Severe Acute Pancreatitis: Case-Oriented Discussion of Interdisciplinary Management

Pietro Renzulli\textsuperscript{a} Stephan M. Jakob\textsuperscript{b} Martin Täuber\textsuperscript{c} Daniel Candinas\textsuperscript{a} Beat Gloor\textsuperscript{a}

Departments of \textsuperscript{a}Visceral and Transplant Surgery, \textsuperscript{b}Intensive Care Medicine, and \textsuperscript{c}Infectiology and Institute for Infectious Diseases, Inselspital, University of Berne, Berne, Switzerland

Key Words
Acute pancreatitis · Surgical treatment · Antibiotic treatment · Intensive care treatment

Abstract
The clinical course of an episode of acute pancreatitis varies from a mild, transitory illness to a severe often necrotizing form with distant organ failure and a mortality rate of 20–40%. Patients with severe pancreatitis, representing about 15–20% of all patients with acute pancreatitis, need to be identified as early as possible after onset of symptoms allowing starting intensive care treatment early in the disease process. An episode of severe acute pancreatitis progresses in two phases. The first 10–14 days are characterized by a systemic inflammatory response syndrome maintained by the release of various inflammatory mediators. The second phase, beginning about 10–14 days after the onset of the disease is dominated by sepsis-related morbidity due to infected peripancreatic and pancreatic necrosis. This state is associated with septic multiple organ systemic failure. The importance of infection on the outcome of necrotizing pancreatitis has been clearly delineated and the preemptive use of broad-spectrum antibiotics that achieve effective tissue concentrations is considered standard management of patients with severe necrotizing pancreatitis, especially if associated with organ failure or extended necrosis. Patients with infected necrosis should undergo a surgical intervention. The standard open technique consisting of an organ preserving necrosectomy followed by a postoperative concept of lavage and/or drainage to evacuate necrotic debris occurring during the further course has recently been challenged by various minimally invasive approaches.

Most episodes of acute pancreatitis are mild and self-limiting with bowel rest, fluid and electrolyte replacement, and pain control, but severe disease complicated by multiple organ system dysfunction develops in up to 20% of cases. The mortality rate in these patients remained around 40% despite many advances in the management of this disease [1, 2]. Recently, an international consensus conference focused on the management of the critically ill patient with severe acute pancreatitis (SAP) [3]. Among many aspects discussed, it became evident that in the most severe cases an interdisciplinary approach is essential for successful treatment. Here we present a case-oriented discussion focusing primarily on the most recent developments of intensive care medicine, treatment of infectious complications and surgical management.
Case Presentation

A 44-year-old woman, with a history of regular alcohol intake and depression was admitted to a regional hospital because of acute upper abdominal belt-like pain, nausea and repeated vomiting (day 1). She was agitated, afebrile and anicteric with a heart rate of 90/min, a blood pressure of 150/105 mm Hg and a respiratory rate of 17/min. Physical examination revealed hematomas on both thighs, varicose veins, slight palmar erythema. Her abdomen was distended and meteoristic with pain on palpation, rebound tenderness and guarding in the upper abdomen. Bowel sounds were sparse and ascites was suspected. Laboratory data on day 1 and 3 are listed in Table 1. Chest X-ray was normal and an abdominal ultrasonography revealed no gross pathology with the pancreas being obscured by meteorism. The patient was transferred to the ward with nil per mouth and intravenous analgetics and fluid management with the diagnosis of acute alcohol-toxic pancreatitis. The initial course was uneventful. On day 3, the patient’s condition deteriorated rapidly and she was transferred to the intensive care unit (ICU) with clinical and laboratory changes indicating severe pancreatitis and beginning sepsis: tachycardia (up to 128/min) and tachydyspnea (up to 21/min), increasing abdominal distension and the development of a Cullen’s sign, elevation of C-reactive protein (CRP) and leukocyte count, reduction of ionized calcium and deterioration of clotting studies. Computed tomography showed profuse necrotizing pancreatitis (>50%) and important bilateral pleural effusions. Blood cultures were taken (no organisms were isolated) and antibiotic treatment with piperacillin/tazobactam was started. Signs of delirium tremens were treated with intravenous diazepam. On the same day, the patient was transferred to the ICU of a tertiary referral center and mechanical ventilation was started.

A Ranson score of 4, an APACHE II-score of 12 and a C reactive protein level of 225 mg/l on day 3 were all indicative of a severe pancreatitis. Due to the rapid clinical deterioration as well as the CT findings of profuse pancreatic necrosis the suspicion of infected pancreatic necrosis arose and early transcutaneous puncture of the necrotic pancreatic tissue was performed despite the fact that early infection occurs only in a minority of patients. Gram stain and cultures, however, remained negative. Piperacillin/tazobactam was replaced by imipenem/cilas-

### Table 1. Laboratory and clinical data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium, mmol/l</td>
<td>2.1–2.55</td>
<td>2.24</td>
<td>1.14</td>
</tr>
<tr>
<td>Ionized calcium, mmol/l</td>
<td>1.13–1.3</td>
<td>–</td>
<td>0.72</td>
</tr>
<tr>
<td>Creatinine, µmol/l</td>
<td>45–102</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Urea, mmol/l</td>
<td>2.9–6.4</td>
<td>2.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>3.66–5.5</td>
<td>7.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Total bilirubin, µmol/l</td>
<td>3–26</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>36–120</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALAT), U/l</td>
<td>6–37</td>
<td>142</td>
<td>83</td>
</tr>
<tr>
<td>Aspartate aminotransferase (ASAT), U/l</td>
<td>10–32</td>
<td>223</td>
<td>28</td>
</tr>
<tr>
<td>Gamma glutamyl transpeptidase (γ-GT), U/l</td>
<td>8–45</td>
<td>748</td>
<td>245</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/l</td>
<td>&lt;480</td>
<td>–</td>
<td>2,973</td>
</tr>
<tr>
<td>Pancreas specific amylase, U/l</td>
<td>13–53</td>
<td>158</td>
<td>201</td>
</tr>
<tr>
<td>Lipase, U/l</td>
<td>13–60</td>
<td>1,301</td>
<td>843</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>&lt;5</td>
<td>3</td>
<td>225</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>120–160</td>
<td>139</td>
<td>88</td>
</tr>
<tr>
<td>Mean cell hemoglobin, pg</td>
<td>27–31</td>
<td>33.2</td>
<td>34</td>
</tr>
<tr>
<td>Mean cell volume, fl</td>
<td>81–99</td>
<td>102</td>
<td>103</td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration, g/l</td>
<td>330–370</td>
<td>325</td>
<td>327</td>
</tr>
<tr>
<td>Leukocyte count, × 10^9/l</td>
<td>3,500–10,500</td>
<td>4,800</td>
<td>7,800</td>
</tr>
<tr>
<td>Thrombocytes, × 10^9/l</td>
<td>130–400</td>
<td>153</td>
<td>104</td>
</tr>
<tr>
<td>Serum osmolality, mosm/kg</td>
<td>280–296</td>
<td>319</td>
<td>–</td>
</tr>
<tr>
<td>International normalized ratio (INR)</td>
<td>0.97</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>RANSON score</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>2</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
tatin as a prophylactic antibiotic therapy according to our treatment protocol at that time [4]. The following week the patient remained intubated but hemodynamically stable. On day 11, the patient developed a diffuse skin rash (exanthema) and fever (>39°C). Imipenem/cilastatin was discontinued for suspicion of an allergic reaction and piperacillin/tazobactam was re-installed. Despite a broad-spectrum antibiotic treatment the C-reactive protein surged to a peak level of 370 mg/l. Because of the deteriorating laboratory values and the continued respiratory and circulatory organ failure we strongly suspected the presence of infected pancreatic necrosis and therefore decided to perform an early explorative laparotomy. Pancreatic and peripancreatic necrosectomy and cholecystectomy were undertaken and several lavage cannula were inserted for continuous postoperative lavage that was continued until day 59. Bacteriological examination of intraoperative tissue samples revealed Enterobacteriaceae, Staphylococcus aureus and Enterococcus spp. within the pancreatic necrosis. All isolated organisms were sensitive to the antibiotics administered so far. On day 14, the patient developed increasing erythema in combination with significant bronchospasm. Piperacillin/tazobactam was discontinued and treatment with cefepime and metronidazole was started. On day 18, the patient developed catheter-related sepsis. The catheter was removed and coagulase-negative staphylococci grew from blood cultures. Cefepime was stopped and ciprofloxacin and vancomycin were added to metronidazole. On day 19, tracheostomy was performed and on day 21 the patient developed purulent maxillary sinusitis. On day 27, ciprofloxacin was stopped. On day 29, the patient became febrile and an elevation of CRP and leukocyte count was noted. Blood cultures were negative and cultures from the drainage tubes showed mixed gram-positive bacteria. Antibiotic treatment was continued with ciprofloxacin and vancomycin. Computed tomography revealed a fluid collection in the left retroperitoneal space and a drainage tube was inserted on day 31. Ciprofloxacin was discontinued on day 36 and vancomycin was stopped on day 39, leaving the patient for the first time without antibiotic treatment. While blood glucose testing revealed no endocrine insufficiency, she needed regular pancreatic enzyme supplementation, while blood glucose testing revealed no endocrine insufficiency.

The Intensive Care Physician’s Viewpoint

From the viewpoint of the intensive care physician, the present case raises a number of important and controversial issues, like the role of predictors for outcome, the occurrence of multi-organ failure as well as the importance of analgesia and nutrition.

Natural Course of Pancreatitis

In patients with SAP the clinical course is characterized by an early toxic phase with distant organ dysfunction of various degrees, lasting approximately 2 weeks, and a later phase with local and regional complications such as pancreatic abscess and pseudocyst formation [5, 6]. These phases are often superimposed, especially when necrosis becomes infected early. Early multiple organ dysfunction syndrome (MODS) occurs as a consequence of various inflammatory mediators that are released from activated leukocytes, and from the local inflammatory process in and around the pancreas [7–10]. The hemodynamic profile of early pancreatitis is usually hyperdynamic although severe myocardial depression may occasionally occur. During the late course of the disease, both local
and systemic septic complications are common. According-
arily, around 80% of deaths in acute pancreatitis are
caused by septic complications [6]. It is often difficult to
separate systemic inflammatory response syndrome
(SIRS) and sepsis in patients with SAP.

Intensive Care for Patients with Complicated Disease
Resuscitation has to be initiated early because the ther-
apeutic window is narrow [3, 11]. Supportive therapy
consists of aggressive fluid resuscitation (third space fluid
losses), correction of electrolyte and coagulation abnor-
malities, oxygen supplementation, and non-invasive or
invasive ventilation. Long-term ventilation may require
tracheostomy as was the case in our patient. Administra-
tions of vasoconstrictors may become necessary when
shock persists despite volume replacement, and renal re-
placement therapies are often required. For the rational
use of all these measures, appropriate respiratory and car-
diovascular monitoring is mandatory. This may include
a pulmonary artery catheter, especially when vasoactive
drugs are used, and when acute lung injury or acute re-
spiratory distress syndrome (ARDS) is present. In addi-
tion, critical illness polyneuropathy may progress to tet-
raplegia with prolonged rehabilitation over months.

Predictors of Outcome in SAP
Outcome prediction can be difficult because mild or
severe local, regional and systemic complications may oc-
cur. Both single laboratory parameters and multiple
scores containing clinical, laboratory and radiological pa-
rameters have been tested (e.g. APACHE II and III, Imrie
score, Ranson criteria, Balthazar score). There is a large
variation in the performance of these scores and the pow-
er of each score to predict severity of pancreatitis, pan-
creatic necrosis, and organ failure [12–20]. Importantly,
early deteriorating rather than high scores may identify
patients at risk for an adverse outcome [15, 21, 22]. Also,
elderly patients and those with a body mass index
>30 kg/m² or with pre-existing co-morbidity are at risk
for a more severe course of the disease [23–26]. Labo-
atory parameters such as C-reactive protein (CRP), serum
creatinine, blood glucose, hematocrit, pancreatic phos-
pholipase A(2) and urinary trypsinogen activation pep-
tide have also been proposed as prognostic variables [16,
27–33]. Reasonably high negative and positive predictive
values were found when single laboratory parameters
were combined with findings from computed tomog-
raphy [18]. Monitoring the inflammatory process may also
help in predicting the outcome [34]: In one study, the
course of procalcitonin was closely related to the presence
of infected necrosis [35]. Others found that clinical judg-
ment was as good as using a score for predicting the out-
come [17].

Systemic Inflammatory Response and Multi-Organ
Dysfunction Syndrome (SIRS and MODS)
A SIRS is defined as a clinical condition with the pres-
ence of at least two of four signs of inflammation [36]. A
SIRS occurs in a variety of circumstances such as infec-
tion, pancreatitis, cardiopulmonary bypass, trauma and
many more. The incidence in both ICUs and wards is as
high as 70% [37]. Approximately 25% of patients with
this syndrome progress to sepsis, and roughly 4% develop
MODS [36–38]. In the course of MODS, neurological
abnormalities occur generally early, followed first by re-
spiratory, cardiovascular and renal failure, and later by
coaagulation abnormalities and hepatic dysfunction [39].
A hypermetabolic state is characteristic of acute pancre-
atitis. The pathophysiology of MODS is unclear, but there
is evidence that episodes of splanchnic hypoperfusion are
associated with endotoxemia and bacterial translocation
which promote local and distant organ failure [40]. Con-
tributory factors include intravascular volume depletion
as a consequence of increased vascular permeability and
abdominal fluid sequestration, and gastrointestinal or
retroperitoneal hemorrhage. There is strong evidence that
during pancreatitis, spillage of toxic substances which in-
clude pancreatic elastase [41, 42] and various infl amma-
tory mediators released locally and systemically as a con-
sequence of the local inflammatory process may be caus-
ally related to remote organ failure [8–10, 43].

Analgesia
Since administration of opiates has been associated
with spasm of the sphincter Oddi, their use has been ques-
tioned in patients with pancreatitis. However, in clinical
practice analgesics such as meperidine, morphine, and
fentanyl are used routinely without proven negative side
effects on the further course of the disease. In some coun-
tries, intravenous procaine has been used for pain relief
in acute pancreatitis. However, intravenous procaine is
neither as effective as opiates [44], nor can it be used to
spare significant amounts of opioid drugs [45].

Theoretically, epidural analgesia may be beneficial and
the effectiveness and safety of epidural anesthesia has
been demonstrated [46, 47]. However, during SAP, cer-
bral dysfunction, coagulation abnormalities and the po-
tential of systemic infection may prohibit insertion of an
epidural catheter in many patients.
**Nutrition**

Withdrawal from enteral nutrition is considered as a part of the standard management based on the fact that enteral feeding stimulates pancreatic secretions [48]. However, there is not sufficient data to assess the concept of ‘gut rest’ in acute pancreatitis on an evidence-based level. On the other hand, the importance of nutritional support is emphasized by the observation that failure to achieve a positive nitrogen balance is associated with an increased mortality in patients with SAP [49]. Traditionally, total parenteral nutrition (TPN) has been advocated in these patients in order to prevent hypercatabolic states and to avoid stimulation of exocrine pancreatic function and the release of proteolytic enzymes. However, randomized trials in patients with SAP have demonstrated that nasojejunal feeding initiated 48 h after ICU admission is safer than TPN, does not exacerbate the disease, is well tolerated and less expensive than TPN [50–52]. In addition, in a randomized prospective trial including 38 patients enteral feeding was associated with significantly fewer complications [53]. In an experimental study it was shown that especially jejunal feeding neither stimulates entero-hormone and pancreatic juice secretion, nor enzyme-protein synthesis and release [54]. In a clinical study of 26 patients with SAP nasogastric feeding was well-tolerated in 22 patients and there was no evidence of clinical or biochemical deterioration on commencing nasogastric feeding [55]. The goal of enteral nutrition, however, is not only nutritional support but also gut mucosal integrity, which can be achieved with lower doses than required for feeding the patient. In several studies comparing TPN versus enteral nutrition this aspect was not sufficiently discussed and patients receiving enteral nutrition were underfed in terms of caloric support whereas those receiving TPN were overfed as documented by blood glucose monitoring, rendering questionable a comparison of the two modes of nutrition based on these data. In summary, according to the data available today it is advisable to start enteral nutrition as soon as possible [3, 56]. In the patient presented in the case report, however, this strategy was not feasible due to persistent paralytic ileus.

**The Infectiologist’s Viewpoint**

From the viewpoint of the infectiologist, the present case raises mainly the issue of infected pancreatic necrosis and its prevention and treatment.

**Infected Pancreatic Necrosis**

Infection of necrotic pancreatic tissue is the most serious complication and the single most important risk factor for mortality in patients with SAP [24, 57]. The risk for infection is associated with the extent of the necrotic process. In patients with less than 50% of necrotic tissue, 23% had documented infection, whereas in patients with >50% necrosis, 84% had infections [57]. Furthermore, the risk of infection increases with duration of the disease, such that within the first week of disease, approximately one fourth of patients has evidence of infection, whereas after 3 weeks, this figure is up to 70%. The importance of the extent of necrosis and duration of disease are related to the pathogenesis of these infections. In necrotic tissue, host defense mechanisms are severely impaired, making it a focus of high vulnerability for infection. Pathogens can gain access to necrotic tissue by various routes, including translocation from the gut and hematogenic or lymphatic spread. Furthermore, invasive procedures harbor the risk of introducing pathogens [58].

**Source of Organisms and Relevant Pathogens in Pancreatic Infections**

The gut represents the most important source for infections of necrotic pancreatic and peripancreatic tissue. This notion is primarily supported by the microbiologic analysis of these infections [57, 59, 60]. Approximately 50–70% of isolated pathogens are gram-negative rods of enteric origin (table 2). Gram-positive cocci are the second most important group and it is likely that many of the staphylococci isolated from pancreatic tissue are the result of hematogenic spread or have been introduced by invasive procedures. Anaerobes (mostly *Bacteroides* spp.) are isolated relatively infrequently, but this may be due in part to the notorious difficulties in isolating these fastidious organisms. Fungal infections, typically caused by *Candida* spp., appear to be increasingly recognized, particularly in patients with prolonged disease and following long-term, broad-spectrum antibiotic therapy [61–64].

There are some noteworthy associations between clinical features of the disease and microbiological findings. Early in the course of necrotizing pancreatitis, gram-negative rods are predominantly isolated. Gram-positive organisms, fungi, and multiple pathogens, on the other hand, are more characteristic of infections occurring in the later phase of the disease. Pre-emptive antibiotic treatment (often called prophylactic antibiotic treatment or antibiotic prophylaxis despite its duration of up to 2–4 weeks) tends to shift the spectrum of pathogens to gram-positive cocci and fungi. Finally, among the various
pathogens observed, gram-negative rods appear to be associated with a significantly increased case fatality, while such an association has not been observed for gram-positive pathogens [65]. The impact of fungal infections on outcome is unclear. Some studies have suggested that fungal infections are associated with increased case fatality, while others have not confirmed such an association [61–64, 66].

The Role of Antibiotics in SAP

Given the importance of infections for adverse outcome and the fact they occur typically days to weeks after the beginning of the acute disease, the role of pre-emptive antibiotic treatment in patients with pancreatitis has attracted considerable interest. Since translocation from the gut appears to be an important source of infection, both selective gut decontamination and systemic antibiotic prophylaxis provide rational approaches and both have been tested clinically.

The effectiveness of antibiotics is dependent on adequate tissue concentrations at the site of infection, and several studies have therefore assessed to what extent various antibiotics penetrate into inflamed and necrotic pancreatic tissue [60]. For the quinolones (ciprofloxacin, ofloxacin), tissue concentrations 2 h after administration are practically identical to serum concentrations (approximately 1 μg/ml) and exceed MICs of susceptible gram-negative rods several fold. For several other antibiotics, including metronidazole, piperacillin, and imipenem/cilastin, tissue concentrations are approximately half of simultaneous serum concentrations and are clearly in excess of MICs of relevant, susceptible pathogens. For meropenem, little clinical data exist, but experimental data suggest that this drug also achieves adequate tissue concentrations [67]. Tissue concentrations of cephalosporins (cefotaxime, cefepime) achieve approximately one third of serum concentrations, but given the high serum concentrations, this degree of penetration is still adequate against the majority of pathogens. Furthermore, animal data suggest that cefepime accumulates in severe pancreatitis to high local concentrations [68]. Aminoglycosides achieve only low tissue penetration rates and loose activity in the acidic, anaerobic environments likely to be present in infected necrotic pancreas. Their role in the treatment of infection within the pancreas (as opposed to systemic infection) is doubtful.

Several clinical trials and two recent meta-analyses have explored the effectiveness of prophylactic antibiotic treatment on mortality and complications of acute necrotizing pancreatitis. The details of the different trials varied substantially, particularly regarding the antibiotics studied and most individual studies did not report statistically significant results. The two meta-analyses suggested a beneficial effect of prophylactic antibiotic therapy on mortality and possibly on pancreatic infections and sepsis [69, 70]. However, concerns have been raised about the conclusions of these meta-analyses, since some of the randomized controlled trials included had important limitations and some trials had insufficient statistical power to allow conclusions regarding mortality. Furthermore, it must be mentioned that the largest randomized double-blinded trial, with 149 patients with SAP was not included in the meta-analyses. This latter recent study did not show any benefit of pre-emptive antibacterial therapy with regard to the frequency of pancreatic infection, surgical intervention and mortality [71]. Thus, the universal administration of antibiotics to all patients with SAP may not be appropriate and conversely it may lead to the selection of difficult to treat, resistant organisms. A more prudent approach may be to limit the use of pre-emptive antibiotics to patients with severe SAP associated with early organ failure or necrosis of more than 50% of the pancreas [3, 71]. If used, broad-spectrum, systemic antibiotics which achieve high tissue concentrations in excess of MICs of potential pathogens (imipenem/cilastin, broad spectrum cephalosporins, quinolones) appear most likely to be effective.
In most studies antibiotics were given intravenously, but also the intra-arterial route and selective gut decontamination have been tested [72–74]. The latter approach compared a control group (antibiotic treatment only when infection was documented) with a group treated with selective decontamination of the gut (colostin sulfate, amphotericin B, and norfloxacin administered orally and per rectum, combined with initial systemic cefotaxime until gram-negative bacteria were eliminated from the rectum and oral cavity) [74]. Based on multivariate analysis taking into account the severity of disease, there was a marginally significant benefit on mortality in the selective decontamination group. However, this approach has received limited interest in clinical practice, likely due to the more cumbersome application of the antibiotics, a lack of evidence for superiority compared to systemic broad-spectrum antibiotics, and the theoretical concern of selecting resistant bacteria.

Several important questions regarding the utility of antibiotics in the management of patients with SAP need to be addressed in future studies. These include the selection of patients most likely to benefit from antibiotics, optimal choice and timing of pre-emptive antibiotic treatment, the significance of fungal infections and the role of anti-fungal prophylaxis, and the possible role of conservative management in patients with documented infection.

The Surgeon’s Viewpoint

From the surgeon’s viewpoint, the present case raises a number of important and controversial issues, like the indications and the timing of surgery as well as the type of surgical techniques to be employed.

Indications for Surgery and Timing of the Intervention

In the management of documented pancreatic infection surgical removal of necrotic tissue is of paramount importance and generally accepted, since conservative treatment alone was associated in some studies with an unacceptably high mortality of up to 100% [4, 75]. The occurrence of infection must be suspected whenever the clinical situation in a patient with necrotic pancreatitis is deteriorating with increasing signs of inflammation (fever, CRP >180 mg/ml, leukocytosis), increasing pain, hemodynamic instability and progressive multi-organ dysfunction syndrome. In these situations, imaging studies followed by aspiration of necrotic tissue for microbiologic studies are necessary [76–78]. Once pancreatic infection is diagnosed surgery should be performed as soon as possible because removal of the septic focus (so-called source control) is the key element in order to overcome sepsis-related MODS [2]. Nevertheless, interest in the conservative therapy of infected pancreas necrosis has recently emerged in selected, clinically stable patients [79]. However, it is not clear whether candidates for conservative treatment can be reliably identified and there is insufficient data for an evidence-based approach. Surgery must currently remain the standard of care in all infected patients with signs of sepsis.

Other indications for surgery that are less well defined and somewhat controversial are the so-called ‘persistent’ organ dysfunction syndrome despite maximal ICU treatment and the presence of sterile pancreatic necrosis involving 50% or more of the pancreas. Persistent organ failure, such as pulmonary, renal insufficiency, or the requirement for catecholamines to support hemodynamic stability are considered indications for surgical therapy by some experts if these conditions persist over more than 10–14 days or deteriorate over a period of 3–5 days despite maximal ICU treatment [4, 80]. Unfortunately there are no accepted guidelines let alone a precise definition of the terms ‘persistent organ dysfunction syndrome’ or ‘non-response’ to ‘maximal ICU treatment’.

Despite the absence of organ failure or signs of ongoing sepsis some patients with extended sterile necrosis may fail to improve owing to persistent pain and gastric outlet obstruction. In such patients surgical debridement is indicated but should be delayed at least three to four weeks after disease onset. The rationale for this is the fact that three weeks or more after the onset of the disease intraoperative bleeding complications are less likely to occur and demarcation between necrotic and viable tissue is easier to assess than earlier in the disease process [2, 80–83]. Importantly, in patients with sterile necrosis improving under therapy a conservative approach is preferred. In a series of 57 patients with sterile necrosis of whom 56 were managed conservatively the mortality rate was 3.5% (2/57) and 1.8% (1/56), respectively [4]. Also, it has to be taken into account that (early) surgery in patients with sterile necrosis may cause or facilitate subsequent infection of peripancreatic/pancreatic tissue thereby worsening the further course of the disease, especially when surgery is performed too early [84].

Another group of patients that may or may not require surgical treatment are those with sterile necrosis and early and rapidly progressing MODS despite intensive care unit treatment. In those patients surgical measures might
not overcome MODS either. These cases may be called ‘fulminant acute pancreatitis’ and, fortunately, they are rarely seen and represent less than 2% of all patients with SAP [85]. In a report from a tertiary referral centre three out of four patients who died early (i.e. within 10 days of the onset of necrotizing pancreatitis) did so because of MODS without apparent bacteremia or sepsis [86]. In a study of 44 patients with severe disease and surgical treatment, the need for an operative intervention within 2 weeks after onset of symptoms was associated with an increased mortality rate [87]. Isenmann et al. [88] analyzed the subgroup of patients with organ dysfunction within 72 h after onset of symptoms (not only those with progressing organ dysfunction despite ICU treatment). Extended pancreatic necrosis was the main predisposing factor for early MODS and these patients were found to develop more frequently intractable organ dysfunction which was considered an indication for surgery. Importantly, the incidence of infected pancreatic necrosis did not differ between those with early organ dysfunction and those with SAP not accompanied by early MODS, suggesting that MODS at this early stage of the disease, in this subgroup of patients, was not caused by pancreatic infection. Mortality was significantly higher in those with early MODS (42 vs. 14%; p = 0.0003). Taken together, the currently available data do not allow either recommending or rejecting surgery in patients with early MODS especially in those deteriorating under maximum ICU treatment. Based on the available data it is the authors’ policy that (strong suspicion of) pancreatic infection still remains the only reason to operate on those patients at an early stage.

**Surgical Technique**

The main goals of surgery are listed in table 3. The treatment of SAP has evolved considerably during the past three decades. Clearly, there is a trend toward organ-preserving and minimally invasive techniques. Pancreatic resection has been mostly abandoned. Because of the difficulties to correctly assess the amount of necrotic tissue the loss of viable pancreatic tissue was often considerable and the morbidity and mortality rate associated with the procedure were high [89–92]. Organ-preserving extensive debridement of necrotic tissue combined with postoperative continuous lavage through drains placed in the retroperitoneal cavities that occurred as a result of removal of necrotic tissue has provided better results in several series [4, 93, 94] (table 4). Planned repeated operative necrosectomies [86, 95, 96] or open packing [97] represent more invasive alternative approaches to the postoperative lavage concept with comparable results in experienced centers (table 4). In a recent retrospective series of 44 patients a combination of surgical techniques (primary closure n = 16, planned staged re-laparotomy n = 14, and open laparostomy n = 14) was used and no difference in mortality between the different techniques

<table>
<thead>
<tr>
<th>Aim of treatment</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Removal of infected necrotic peri- and intrapancreatic tissue | – most efficiently done by open necrosectomy  
– minimally invasive retroperitoneal pancreatic necrosectomy may alternatively be used and repeated several times  
– cannot be attained by non-operative drainage procedures |
| Removal of sterile necrotic peri- and intrapancreatic tissue | – only necessary if extended areas of pancreatic and peri-pancreatic tissue preclude amelioration of the patients’ condition after the third or fourth week  
– may be done by minimally invasive techniques, particularly if necrotic tissues are liquefied with only minor amounts of solid debris |
| Evacuation of further necrotic tissue if the necrotizing process is ongoing/continuing | – additional/continued therapy mandatory (either repeated minimally invasive retroperitoneal necrosectomy, or lavage or repeated laparotomies) |
| Preservation of intact vital pancreatic tissue | – easier, if surgery (open or minimally invasive) is delayed until demarcation of necrosis has occurred (usually after 3–4 weeks) |
| Removal of pancreatogenic exsudate from the peritoneal cavity and the lesser sac | – theoretically indicated to prevent systemic uptake of vasoactive and toxic substances, but not superior to intensive care treatment |

See text for details. Adapted from [81].
was found [87]. However, the semi-open/open method seems to be associated with a higher local complication rate [87, 98].

Recently the traditional open techniques have been challenged by less invasive techniques including percutaneous drainage, retroperitoneal CT-guided or transabdominal/retroperitoneal laparoscopic approaches [99–105]. When comparing open with minimally invasive techniques it is of paramount importance to discriminate between removal of infected necrotic debris and drainage of primarily liquid collections in and around the pancreas as the latter is associated with a more benign natural history. Zhou et al. [104] published a series of 13 patients treated laparoscopically and included patients with massive fluid collections and/or infected necrosis in the acute phase of the disease as well as patients with well-defined pancreatic or peripancreatic pseudocyst/abscess, rendering impossible a comparison to open techniques.

Minimally invasive techniques are characterized by the advantage of representing a minor interventional burden to the (usually) already severely ill patient. On the other hand it takes multiple repeated interventions spread over 2–4 weeks to remove all the necrotic debris [99–101]. In a series of 24 patients with pancreatic infection treated with minimally invasive retroperitoneal pancreatic necrosectomy, 6 patients (25%) died and 5 needed an additional open intervention [100]. These figures are comparable to a series of 28 patients treated with open necrosectomy and closed postoperative lavage.

### Table 4. Mortality rates in patients with SAP, treated by open surgery or minimally invasive techniques

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients treated</th>
<th>Technique</th>
<th>Deaths (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley, 1987 [97]</td>
<td>28</td>
<td>open drainage</td>
<td>3 (11)</td>
<td>consecutive patients with infected pancreatic necrosis</td>
</tr>
<tr>
<td>Borie et al., 1994 [93]</td>
<td>157</td>
<td>necrosectomy and continuous lavage</td>
<td>28 (18)</td>
<td>prolonged drainage with the aim of controlling secondary necrosis</td>
</tr>
<tr>
<td>Farkas et al., 1996 [94]</td>
<td>123</td>
<td>necrosectomy and continuous lavage</td>
<td>9 (7)</td>
<td>all patients with infected necrosis</td>
</tr>
<tr>
<td>Fernandez et al., 1998 [82]</td>
<td>64</td>
<td>necrosectomy and closed suction drains</td>
<td>4 (6.2)</td>
<td>no difference between patients with infected or sterile necrosis</td>
</tr>
<tr>
<td>Tsiotos et al., 1998 [86]</td>
<td>72</td>
<td>planned re-operative necrosectomies</td>
<td>18 (25)</td>
<td>only 4 early and 14 late deaths</td>
</tr>
<tr>
<td>Freeny et al., 1998 [99]</td>
<td>34</td>
<td>(repeated) percutaneous drainage</td>
<td>4 (12)</td>
<td>14 patients with necrosis equal to or more than 50% of the pancreas</td>
</tr>
<tr>
<td>Büchler et al., 2000 [4]</td>
<td>28</td>
<td>necrosectomy and continuous lavage</td>
<td>6 (21)</td>
<td>27 patients with infected necrosis</td>
</tr>
<tr>
<td>Carter et al., 2000 [101]</td>
<td>10</td>
<td>minimally invasive retroperitoneal necrosectomy</td>
<td>2 (20)</td>
<td>only 40% of patients required ICU after surgery</td>
</tr>
<tr>
<td>Gotzinger et al., 2002 [96]</td>
<td>340</td>
<td>necrosectomy (72%) combined with pancreatic resection (28%), re-operations planned or ‘on-demand’/drainage by open packing/laparostomy</td>
<td>133 (39)</td>
<td>270 patients required re-operations (1–18) surgery performed after a mean of 12 days (1–31 days)</td>
</tr>
<tr>
<td>Connor et al., 2003 [100]</td>
<td>24</td>
<td>minimally invasive retroperitoneal necrosectomy</td>
<td>6 (25)</td>
<td>all patients with infected necrosis and necrosis &gt;50%</td>
</tr>
<tr>
<td>Tzovaras et al., 2004 [87]</td>
<td>44</td>
<td>different open techniques</td>
<td>8 (18)</td>
<td>all patients with necrosis &gt;30%</td>
</tr>
</tbody>
</table>
in which 21% (6/28) died and another 6 needed re-operation [4] (table 4).

Overall, the exact role of minimally invasive necrosectomy has yet to be defined. Based on the currently available data we conclude that the surgical strategy needs to be tailored to the individual findings such as clinical status, extent of necrosis and debris, time from onset and co-morbidity of the patient, especially in the subgroup of those with persistent MODS.

References

Clinical Management of Severe Acute Pancreatitis

Pancreatology 2005;5:145–156


41 Ammori BJ: Role of the gut in the course of severe acute pancreatitis. Pancreas 2003;26:122–129.


