Commentary

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23.1 Introduction

Acute pancreatitis is a relatively common, potentially life-threatening disease, with annual costs exceeding $2 billion in the United States alone where more accurate estimates are available (Fagenholz et al. 2007; Shaheen et al. 2006). Approximately 20 % of patients develop severe acute pancreatitis, defined by organ failure or necrotizing pancreatitis (Banks and Freeman 2006). Mild pancreatitis is associated with a mortality of 0–1 %, whereas the mortality of severe pancreatitis ranges from 15 % for the severe form without infection to as great as 30 % for those patients who develop infected necrosis (Besselink et al. 2009). Sterile pancreatic necrosis and sterile peripancreatic collections can usually be treated conservatively. In contrast, secondary infection of necrosis – usually presenting clinically 3–4 weeks after the onset of disease – requires some form of active intervention in most cases (Besselink et al. 2009); if left untreated, mortality of infected necrosis approaches 100 % (Banks and Freeman 2006).

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23.2 Clinical Presentation

It is widely accepted to base the diagnosis of acute pancreatitis on two of the following criteria: (a) severe abdominal pain, (b) serum amylase or lipase activity more than three times greater than the institution's upper limit, and findings of acute pancreatitis on (c) contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI). Usually, the first two criteria are present for confirmation of the diagnosis, and CECT is required only in those patients who present after several days of abdominal pain, when the serum amylase and lipase levels have normalized or in patients with organ failure of unknown origin. CECT will often fail to demonstrate the presence pancreatic necrosis and peripancreatic collections in the first 72–96 h of disease. For confirmation of the presence of necrosis, intravenous, not oral, contrast administration is required.

> Ultrasonography may show pancreatic swelling, but bowel gas can prevent adequate visibility of the pancreas.

In this early stage, abdominal ultrasonography is essentially inadequate and unreliable in visualizing the pancreas. Detection of gallstones in search of the cause of the disease represents the only potential indication for abdominal ultrasonography at this time point in the course of

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acute pancreatitis. In order to detect necrosis, CECT or MRI are far superior.

Recent insights in pathophysiology have proven very helpful, not only for understanding the disease but also to serve as a justification for new forms of treatment.

Severe acute pancreatitis normally runs a biphasic course. The first phase is characterized by a systemic inflammatory response syndrome (SIRS) and lasts about 2 weeks. Infection of necrosis is rare in this phase, but other systemic infections needing antibiotic treatment do occur during this phase of SIRS. In a recent study on 731 acute pancreatitis patients focusing on the timing of infection and the time frame available for prevention of infection, bacteriaemia and pneumonia (ventilator associated) were diagnosed most often in the first week of admission, whereas infection of the pancreatic and/or peripancreatic necrosis became manifest clinically in about the fourth week of disease (Besselink et al. 2009). Organ failure in this first phase of the disease is considered, therefore, not to be related to infection but rather to the effect of severe systemic inflammatory response.

The second phase of severe acute pancreatitis is characterized by a counteractive anti-inflammatory response syndrome (CARS), a phase wherein the patient becomes (highly) susceptible to infection. Organ failure in the second phase of severe acute pancreatitis (the CARS phase) is related to infections, such as infected necrosis. During this second phase, the necrosis becomes encapsulated, most likely by a similar sort of process as the formation of an abscess.

The impact on treatment of this pathophysiological concept is that in the SIRS phase there is essentially no place for surgery for the removal of (infected) necrosis, whereas in the second phase timing and type of intervention dominate treatment. The crucial elements in timing are: the moment of clinical manifestation of infection and the completion of encapsulation.

23.3 Predicting Severity

> C-reactive protein levels over 150 mg/l, an APACHE II score greater than 8 in the first 24 hours, or persistent organ failure in the first 24 hours, are established, clinically useful predictors of severity….

The clinical course of acute pancreatitis is highly unpredictable and may vary from full recovery within a single day to multi-organ failure and mortality within the first day or two. There is considerable confusion on how these "predictive scoring" systems can be or should be used in clinical practice, for several reasons: (1) there is no form of conservative or operative method to prevent the disease from progressing from a mild to the severe form, other than aggressive fluid administration to prevent dehydration or a "low flow state." This approach may prevent development of multiple organ failure or small bowel ischemia, but controlled studies are not available.

The most frequently used scores and cut-off points are listed in Table 23.1. If a patient meets one of the cut-off values for "predicted severe pancreatitis," this only means that such a patient is at greater risk of developing the severe form of the disease. The clinical value of the stigma "predicted severe pancreatitis" is limited, because the positive predictive value (the chance of truly developing severe pancreatitis) is around 50–70 %. With a negative predictive value of 85–90 %, patients with predicted mild pancreatitis run a 10–15 % risk of developing the severe form of disease.

"Predictive scoring" and Classifications Systems like the Atlanta Classification are indispensable in clinical studies to inform the reader about the characteristics of the population under study, but these scores do not help the clinician in their difficult task of taking care of the individual patient with severe acute pancreatitis.

> … and persistent organ failure in the first 24 hours, are established, clinically useful predictors of severity….

The same study on the timing of infection and the time frame available for prevention of infec-

Table 23.1 Most used predictive laboratory scoring systems in acute pancreatitis and their cut-off for predicted severe pancreatitis

Predictive score	Cut-off
APACHEII[a] score	≥8 in first 24 h
BISAP[b] score	≥3 in first 24 h
Modified Glasgow (or Imrie) score	≥3 in fist 48 h
Ranson score	≥3 in fist 48 h
Urea at admission	>60 mmol/L
C-reactive protein	>150 U/L in first 72 h

[a]*APACHE* Acute physiology and chronic health evaluation
[b]*BISAP* bedside index for severity in acute pancreatitis

tion, showed that organ failure is not so much a predictor of severity, but it turned out to be the most important determinant for mortality in acute pancreatitis (Besselink et al. 2009).

23.4 Classification of Severity

The updated Atlanta classification of acute pancreatitis continues to be developed. This classification may include a clinical subdivision into either *mild* or *severe* disease.

In the early phase, this subdivision is based on clinical parameters only, whereas in the weeks that follow, the development of complications prolonging hospitalization, either requiring active intervention (operative, endoscopic, laparoscopic, or percutaneous) or other supportive measures (such as need for respiratory ventilation, renal dialysis, or nasojejunal feeding) and morphologic changes on CECT, dominate the clinical picture. In this phase, classification relies on radiologic findings and is dominated by the presence or absence of intra- and/or extrapancreatic collections and necrosis and whether these collections are infected or not.

23.5 Conservative Management

In the first phase of severe pancreatitis, adequate fluid resuscitation represents the mainstay of treatment (Mao et al. 2009). A fluid regime guided by urine output (goal 1 ml/kg h urine production) is sufficient in the initial phase, as long as organ failure is not present yet. In this phase of the disease, we maintain that there is no room for necrosectomy, radiologically, endoscopically, or operatively in an attempt to "turn the tide." Intra-abdominal bleeding not able to be controlled by arterial coiling or development of the intra-abdominal compartment syndrome are the only reasons for operative intervention in the SIRS phase.

23.5.1 Management in the CARS Phase and Thereafter (2–12 Weeks)

When there has been no improvement or actual clinical deterioration after initial improvement, infection of the pancreatic and/or peripancreatic collections must be sought, excluded, or treated. In an attempt to anticipate on further deterioration, some groups have advocated weekly fine needle aspiration (FNA) of the collection to confirm or exclude infection. Our group does not support this strategy. There is a risk of a false-negative results, and infection may be introduced by FNA. Moreover, clinical deterioration, accompanied by a negative result of the FNA should not withhold the clinician from intervention. Based on a recent randomized controlled trial (RCT) on treatment of infected necrosis, we refrain from routine FNA, because 92 % of patients proved to have infected necrosis at the initial intervention, while only a small minority had infection discovered only on FNA (Van Santvoort et al. 2010). Gas in peripancreatic collections are, however, pathognomonic for infected necrosis.

Once the necrosis becomes infected, mortality increases dramatically from about 15 % to around 30 %, so the prevention of infection is an ultimate goal of treatment in the early phase of the disease (Besselink et al. 2009).

Systemic intravenous antibiotics, selective bowel decontamination, enteral probiotics and enteral nutrition all have been proposed to lessen the rate of infection.

23.5.2 Systemic Intravenous Antibiotics

Many studies have addressed the effect of systemic antibiotic prophylaxis in lessening the rate of infectious complications in (predicted) severe acute pancreatitis (De Vries et al. 2005, Wittau et al. 2011). The initial, non-blinded, non-placebo controlled, randomised trials suggested rather dramatic positive effects.

> …A Cochrane meta-analysis in 2006 described a decrease in mortality using prophylactic antibiotics in necrotizing pancreatitis. For these reasons, the use of prophylactic antibiotics remains a viable option to us….

Enteral nutrition is hypothesized to decrease small bowel bacterial overgrowth by a positive effect on small bowel motility, which limits intraluminal bacterial overgrowth and by a positive effect on intestinal mucosal barrier function which decreases bacterial translocation. This cascade of events could lead to a decrease in infectious complications (super infection by bacteria entering the systemic circulation) (Eckerwall et al. 2007; Petrov and Zagainov 2007; Petrov et al. 2009, Petrov et al. 2010). In predicted severe pancreatitis, we now start enteral nutrition by nasojejunal feeding if the patient is not expected to resume a normal diet within approximately 3 days.

The optimal route for the administration of enteral feeding – through a nasojejunal or a nasogastric feeding tube – has yet to be established. Two small, randomized trials involving 80 patients found no difference in tolerance for feeding and complications rates by either route of delivery. The overall mortality was rather high, and the studies may have missed relevant differences in complications, such as aspiration, due to their small size. Results of ongoing larger studies should be awaited before using nasogastric feeding routinely in patients with severe acute pancreatitis.

23.5.3 Selective Bowel Decontamination (SBD)

Only one RCT studied the value of SBD in acute pancreatitis (Luiten et al. 1995). The study demonstrated a decrease in mortality in the SBD group. Nevertheless, this therapy has not gained wide acceptance, but the data suggest that the concept of early intervention in the cascade of events – small bowel bacterial overgrowth, mucosal barrier failure, bacterial translocation, systemic infection – deserves further exploration.

23.5.4 Probiotics

Several studies including two small RCTs from Hungary suggested a beneficial effect of prophylactic probiotics in predicted severe pancreatitis (Van Santvoort et al. 2008). In the large Dutch probiotics trial (PROPATRIA) in patients with predicted severe acute pancreatitis, no effect on infectious complications was found; more worrisome, however, was a more than twofold greater mortality rate in the probiotics group. Although there is no satisfactory answer yet to this puzzling outcome, at this stage it seems that the prophylactic probiotics as administered in this study should no longer be given to patients with "predicted severe acute pancreatitis."

23.6 The Role and Timing of Intervention

The large differences in outcome of series from the last decades illustrate a wide variation in the indication for intervention, technique, timing, and selection of patients included in the different studies. Most of the studies published are retrospective in nature and only two RCT's have been conducted (Van Santvoort et al. 2010; Mier et al. 1997):

- Differences in the indications for intervention: this chapter shows clearly that the Magdeburg group also struggles with a clear description of the indications for intervention, illustrated by "early intervention (<3–4 weeks) or the operative treatment of sterile necrosis, should be reserved for select cases." These are two different indications for intervention "early intervention (<3–4 weeks)" and "the operative treatment of sterile necrosis." Early intervention for the treatment of necrosis without documented or highly suspected infection has no place in our

opinion in the treatment of necrotizing pancreatitis early in the disease, even if the patient's clinical condition is deteriorating. A small RCT on operative necrosectomy in this phase was performed in 1989. In this study, intervention within 72 h ("early") was compared with operation after 12 ("late") days (Mier et al. 1997). The authors terminated the study prematurely because of a much greater, though not yet statistically significant, mortality for operative intervention within 72 h (58 vs. 27 %). After this study, operative necrosectomy as the primary therapy for acute pancreatitis in the absence of infection was essentially abandoned. Currently uncontrollable bleeding and abdominal compartment syndrome represent what we believe to be the only indications for operative intervention in the first 2–3 weeks of the disease.

- "The operative treatment of sterile necrosis, should be reserved for select cases," raises the question about patient selection. In our practice, sterile necrosis is treated by some form of interventional necrosectomy when causing persistent mechanical obstruction of the duodenum or the common bile duct, or when it's leading to "failure to thrive" or what others have called "the persistent unwell." There are no controlled series on this controversial topic, and many operative and endoscopic series reporting on technical success are a mixture of infected and sterile pancreatic and peripancreatic collections.
- Other topics of debate are: "infection of pancreatic necrosis is a well-accepted indication for operative intervention" and "in contrast, infected necrosis does not mandate operative treatment." We regard both of the statements as true in the sense that infection of necrosis is a well-accepted indication, but, indeed, not all infected cases need aggressive operative necrosectomy and some may not even require a more minimal access necrosectomy by percutaneous, endoscopic or laparoscopic type interventions.
- In the Dutch RCT on intervention in infected necrosis, infection with signs of sepsis was the only indication for intervention and all attempts were made to delay intervention for 30 days after onset of the disease. This approach led to an overall mortality of 17 %; the patients had a mean APACHE score of 15 and an infection rate of 92 %. Several patients developed infected necrosis with signs of sepsis before 30 days of onset of the pancreatitis, but because the protocol called for delay of necrosectomy until at least 30 days after onset, operative intervention was successfully postponed to 30 days, with intravenous antibiotic support. There is also uncontrolled data showing that necrosis with gas on CECT, can disappear on occasion without any form of intervention.
- The experience of the Magdeburg group in 2006 and 2007 is listed in Tables 3.2 and 3.3. These tables highlight another important feature of severe necrotizing pancreatitis; the Magdeburg group is a well-respected, experienced center, yet still only about five cases are managed operatively each year. Many other centers have similar numbers and, consequently, controlled studies from other expert centers are difficult to conduct and need many years to be built up, thus the need for organized multicenter trials.
- Differences in the techniques applied: the Magdeburg group describes their experience with open necrosectomy, the "therapeutic flow" (in Fig. 3.1) and the advantages of this approach. Their approach ("finger fracture") to open the necrotic collection is very similar to ours. When only a limited entrance to the collection is made, the cavity created after the necrosectomy can be closed adequately by suturing the opening closed using the greater omentum and the backside of the stomach, in order to create a closed system for continuous postoperative lavage; the drains can be guided out the right and left flank. We prefer a limited opening to the lesser sac collection rather than a large opening as shown on Fig. 3.5a, because we feel that adequate lavage with large amounts of fluid is more important than attempts at complete removal of all small remnants of necrosis in the far extremes of the often widely extending cavities. Creating a really closed compartment for lavage of the lesser sac, with infracolic extensions behind the right and left

colon – is crucial for successful long term lavage. The use of multiple drains is advisable for collections extending infracolically behind the right and left colon; non-productive drains can easily be removed early. We stop the lavage when the cavity has collapsed and not "when the draining fluid has become clear." When the sinogram demonstrates collapse of the cavity, we stop the lavage and remove the drains step-by-step over a period of 7–10 days.

- The statements of the Magdeburg of "some groups utilize radiologic percutaneous drainage or laparoscopic or endoscopic techniques" and "at this time, minimally invasive necrosectomy is far from the standard practice in treating many patients requiring necrosectomy" are important, because their approach to this disease illustrates that any operative or nonoperative approach and any operative technique, once adopted with clinical results apparently accepted by experienced clinicians like the Magdeburg group, can only be "attacked" successfully and replaced new techniques, when successfully tested in controlled studies. Recent studies, however, do show that "minimally invasive necrosectomy is" not all "that far from the standard practice." The RCT from the Netherlands (Van Santvoort et al. 2010) and a recently published systematic review (Van Baal et al. 2011) show that about 30–55 % of patients may need no further treatment after successful percutaneous catheter drainage. So, percutaneous or transgastric catheter drainage (PCD or TCD), has now become our accepted first step of interventional treatment for patients with infected pancreatic necrosis. If PCD/TCD is not successful, operative or endoscopic (Seifert et al. 2009) necrosectomy is the next step. Controlled studies have to show which operative approach or technique is the best option, the videoscopic-assisted retroperitoneal debridement (Horvath et al. 2001, Van Santvoort et al. 2007, Horvath et al. 2010), a laparoscopic approach (Raraty et al. 2010), endoscopic (Papachristou et al. 2007) or open necrosectomy (this chapter). Probably a tailored approach depending on patient condition and the extent and location of the necrosis after failure of PCD/TCD will be the future approach.
- Differences in timing of operative intervention: in the Dutch RCT (Van Santvoort et al. 2010), delay of necrosectomy until at least 4 weeks after onset of disease was adhered to rigidly, because this time interval was based on a study showing that waiting for 4 weeks improved outcome in terms of mortality (…). In the Dutch RCT, it was found that at 2–3 weeks encapsulation was often incomplete and that after waiting another 10 days or 2 weeks, encapsulation of the necrotic collection matured, thereby allowing a safe necrosectomy. Therefore, based on this experience, we maintain that planning some form of necrosectomy at 3 weeks, because "pancreatic necrosis is usually well demarked after about 3 weeks from onset of acute pancreatitis…" may not be the best strategy. We fully agree with the statement "demarcation is of paramount importance" and that indeed "removing the well-demarked necrosis reduces the risk of bleeding and preserves still vital parenchyma." If, in some cases, in the RCT, demarcation or encapsulation was completed at 2 weeks, we still waited for another 2 weeks, under antibiotic coverage to protect against bacteriaemia and sepsis. Currently, a strategy of "wait and encapsulate" has well-documented advantages, but the exact and optimal interval needs further determination.

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