients are at high risk of death

from cardiovascular or pulmonary failure. Years ago, early surgical intervention was favored, especially if systemic organ complications were requiring a quick response.[29,39,40] Furthermore, if diagnosis remained unclear despite various examinations, surgery had been requested.[41] Today, there is general agreement that surgery in severe pancreatitis should be performed as late as possible. The rationale for late surgery is the ease of identifying well-demarcated necrotic tissue from the viable parenchyma, with the effect of limiting the extent of surgery to pure debridement. This approach decreases the risk of bleeding and minimizes the surgery-related loss of vital tissue which leads to surgery-induced endocrine and exocrine pancreatic insufficiency.[42]

Mortality rates of up to 65% have been described with early surgery in severe pancreatitis,[8,43–45] questioning the benefit of surgical intervention within the first days after onset of symptoms. In the single prospective and randomized clinical trial comparing early (within 48–72h of symptoms) versus late (at least 12 days after onset) debridement in patients with severe pancreatitis, the mortality rates were 56% and 27%, respectively.[44] Although the difference did not reach statistical significance, the trial was terminated because of the evident risk of early surgery.

In our experience, surgery should not be performed earlier than 4 weeks after the onset of symptoms. The optimal surgical conditions for necrosectomy are present in the later phase of the disease, when necrosis is demarcated. The initial hemodynamic instability can be treated effectively in the ICU. As we avoided surgery in the early course of the disease, we had hardly any deaths, even in patients with multiple organ failure. In conclusion, only in the case of proven infected necrosis or in the rare case of a complication such as massive bleeding or bowel perforation, must early surgery be performed.[4]

Surgical procedures (Table 2)

In most patients with necrotizing pancreatitis, surgery is performed to remove infected necrotic pancreatic tissue. The aim is to control the focus, so that further complications are avoided by stopping the progress of infection and the release of proinflammatory mediators. However, resection procedures such as partial or total pancreatico-duodenectomy that also remove vital pancreatic tissue or healthy organs are associated with high rates of mortality and postoperative exo- and endocrine insufficiency.[39,46–48] Because in many cases of necrotizing pancreatitis only the external parts of the gland are necrotic, whereas the parenchyma in the center is not affected, this so-called "superficial necrotizing pancreatitis' can mistakenly be considered as total pancreatic necrosis, leading to a wrong surgical procedure. Therefore, the surgeon should be aware of the preoperative morphology of the pancreas, and should use modern imaging techniques, such as contrast-enhanced CT, which provide reliable information about viable pancreatic parenchyma. Thus, pancreatic resection procedures with subsequent exo- and endocrine insufficiency can be avoided in most cases.

In the past, various surgical procedures have been propagated for the treatment of necrotizing pancreatitis. Peritoneal dialysis did not decrease mortality significantly.[49] With the employment of different surgical strategies such as tube drainage,[50] debridement of necrosis combined with suction drainage,[51–53] or pancreatic resection,[46,47] mortality rates also remained high. Consequently, surgical procedures have been combined with a postoperative concept that maximizes further evacuation of debris and exudate. In this respect, considerable attention has been focused on three comparable procedures: necrosectomy combined with the open-packing technique;[54] planned, staged relaparotomies with repeated lavage;[16] and closed continuous lavage of the

Table 2. Surgical modalities in acute necrotizing pancreatitis

Treatment	Outcome
Pancreatic resection	High rate of postoperative complications, exo- and endocrine pancreatic insufficiency
Peritoneal dialysis Tube drainage	No effect on the retroperitoneal process
Necrosectomy and closed continuous lavage Necrosectomy and planned relaparotomy Necrosectomy and open packing	Good results in experienced centers
Interventional percutaneous drainage procedures	Experience limited, further results are required

retroperitoneum.[27,55] In the hands of experienced surgeons, mortality rates below 15% have been described for either of these approaches. However, a relationship between repeated surgical interventions and morbidity has been reported. Gastrointestinal fistula, stomach outlet stenosis, incisional hernia, or local bleeding have frequently been observed after multiple relaparotomies.

Bradley[15] reported the results of 71 patients with infected necrosis managed by open drainage with scheduled abdominal reexploration (=open packing). Morbidity was high, with external pancreatic fistulas occurring in 46% of patients, hernias in 32%, and massive venous hemorrhage in 7%. The overall mortality in this series was 15%. Sarr et al.[16] treated 23 consecutive patients with necrotizing pancreatitis by planned, staged relaparotomies with repeated lavage. Also in their series, a significant number of pancreatic and colonic fistulas was reported (in 26% and 22% of patients, respectively), whereas the mortality rate was equally low (17%).

The approach at our institution is necrosectomy with subsequent closed continuous lavage of the lesser sac.[4] In a series of 121 patients with necrotizing pancreatitis (from 1993 to 2001), infected necrosis was verified in 34% (41/121) of patients at a mean of 26 days (range, 10–49 days). All but 2 patients with infected pancreatic necrosis underwent necrosectomy and subsequent continuous closed lavage. In these 2 patients, infected necrosis was associated with rapid clinical deterioration, and the positive culture results were not obtained in a timely fashion. In 3 patients with sterile necrosis, surgery was performed because of persistent organ failure despite maximum intensive care treatment. Overall, the surgical approach was successful in 83% (35/42) of patients as a single intervention. Relaparotomy or reintervention had to be performed in only 17% (7/42) of patients. Pancreatic abscesses were found in 7 patients; four of these were drained interventionally. The mortality of the patients with sterile necrosis was 2.5% (2/80), compared with 24% (10/41) in patients with infected necrosis (Fig. 1). The difference in mortality between sterile and infected necrosis was significant ($P < 0.01$). In contrast to the series published by Bradley[15] and by Sarr et al.,[16] pancreatic fistula occurred in only 19% (8/42) of all surgically treated patients in this series. The overall mortality of patients with necrotizing pancreatitis was 9.9% (12/121).

Recently, nonsurgical approaches, such as interventional drainage of pancreatic necrosis, using percutaneous techniques, have been introduced. Even in infected necrosis, single-center reports in — so far — small patient groups have demonstrated that some patients recover with nonsurgical[56–58] or limited surgical management. However, about 50% of patients managed by percutaneous drainage had to be reoperated on at a later time point. Therefore, the nonsurgical management of infected necrosis has to be regarded as an experimental approach, and should be strictly limited to well-defined subsets of patients enrolled in randomized controlled trials.

Summary

Surgical management of necrotizing pancreatitis has changed significantly in the past few years. In contrast to the "aggressive" and early surgical interventional of the past, there is now a strong tendency towards a more conservative approach. Administration of prophylactic broadspectrum antibiotics that have good penetration into the pancreatic gland and that cover the microorganisms typically found in infected pancreatic necrosis is crucial in the early course of the disease. By this means, infection of pancreatic necrosis is reduced and delayed. However, if clinical signs of sepsis develop, FNA of pancreatic or peripancreatic necrosis should be performed to differentiate between sterile and infected necrosis. There is strong evidence that infected necrosis is a clear indication for surgical intervention, and surgery should consist of debridement of necrosis with a postoperative regimen that maximizes the removal of further generated debris and exudate, e.g., closed continuous lavage. Sterile necrosis should be treated nonsurgically unless associated multiple organ failure either does not respond or progresses despite maximal ICU therapy within 4 weeks. However, a clear definition of these "nonresponders" is needed to clarify the role of surgery in this subset of patients with sterile necrosis. Applying the recommended therapeutic strategy, which comprises early application of antibiotics combined with restricted indication for surgical intervention, fewer patients with acute necrotizing pancreatitis undergo surgery, and the interventions are performed later in the course of the disease, ideally when necrosis has become well demarcated.

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