Acute pancreatitis – from cellular signalling to complicated clinical course

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Abstract
Acute pancreatitis (AP) is a common disease that has a mild to moderate course in most cases. During the last decade, a change in diagnostic facilities as well as improved intensive care have influenced both morbidity and mortality in AP. Still, however, a number of controversies and unresolved questions remain regarding AP. These include prognostic factors and how these may be used to improve outcome, diagnostic possibilities, their indications and optimal timing, and the systemic inflammatory reaction (systemic inflammatory response syndrome – SIRS) and its effect on the concomitant course of the disease and potential development of organ failure. The role of the gut has been suggested to be important in severe AP, but has recently been somewhat questioned. Despite extensive research, pharmacological and medical intervention of proven clinical value is scarce. Various aspects on surgical interventions, including endoscopic sphincterotomy, cholecystectomy and necrosectomy, as regards indications and timing, will be reviewed. Last, but not least, are the management of late complications and long-term outcome for patients with especially severe AP.

Key Words: Acute pancreatitis, pathophysiology, management, outcome

Definition
To date, the most generally used definition of acute pancreatitis (AP) and its severity has been the Atlanta classification [1]. According to this, AP is an acute inflammatory process in the pancreas with various degrees of involvement of local or other organ systems. Severe AP, occurring in 15–20% of all cases of AP, is defined as the occurrence of organ failure, ≥3 Ranson criteria, an APACHE II score ≥8 or local complications like pancreatic necrosis, pseudocyst development or pancreatic abscess formation. The Atlanta classification has been discussed concerning its relevance in defining the true severity of AP and it has been reported that resolution of organ failure within 48 h suggests a good prognosis [2]. A number of prognostic factors, as will be mentioned and discussed below, probably have to be included in an updated version on severity scoring in AP.

Incidence
The reported incidence of AP has varied widely, but seems to be about 300 cases or more per million inhabitants and year in western Europe [3–5]. The aetiology varies, but dominating factors are biliary disease (now in most series representing about 40% of all cases of AP), alcohol disease and a variety of causes like post-ERCP, hyperparathyroidism (HPT), immunological causes and side effects of pharmacological treatment. Recurrent disease is seen in at least 20% of patients with AP and a severe (usually necrotizing) pancreatitis has been reported in general in 15–20%, with an associated mortality rate ranging up to 20% [5].

Determination of severity
The most commonly used severity determination has been the Atlanta classification, discriminating between mild and severe AP, but in addition to pancreatic necrosis, this has also taken acute fluid collection, pancreatic abscesses and pseudocyst formation into consideration [1]. Of less use today are the Ranson criteria [6] and the Glasgow score [7]. Still valid for patients with critical illness and roughly discriminating between severe and mild disease is the
APACHE II score, in cases of AP often used in an attempt to discriminate patients with prognosticated severe AP with an APACHE II score in general above 8 [8,9]. From a radiological point of view, the computed tomography (CT)-based Balthazar score with a grading from A to E has been, and is still to some extent used [10]. In patients treated in the intensive care unit (ICU) due to organ failure, more recent organ failure scores like the SOFA (Sepsis-related Organ Failure Assessment) score can be applied [11].

**Prognostic factors**

The first episode of AP has been regarded as the potentially severe one, with a risk of resulting in a complicated course and subsequent mortality. However, attacks of severe AP may occur also in recurrent episodes of AP and may thus also be associated with mortality. It has been demonstrated that mortality also occurs in patients with recurrent AP, although the associated mortality rate is reported to be about half of that seen in patients with their first attack of AP [5].

Age has often been demonstrated as a prognostic factor. An age exceeding 65 years has been associated with an increased mortality [12]. This is most probably due to associated underlying diseases resulting in an increased ASA (American Society of Anesthesiology) score and an impaired capability of coping with critical illness and its complications in general.

Obesity, defined as a body mass index (BMI) exceeding 30, has been identified as a prognostic factor of importance, increasing both morbidity and mortality. The reasons for this are still not fully elucidated, but may include an increased number of underlying diseases and increased severity of disease caused by extrapancreatic factors like pulmonary dysfunction, exacerbated by the increased abdominal pressure in the obese patient [13].

Prognostic factors of clinical importance at admission to hospital are still rarely defined, but are of course of outmost importance to improve future management of AP patients. Hypovolaemia resulting in a systolic blood pressure <100 mmHg at admission has been shown to correlate with an increased mortality in patients with expected severe AP [14]. This probably illustrates the systemic dissemination of disease and an increase in endothelial barrier permeability early on, as a consequence of more profound SIRS in severe disease, correlating with the magnitude of the pro-inflammatory response.

The levels of activation peptides, i.e. the cleavage products of pancreatic pro-enzymes, may be of potential future clinical use [15]. A rise in the level of trypsinogen activating peptide (TAP) in urine during the first days has been reported to correlate with levels of C-reactive protein (CRP), levels of interleukin-6 (IL-6), the extent of pancreatic necrosis and severity [16].

The magnitude of the pro-inflammatory response seems to correlate with severity and the concomitant course of the disease. CRP levels exceeding 150 mg/L within the first 72 h of the disease correlate with the occurrence of necrotizing pancreatitis and the degree of severity [17–19]. Levels of the pro-inflammatory cytokines IL-6 and IL-8 may be of future clinical use, as levels have been found to correlate with severity and thus may represent prognostic factors, in time preceding the increase in CRP [20,21]. Also of prognostic importance is the persistent SIRS associated with multiple organ dysfunction syndrome (MODS) and mortality, as has been demonstrated recently [22]. Furthermore, pancreatic necrosis, its extent and especially potential bacterial contamination, highly correlate with the prognosis in AP [23,24].

The occurrence of organ dysfunction and not least the number of failing organs correlate with mortality, as has been demonstrated both in severe AP, but also in other types of critical illness [5,25]. It should be stated that more recent findings emphasize that the progression of organ failure is associated with mortality, but early organ dysfunction frequently resolves spontaneously and thereby is without demonstrable impact on prognosis and has no association with mortality [26].

Inflammatory response and course in acute pancreatitis

The acute phase response during the course of AP is the net response of the pro-inflammatory and simultaneously occurring anti-inflammatory response. During the initial phase this may frequently result in a hyperinflammatory state, the development of SIRS and potentially organ dysfunction. Less known is the hypoinflammatory state (compensatory anti-inflammatory response syndrome – CARS) that may follow later on during the course of critical illness, as initially described by Bone et al. [27,28]. Hypothetically, during this later phase, the patient may be more vulnerable to, for example, bacterial translocation or the trauma added by a surgical intervention. This could potentially lead to the combination of MODS and sepsis (Figures 1 and 2), as seen during later phases of critical illness [27,28].

Mortality in severe AP may range up to 20% or more. As mentioned, mortality is most often caused by organ dysfunction during the initial phase and frequently by the combination of MODS and sepsis during the later phase of disease (after the initial week). Less reported is the frequent prehospital mortality encountered, especially in patients with underlying alcohol-induced pancreatitis, who may account for up to one-third of the total number of patients succumbing to AP. It has also been reported
that 30–40% of patients with AP are not diagnosed before autopsy. Despite improvements in the initial resuscitation of patients with AP, mortality during the first week (caused by organ dysfunction) is still reported to be in the range of 35–50% of total deaths in pancreatitis after admission [5,29–31].

**Gut barrier failure and systemic inflammatory response**

Gut barrier failure in severe AP, as an example of critical illness, does not just involve the gut barrier and an increase in permeability (as seen both experimentally and clinically) [32–35], leading to translocation of enteric bacteria, for example. The gut barrier failure also involves alterations in immunocompetent cells within both the gut wall and adjacent lymph nodes (gut associated lymphoid tissue – GALT). Overall, a number of underlying changes have to occur to allow failure of the intestinal barrier to develop [36]. These mechanisms involve a decrease in both the systemic and intestinal microcirculation, leading to ischaemia and reperfusion injury and the release of oxygen free radicals. The increases in permeability, as mentioned above, are essential in the development of barrier failure and include an increase of both the endothelial and the mucosal epithelial barrier permeability. The change in systemic and local immune function may give rise to an exaggerated initial hyperinflammatory response, with the excessive release of various cytokines and mediators. In cases with severe AP, intestinal motility is impaired, thereby decreasing enteric bacterial clearance by the normal propulsive activity, allowing overgrowth of enteric bacteria. By action of bacterial lipases and proteases, for example, morphological changes may occur, followed by attachment and colonization of bacteria to the mucosa. Some of these mechanisms are summarized in Figure 3.

The magnitude of the acute inflammatory response and release of cytokines and mediators correlates with the development of systemic complications and organ dysfunction [37–40]. Persistent SIRS is associated with the development of MODS and mortality and represents an early prognostic indicator of the degree of severity in AP [22]. It has gradually become more evident that ischaemia and reperfusion injury, together with increases in endothelial barrier permeability, may represent the most important and central mechanisms. In the clinical setting, initial aggressive fluid resuscitation can minimize the effect of ischaemia and reperfusion injury and this concept is now introduced in modern management of critical illness, including severe AP [14,32,41,42].

**Pharmacological and medical intervention**

Despite extensive research efforts, there is a lack of specific medical/pharmacological interventions in AP that have been of any proven clinical value. Among studied agents, the use of protease inhibitors has been unsuccessful, and no effect has been proven by the use of somatostatin analogues. In a meta-analysis, studies using the platelet activating factor antagonist Lexipafant failed to demonstrate any significant difference in multiple organ failure or mortality [43]. However, lessons can be learned from general management in critical illness, that probably can also be applied in patients with severe AP. Low dose steroids have been reported to decrease mortality in septic shock and adrenal failure [44]. Of profound interest and of rapid clinical implementation is the study demonstrating benefits of intensive insulin treatment, keeping blood glucose levels within the lower range. This reduces mortality in intensive care, especially in cases with multiple organ dysfunction and an identified septic source [45].
One of the interesting future lines of development may be the use of the anti-inflammatory properties provided by anticoagulatory agents. A complex cross-talk seems to be going on between inflammation and coagulation. Already in clinical use is recombinant activated protein C that has been reported to decrease mortality in patients with severe sepsis [46], decreasing the inflammatory response [47]. It also seems that anti-inflammatory effects can be seen following the administration of other inhibitors of different steps in the coagulation cascade. Anti-inflammatory effects have thus been reported experimentally following the administration of tissue factor pathway inhibitor and by inhibiting factor VIIa and, to some extent, factor Xa [48,49].

**Antibiotic prophylaxis**

Several studies using different types of antibiotics in patients with different severity, sometimes mixing both mild and severe AP, have pointed out an overall beneficial effect. In a meta-analysis, a positive effect on outcome has been reported in severe (necrotizing) acute pancreatitis [50,51]. However, some reports have pointed out the risk of fungal infections. In particular, candida infection has been reported to be associated with an increase in mortality [52]. More recently, meta-analyses have reported that only antibiotic prophylaxis using carbapenem has been of value [43] and the use of prophylactic antibiotics does not prevent infection of the pancreatic necrosis or the associated mortality in acute necrotizing pancreatitis [53]. Thus, at present, the use of antibiotic prophylaxis is controversial. Improved general management, including initial fluid resuscitation, early enteral nutrition and the administration of, for example, probiotics, may provide a better 'upstream' effect, preventing permeability changes and translocation from the gut.

**Enteral nutrition – of value in AP?**

The use of early enteral nutrition in AP has been studied in a number of publications and summarized findings point to its feasibility, cost reduction, a decrease in septic complications, hospital stay, modulation of the inflammatory response and facilitation of gut function. Weaknesses, though, have been that most studies have included only a limited number of patients, with in general a substantial delay before the initiation of enteral nutrition, using a non-defined enteral formula and a mix of patients with varying severity of disease [54–59]. By using the addition of probiotics (Lb. Plantarum 299) to enteral nutrition in patients with prognosticated severe AP, the incidence of sepsis and need for surgical intervention could be significantly decreased, as evaluated in 45 patients [60]. By tradition, a more distal positioning of the enteral tube has been advocated, aiming at reaching a position of the tip at about the level of the ligament of Treitz. Enteral nutrition provided through a nasogastric tube has also been successful in severe AP in 22 of 26 patients [61]. The use of nasogastric early enteral nutrition has also been demonstrated to be feasible and without side effects as compared with traditional treatment of 'pancreatic rest', and this regime provided better blood glucose control in patients with prognosticated severe AP [62]. In patients with mild AP, a recent randomized clinical study has demonstrated that by allowing patients to eat directly, hospital stay decreased by one-third without any notable side effects or increase in, for example, refeeding pancreatitis [63].

**Endoscopic retrograde cholangiography (ERC) and sphincterotomy**

The role of ERC and sphincterotomy in biliary pancreatitis has been widely debated, although randomized clinical studies on the subject are limited. At least previously, a more aggressive, i.e.
early, ERC intervention has been advocated. In patients with lack of treatment effect within 48 h, bile duct clearance was reported to result in a decrease in morbidity in patients with severe AP [64,65]. These studies were then followed by a multicentre German study, reporting that only biliary pancreatitis patients with signs of non-resolving biliary stasis or cholangitis/sepsis had any benefit from ERC and sphincterotomy [66].

Indications for surgery
From a previously quite aggressive surgical attitude in necrotizing pancreatitis, the trend has gradually become more ‘conservative’. At present, surgery in pancreatic necrosis is rarely indicated during the first 2 weeks. Indications for surgery include infected pancreatic necrosis, and sepsis and organ failure that do not respond to conventional treatment. Furthermore, abscess formation requires drainage. It is important to emphasize that cholecystectomy in gallstone-induced AP should be performed during the same hospital stay or at least in immediate association with the acute episode, as 10% of cases will recur within a 4–6 week period with a new attack of AP [43].

Pseudocysts and complications
Complications during the acute phase include development of sepsis and organ failure, and in the longer term, abscess formation, development of pseudocysts or pancreatic insufficiency, both exocrine and endocrine, are to be considered. Pancreatic pseudocysts occur in about 5% of all patients with AP. A variety of treatment modes exist and for most, a gradual increase in ‘invasiveness’ in the treatment could be practised. Thus, conservative management can be performed, not only for small size cysts but also for larger (≥ 8 cm pseudocyst) without an increase in the number of recurrences [67]. In cases of treatment failure (non-resolving pseudocysts), or when symptoms require drainage, percutaneous puncture and drainage may be tried, although keeping in mind that the recurrence rate may be high, especially if communication with the main pancreatic duct exists. In these situations, the insertion of a cystogastrostomy, either by the percutaneous or endoscopic route, should be considered. However, the selection of patients is important – excluding cases with a need for debridement of necrotic tissue or patients with major ongoing infection. Internal surgical drainage and necrosectomy still play a role, but note that this can be performed in a less invasive manner, either laparoscopically or endoscopically by a transgastric or transduodenal approach.

Long-term follow-up
The effects on a long-term basis depend on the extent of the pancreatic necrosis during the acute phase and, of course, reiterated ‘trauma’ by recurrent episodes of AP. Following the acute phase of pancreatitis, a slow recovery has been noted in the exocrine dysfunction [68]. At long-term follow-up, chronic pancreatitis develops in about 20% of patients and diabetes mellitus in up to 30%. However, results overall are promising, with patients regaining a good pancreatic function and quality of life, although after a quite prolonged period of rehabilitation [69,70].

In conclusion, cornerstones in the management of AP include restoration and maintenance of microcirculation so as to minimize ischaemia and reperfusion injury, thus emphasizing the importance of initial and adequate fluid resuscitation. The integrity of the gut barrier function is also important, in which, to some extent, early enteral oral nutrition may be of benefit. The value of immunonutrition and probiotics needs further studies, as does the optimal timing of enteral nutrition. Lessons are to be learned from critical illness in general concerning how to optimize organ supportive therapy, the use of low dose steroids and intensive insulin treatment/blood glucose control. The use of prophylactic antibiotics in severe necrotizing pancreatitis is now questioned. Surgical intervention against pancreatic necrosis has come to be much more selective than before and the same is true for indications for ERC and sphincterotomy. Recurrent gallstone-induced pancreatitis could, however, in almost all cases be avoided by early cholecystectomy and clearance of the bile ducts. In general the long-term results are quite satisfying. Further research is needed to achieve improved future outcome, not least to clarify underlying pathophysiological mechanisms and the dynamics of the disease process. Updated guidelines should be provided and available to support the management of patients with AP.

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References
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