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New developments in understanding of pathophysiology, diagnosis and treatment of severe acute pancreatitis

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Abstract

Severe acute pancreatitis (SAP) remains being a clinical challenge, carrying significant burden of morbidity, mortality and patient related cost. In general, acute pancreatitis may vary in severity, from mild, self-limiting pancreatic inflammation to life-threatening pancreatic necrosis. Gallstone induced obstruction and alcohol abuse are the most common causes of pancreatitis in adults. Continuing interest in new biological markers and predictive models for timely identification of severe acute pancreatitis cases emphasizes clinical importance of early severity prediction. Among those markers, IL-6, IL-10, procalcitonin, and trypsinogen activation peptide are most likely to be used in clinical practice. Although all scoring systems had reliable accuracy in predicting pancreatitis severity and outcome, SOFA score performed.

The treatment of mild disease is mainly supportive, while severe episodes require management by a multidisciplinary team including gastroenterologists, interventional radiologists, intensive care specialists, and surgeons. There are some unresolved issues pertinent to treatment, including indications for antibiotic prophylaxis, optimal route for nutritional support, selective intestinal decontamination and surgical management of pancreatic infection. The purpose of this review is to present advances in pathophysiology, diagnosis, and management of SAP.

Keywords: severe acute pancreatitis, pathophysiology, diagnosis, management

The incidence of acute pancreatitis has increased dramatically over the last two decades. At present, only in USA, acute pancreatitis accounts for more than 200,000 hospital admissions per year. In 80% of cases, acute pancreatitis is relatively mild; nevertheless, almost 20% of patients eventually develop severe disease associated with local and extrapancreatic complications. The mortality rate associated with SAP remains between 10 and 30 percent, despite recent advances in the management of the disease [1].

According to the Atlanta Symposium (1992), SAP is defined as pancreatitis associated with organ failure and/or local complications (e.g. pancreatic tissue necrosis, pseudocyst, or abscess formation) [2]. Important risk factors for the development of pancreatitis in adults are: presence of gallstones (38% of cases) and excessive alcohol consumption (36%). Hypertigliceridemia, defined as serum triglyceride concentrations higher than 11 mmol/L, may be both a precipitating factor or worsen acute pancreatitis induced initially by other condition. Hypercalcemia is another, though relatively inconsistent, cause: incidence of pancreatitis is generally low in patients with chronic hypercalcemia so additional factors are probably required to induce the disease. Additional, relatively rare causes include: mechanical obstruction of pancreatic duct (e.g. related to neoplasm or pancreas divisum), drugs (e.g. azathio-
prine, thiazides, estrogens etc.) and direct trauma to pancreas [3-5]. Pathophysiologic complexity of the disease precludes identification of a specific cause/s for each and every episode of SAP.

Clinical features

Severe acute pancreatitis develops in two phases. The initial phase is dominated by the systemic inflammatory response syndrome (SIRS) that usually evolves during the first week of the disease and may either resolve spontaneously or culminate in SAP development. The second phase (progression of SAP) is dominated by features of necrotizing pancreatitis, the most significant of which is infected variant of pancreo-necrosis complicated with multiple organ dysfunction (MOD) syndrome. Approximately 50% of the patients developing infected pancreo-necrosis do so within the first 21 days of the disease.

Pathophysiology

The pathogenesis of acute pancreatitis has been classically related to inappropriate conversion of trypsinogen to its active form (trypsin) along with lack of prompt quenching of active trypsin inside the pancreas itself. This, in turn leads to autodigestion of the gland tissue and local inflammation. Consequently, acute pancreatitis develops, though, only in cases when intracellular protective mechanisms utilized to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. These mechanisms include synthesis of trypsin as inactive pro-enzyme trypsinogen, autolysis of trypsin, enzyme compartmentalization, synthesis of specific trypsin inhibitors such as serine protease inhibitor Kazal type 1 (SPINK1), as well as relatively low intracellular ionized Ca\(^{2+}\) concentrations [6]. Tumor necrosis factor \(\alpha\) (TNF\(\alpha\)) is released by macrophages localized within the pancreatic tissue. This acute inflammatory response per se causes substantial tissue damage and may progress beyond the pancreatic injury, leading to a SIRS, MOD or death. In severe acute pancreatitis, monocytes show impaired nuclear factor kB and STAT1 activation, which may increase susceptibility to secondary infections. Monitoring of monocyte signaling profiles may aid in finding new therapeutic approaches and predictors of outcome of severe acute pancreatitis [7].

Diagnosis

The initial clinical presentation of SAP is manifested by upper-abdominal pain and vomiting combined with elevated serum levels of pancreatic enzymes. In gallstone pancreatitis, the pain is typically sudden, sharp and epigastric. In SAP related to hereditary or metabolic abnormality or alcohol abuse, the onset may be less abrupt and the pain on many occasions is poorly localized. Extension of inflammatory exudates from the peripancreatic region to the diaphragm can lead to shallow respiration.

A rise in concentration of serum amylase is expected in acute pancreatitis, but this increase is not always obvious and easily identified, especially early in the course of the disease or in relatively mild cases. Pancreatic lipase levels are also elevated. The levels of both enzymes remain elevated with ongoing pancreatic inflammation, with amylase typically returning to normal shortly prior to lipase, in the resolution phase. Serum amylase concentrations may be high in the absence of acute pancreatitis as happens in macroamylasemia, in patients with reduced glomerular filtration rate, diseases involving salivary glands, as well as in extrapancreatic abdominal inflammatory pathologies such as acute appendicitis, cholecystitis, intestinal obstruction, ischemia or perforation, peptic ulcer, and gynecological conditions [8]. Thus, serum lipase concentration is a preferential diagnostic tool in patients with delayed presentation of SAP [9]. An increase in liver enzymes in a patient without history of alcohol abuse is the best single laboratory predictor of biliary pancreatitis: a level of more than three times the upper limit of normal has a positive predictive value of 95 percent. Unfortunately, normal liver enzymes do not reliably rule out the diagnosis and 15-20% of patients with acute pancreatitis of biliary origin will have normal liver function tests [10].

Imaging studies

Abdominal imaging either by computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasonography are all useful in confirming the diagnosis of pancreatitis. Each technique has its own advantages and pitfalls. Transabdominal ultrasonography (US) is more sensitive than both CT and MRI for identifying gallstones and biliary sludge as well as for detecting bile duct dilatation, but it is less useful for detecting stones in the distal bile duct [11]. Endoscopic ultrasonography (EUS) supersedes that caveat and is probably the most accurate test for diagnosing or ruling out biliary causes of acute pancreatitis as well as the ability to guide interventions. The use of ERCP in acute pancreatitis is controversial and not a first-line test.

On the other hand, contrast-enhanced CT has 87-90% sensitivity and 90-92% specificity in confirming the diagnosis of SAP.
the diagnosis of SAP in its early stages or for later assessing of complications such as, fluid collections, abscesses, pseudocysts, pseudoaneurysms of adjacent arteries, peripancreatic vein thrombosis and pancreatic necrosis (Fig 1, panels D and E). Diagnostic potential of magnetic resonance cholangiopancreatography (MRCP) is now almost as good as ERCP, with pancreatic MRI as the main imaging technique to investigate bilio-pancreatic pain, chronic pancreatitis, and cystic pancreatic tumors at many institutions.

**Clinical course**

It is critical to identify patients at high risk for severe disease, since they require close monitoring and prompt intervention. Recognized markers of the risk for severe acute pancreatitis include, but are not limited to: specific laboratory tests aimed at evaluating the systemic inflammatory response (i.e. C-reactive protein), scoring systems that assess inflammation or organ failure (i.e. Ranson’s score, sequential organ failure assessment (SOFA) score, etc.) and imaging abnormalities. It is imperative to identify the patients at risk within 24 hours of presentation. In a prospective study Juneja et al. had shown that SOFA score (Table 1) had a greater efficacy for predicting severity and 30-day mortality than the other scores employed by the authors [13]. The incidence of pulmonary complications is high in severe pancreatitis, ranging from 15 to 55% [14].

A number of biological parameters have been evaluated as prognostic markers in both laboratory and clinical settings. For instance: C-reactive protein (CRP) is readily available and rises with disease severity. Inflammatory mediators such as interleukin (IL)-8 and IL-6 show promise as early indicators of severe disease but await general availability and further clinical validation [15]. Several other markers of inflammation have been investigated in this regard, including serum procalcitonin, soluble IL-2 receptors, and soluble E-selectin [16], yet the clinical value of these prognostic markers requires further thorough investigation.

A growing body of evidence suggests that assays for trypsinogen activation peptide (TAP) may serve as a useful marker of disease severity [17, 18]. Recent reports of high sensitivity and specificity of elevated urinary TAP values in SAP [19, 20] are quite promising; similarly, a recent report focusing on plasma TAP levels suggested that SAP could be recognized with sensitivity and specificity of 70% and 78% [21, 22].

CT scan has upmost value in estimating the prognosis of disease. The severity of acute pancreatitis by the degree of changes is classified into five grades (0-4) on unenhanced CT scan, whereas the degree of pancreatic necrosis is measured by contrast-enhanced CT scan. The sum of these two scores is used to calculate the CT severity index for acute pancreatitis (Table 2) [17, 23]. There are no specific radiologic features that identify infection of pancreatic tissue except the rare presence of air bubbles within the necrotic pancreas on CT scan [24].

Pancreatic necrosis is the most devastating local complication of acute pancreatitis. Pancreatic necrosis is defined as areas of devitalized parenchyma and is usually associated with peripancreatic fat necrosis. Approximately 15% of cases of acute pancreatitis are necrotizing and the remaining 85% are interstitial. Diffuse or focal areas of non-viable parenchyma are initially sterile but may become infected by bacteria of gut intestinal origin. The condition is associated with late additional complications and death if the necrotic tissue becomes infected. The use of dynamic contrast-enhanced CT is perhaps most useful in its ability to

**Table 1. Sequential Organ Failure Assessment score (SOFA score)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tr>
<td>Respiration (PaO₂/FiO₂[mHg])</td>
<td>&gt; 400</td>
<td>≤ 400</td>
<td>≤ 300</td>
<td>≤ 200 with respiratory support</td>
<td>≤ 100 with respiratory support</td>
</tr>
<tr>
<td>Coagulation Platelets (x10^3/μL)</td>
<td>&gt; 150</td>
<td>≤ 150</td>
<td>≤ 100</td>
<td>≤ 50</td>
<td>≤ 20</td>
</tr>
<tr>
<td>Liver Bilirubin (mg/dL)</td>
<td>0-1.2</td>
<td>1.3-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt; 12.0</td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt; 70 mmHg</td>
<td>Dopamine ≤ 5, or Dobutamine (any dose)</td>
<td>Dopamine &gt; 5, or Epinephrine &lt; 0.1, or Norepinephrine &lt; 0.1</td>
<td>Dopamine &gt; 15 or Epinephrine &gt; 0.1 or Norepinephrine &gt; 0.1</td>
</tr>
<tr>
<td>Central nervous system Coma scale</td>
<td>15</td>
<td>14-13</td>
<td>12-10</td>
<td>9-6</td>
<td>6 and &gt;</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt; 110 (C)</td>
<td>111-170 (C)</td>
<td>171-299 (C)</td>
<td>300-440 (C) or &lt; 500 (UO)</td>
<td>&gt; 440 (C) or &lt; 200 (UO)</td>
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demonstrate pancreatic necrosis. CT diagnosis of pancreatic necrosis requires identification of distinct areas of non-enhanced pancreatic parenchyma being at least 3 cm in size or involving more than 33% of the pancreas [25] (Figure 1). Recent data support the use of MRI as an alternative: MRI and CT have been shown to have comparable sensitivity and specificity for SAP evaluation and diagnosis [26]. No data support the use of CT to diagnose necrosis or to predict severity within the first 24 hours, while sensitivity of pancreatic necrosis identification approaches 100%, four days after pancreatitis commenced [27]. Patients with clinical and biochemical features of acute pancreatitis who do not improve with conservative management must undergo an abdominal CT scan with oral and intravenous contrast.

Up to 57% of patients hospitalized with acute pancreatitis will have fluid collections. If those collections continue to enlarge they will cause pain, become infected (as suggested by the presence of not otherwise explained fever, leukocytosis, or gas) or compress adjacent organs. Fluid collections with very high levels of pancreatic enzymes are usually associated with pancreatic-duet disruptions and may eventually lead to pseudocyst formation (usually over a period of several weeks), ascites, or pleural effusions [28]. The natural course of pancreatic pseudocysts after acute pancreatitis and the reasons for their spontaneous

<table>
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<th>Table 2. CT severity index score</th>
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<td>Unenhanced CT scan</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Pancreatic Changes</td>
</tr>
<tr>
<td>Normal Pancreas</td>
</tr>
<tr>
<td>Pancreatic enlargement</td>
</tr>
<tr>
<td>Pancreatic and peripancreatic changes</td>
</tr>
<tr>
<td>Single fluid collection</td>
</tr>
<tr>
<td>Two or more fluid collections</td>
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CT scan based severity index for acute pancreatitis. Accumulated score > 7 predicts high morbidity and mortality.

Fig. 1. 64 year old male with abdominal pain. Axial and coronal Contrast Enhanced CT images demonstrate diffusely decreased density of the pancreatic gland with spearing of pancreatic head representing subtotal pancreatic necrosis (panels A and C, arrowheads). Common manifestations of acute pancreatitis such as extensive retroperitoneal and mesenteric fat stranding (panels B and C, white arrows) and anteriorly located ilegmonous collection (panel B, asterisk) are prominent in this case. Evolution of pancreatitis. 55 years old male has presented originally with acute pancreatitis with relatively minimal radiological changes: fat stranding in the peripancreatic fat limited to body and tail of the pancreas (panels D, white arrows). Clinical deterioration was followed by subsequent imaging that has shown pancreatic pseudocyst in the distal pancreas (panel E, white arrows), as well as additional adjacent pseudocyst in the anterior abdomen posterior to the stomach (panel E, arrowheads). Free ascites and subcutaneous fat stranding (panel E, white asterisk) are noted.
resolution remain unknown. In his prospective study of 369 patients Lankisch investigated the prognostic factors for development of pancreatic pseudocysts and for their spontaneous resolution after a first episode of acute pancreatitis [29]. Follow-up examination 3 and 6 months after discharge, showed pancreatic pseudocysts in 36 (10%) patients (30 with and 6 without prior fluid collection), and in 27 (7%) patients (25 with and 2 without pancreatic pseudocyst after 3 months), respectively. The prognostic factors for their development were alcohol abuse and an initial severe course of the disease. Spontaneous complete resolution of the pancreatic pseudocysts occurred in 11 (31%) of the 36 patients. Prognostic factors for the spontaneous resolution were no or mild symptoms (nausea, vomiting, abdominal pain) and a maximal cyst diameter of < 4 cm [29].

**Pancreatic infection**

Infection of necrotic pancreas tissue must be suspected in case of unexplained fever, leukocytosis, and a lack of patient’s condition improvement or unexpected deterioration – usually after the first week of illness. Pancreatic infection occurs typically in the setting of pancreatic necrosis and, rarely, in association with extrapancreatic fluid collections and/or pancreatic pseudocysts. Mortality in infected necrosis is nearly 25%. Approximately 50% of patients who have necrotizing pancreatitis develop organ failure, compared with less than 10% of patients who have purely interstitial pancreatitis [30].

**Diagnosis of infected pancreatic necrosis**

Unfortunately there are no reliable clinical parameters capable of distinguishing between sterile and infected pancreatic necrosis. Clinical markers of systemic inflammation are usually present in infected necrosis, but may as well be present in patients with severe sterile necrosis [31]. Elevated procalcitonin levels seem to be promising as a marker for infection in necrotizing pancreatitis, with several small studies reporting 75% to 94% sensitivity and 83% to 91% specificity [32, 33].

The ability to use image-guided percutaneous aspiration to diagnose infection in patients with pancreatic necrosis has therefore been a major advance (Figure 2). Positive cultures obtained by fine needle aspiration (FNA) are the gold standard for confirming infection in necrotic pancreas. More specifically, CT-guided fine needle aspiration has been reported to have a sensitivity and specificity for diagnosis that exceed 95% [34], while ultrasound guidance achieves a sensitivity and specificity of 88% and 90%, respectively [35]. Samples have to be evaluated for aerobic, anaerobic, and fungal growth. The interval from initial presentation to the development of pancreatic infection can take up

![Diagram of Pancreatic Necrosis Diagnosis and Treatment Work-flow](image)

Fig. 2. Pancreatic necrosis diagnosis and treatment work-flow
to 3 weeks. For this reason, repeated CT-guided aspirations may often be necessary [36]. Even if the patient continues with clinical picture of sepsis/SIRS the intervention is usually delayed until after the first 7 to 10 days of illness and there are two reasons for that. Approximately one half of pancreatic infections are documented during the second and third week of illness. A second reason is that during the initial 7 to 10 days of acute pancreatitis, fever, leukocytosis, and organ failure are caused by a severe inflammatory response and cytokine release.

Microbiology of pancreatic infection

Gut-derived gram-negative bacteria, including *Escherichia coli*, *Klebsiella*, and *Pseudomonas*, are the most common pathogens identified in pancreatic infections. Gram-positive organisms, including *Staphylococcus aureus* and *S. enterococcus* species, are also found at infected pancreatic necrosis sites. Resistant gram-positive cocci, along with fungi, are an increasing concern in patients who are exposed to broad-spectrum antibiotics [37, 38].

Management of SAP

Besides specific treatment (mostly for gallstone-induced pancreatitis), the early therapeutic strategies are identical in all patients with acute pancreatitis.

**a. Medical treatment options**

An algorithm for the diagnosis and management of acute pancreatitis is suggested in Figure 3. The cornerstone of initial management is aggressive extracellular fluid (ECF) volume expansion to replenish the often massive third-space losses. Inadequate fluid resuscitation not only predisposes to systemic complications, particularly acute kidney injury, but also has recently been shown to pose a significant risk for further pancreatic injury [39].

Determination of cause of pancreatitis is of paramount importance for guiding immediate management and preventing recurrence.

Persistent biliary obstruction worsens the outcome and increases the severity of acute pancreatitis and predisposes the patient to bacterial cholangitis. When
the diagnosis of biliary pancreatitis is established, endoscopic retrograde cholangiopancreatography (ERCP) must be immediately performed combined with endoscopic sphincterotomy in order to extract impacted gallstones and drain infected bile. If suspicion of gallstone pancreatitis remains high despite a normal percutaneous ultrasonography or CT scan, endoscopic US must be performed, as a gold standard diagnostic procedure for bile duct stones. Although early ERCP is not routinely recommended in relatively mild pancreatitis cases, its importance in acute biliary pancreatitis with biliary obstruction or cholangitis is undisputed. More controversial is the utilization of early ERCP and papillotomy in acute biliary pancreatitis without obstruction. Both Neoptolemos et al. [40] and Fan et al. [41] demonstrated a significant reduction in morbidity with trend towards lower mortality when patients with acute pancreatitis underwent “early” ERCP. On the other hand, a recent multicenter randomized trial by Fölsch et al. [42], designed to exclude patients with proven biliary sepsis or obstruction, demonstrated increased complications and mortality in the ERCP group. Therefore, it was suggested that early ERCP might be harmful in the absence of ongoing obstruction and there is insufficient evidence to recommend ERCP in acute biliary pancreatitis in the absence of biliary obstruction or infection. Recent advances in diagnostic radiology suggest that MRCP is a valid diagnostic alternative.

SIRS that causes organ failure in SAP is similar to that caused by severe sepsis, because of that the use of recombinant human activated protein C (rhAPC) in the management of SAP has been investigated in experimental and clinical studies. The experimental evidence of disease amelioration in SAP following intervention with rhAPC has not been revealed in the small clinical trials [43].

Nutritional support in SAP patients

Clinical and experimental studies show that bowel rest is strongly associated with intestinal mucosal atrophy leading to infectious complications as a result of bacterial translocation from the gut. In recent years, increasing evidence suggests that enteral nutrition (EN) may be feasible and safe even in cases of severe pancreatitis [44]. Enteral nutrition helps to avoid alterations in intestinal barrier function observed with total parenteral nutrition (TPN) [45], additionally avoiding the cost of and catheter-related complications associated with TPN and should be implemented sooner than later after adequate fluid resuscitation. Moreover, TPN is known to be associated with enhanced proinflammatory response. Although mortality rate is not substantially different in patients treated with parenteral or enteral nutrition, the incidence of infections [46, 47], surgical interventions [47], and non-infectious complications [47] is clearly reduced in the enteral nutrition treatment group. However, TPN should still be reserved for patients who cannot obtain sufficient caloric intake via enteral nutrition or in whom enteral access cannot be maintained [48].

The type of EN (gastric vs. jejunal) is also a matter of ongoing debate [49]. Recently published studies show no significant clinical difference between early nasogastric and nasojejunal feeding [46, 50, 51]. In relation to formulations, polymeric as compared with elemental or semielemental did not increase the risk of infections, feeding intolerance, or mortality in acute pancreatitis [52].

However, noncompliance in adhering to guidelines was documented in Davies’s study and is a revelation that guidelines and actual practice defer in many situations. Nutrition in SAP has been discussed and researched over the years and still there is dominance of what treating doctors think rather than follow protocols and evidence [53].

Selective digestive tract decontamination

Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are infection-prevention measures used in the treatment of some patients in intensive care, but reported effects on patient outcome are conflicting [54]. Breakdown of enteral barrier integrity, systemic and local immunosuppression and bacterial overgrowth due to the decrease in intestinal motility are postulated as important factors in the mechanism of bacterial translocation (BT) in SAP [55] providing rationale for SDD. Topical oropharyngeally administered non-absorbed antimicrobials (i.e. polymyxin B, tobramycin or amphotericin B) cover a wide range of gram-negative and fungal infections and is combined for the first 3-4 days, with a broad-spectrum systemic antibiotic, (i.e. cefotaxime). Bowel treatment to prevent infectious complications has attracted interest, and SDD and EN therapies have been introduced in patients with SAP. De Jonge and colleagues assessed the effects of SDD in an intensive care population [56] showing substantial reduction in mortality (24 % vs. 31%) and a shorter length of ICU stay (6.8 vs. 8.5 days) in patients treated with SDD. It did not increase bacterial resistance on follow-up of more than 2 years. Luiten et al. [57] randomized patients with SAP to oral and rectal administration of non-absorbable antibiotics. Mortality was decreased in the selective decontamination group, predominantly due to late mortality reduction and decrease in gram-negative pancreatic infection.

Since the effect of SDD in avoiding the breakdown of intestinal integrity is uncertain, the adoption of definitive recommendations regarding the use of gut decontamination in SAP requires further investigation.
Antibiotic treatment

Infection of necrotic pancreas generally involves aerobic and anaerobic bacteria of GI origin, and may be mono- or polymicrobial.

The benefit of antibiotic prophylaxis is seriously debated. Since pancreatic infection is the leading cause of morbidity and mortality in SAP, early prevention of infected necrosis seems to be reasonable treatment option. Unfortunately, prospective and randomized trials as well as meta-analyses showed at best, only weak benefit. In some cases the treatment might be even disadvantageous due to the risk of bacterial resistance and fungal superinfection development [58]. A recent meta-analysis of randomized controlled trials concludes that prophylactic antibiotics do not prevent infections in patients with pancreatic necrosis nor they decrease mortality [59]. When infection is suspected and fine-needle aspiration of the pancreas for bacteriology is performed, the accepted treatment is to start with antibiotics, usually with intravenous imipenem or meropenem, a treatment continued for 14 days [60]. This treatment is rapidly stopped if infection is not confirmed. However, given the availability of other agents with adequate pancreatic tissue penetration, there is no sufficient evidence to support the use of intravenous carbapenems as a first-line treatment [61]. Consequently, carbapenems should be reserved for pancreatic infections proven to be secondary to multi-resistant organisms [61].

Treatment of microbiologically confirmed pancreatic infection is guided by the results of culture and sensitivity. Fluoroquinolones and carbapenems provide excellent gram-negative coverage and achieve adequate tissue concentration in the pancreas, compared to ampicillin and gentamicin [62, 63]. Since the prevalence of gram-positive organisms seems to be increasing, with *S enterococcus* and *S aureus* accounting for 30% of isolates in at least one recent review paper [64], appropriate coverage which will include these organisms taking into consideration the possibility of resistant strains, is strongly advised.

b. Surgical treatment options

Although recent years have brought increasingly conservative trends in the management of sterile pancreatic necrosis, infection remains an absolute indication for intervention [65].

In the majority of patients with acute pancreatitis, the process is limited to parenchymal edema without necrosis. In these patients, surgical therapy is largely limited to the delayed treatment of local complications, such as pseudocysts, and to the use of cholecystectomy to prevent recurrent episodes. In 10% and 30% of patients, a progress to severe illness is observed, including pancreatic and peripancreatic necrosis, and systemic inflammatory response syndrome (SIRS). This latter group of patients may require debridement or other surgical interventions during the acute phase of the disease.

While some authors believe that patients with severe disease benefit from debridement regardless of the status of infection [66], others, recently adopted a more conservative surgical approach in patients with sterile necrosis [67]. Büchler et al. [68] followed 86 conservatively treated necrotizing pancreatitis patients and reported a surprisingly low mortality rate of 10% and the need for operation in the absence of documented infection in only one patient. Non-randomized series suggest better outcomes with delayed versus early debridement, when “organized pancreatic necrosis” – a process of maturation of the inflammatory tissue with clear demarcation from healthy pancreatic and peri-pancreatic tissue has already occurred.

Patients with infected pancreatic necrosis account for the majority of the deaths from acute pancreatitis, and the absolute need for debridement is widely accepted, since mortality in these cases without debridement is virtually 100%. The correct timing of debridement has not been established [69]. Some authors intervene within 24 h of the diagnosis, irrespective of the patient’s clinical condition. Others postpone intervention, allowing the areas of necrosis to organize and demarcate, even in the presence of organ failure, since organ failure can frequently be stabilized by conservative, intensive care therapy [69]. A delay in surgical debridement may allow encapsulation of the necrotic tissue as organized necrosis which can be removed more easily and safely sometimes via less invasive laparoscopic or endoscopic approaches.

The three major technical drainage approaches include open transabdominal debridement followed by drainage placement and closure (closed suction or Penrose drains), open transabdominal debridement with placement of several soft drains in the retroperitoneum for continuous lavage, or open transabdominal debridement with open packing and planned re-exploration. If debridement is thought to be inadequate, postoperative closed, high-volume lavage via large drains in the lesser sac has been described with some success in avoiding residua of necrotic tissue [70, 71].

Recently, minimally invasive approaches to the treatment of infected peripancreatic and/or pancreatic necrosis such as percutaneous endoscopic and laparoscopic techniques have been described [72-75]. Minimally invasive retroperitoneal necrosectomy uses percutaneous insertion of an operating nephroscope to access the area of pancreatic necrosis, followed by debridement, and irrigation, and the placement of drains for continuous retroperitoneal lavage [76].
In a meta-analysis published by Heinrich et al. [46] it was concluded that single necrosectomy and continuous postoperative lavage (CPL) with large-bore surgical drains without planned re-laparotomies is the preferred strategy for surgical treatment of infected (peri-) pancreatic necrosis.

This strategy is also supported by a recent national Dutch survey demonstrating that single necrosectomy and CPL results in lower (25%) mortality (13/53 patients) [77].

Patients with infected necrosis and organ failure and/or significant comorbidity may benefit from radiologically guided placement of percutaneous drainage (PCD) catheters. The goal of percutaneous catheter placement before the organized necrosis stage is to drain necrotic material as a temporary measure. In some cases, percutaneous catheter drainage of organized infected necrosis may be ineffective owing to the inability to eliminate semisolid materials. The results of Z. Tong’s study show that the mean computed tomographic density and distribution range of infective pancreatic necrosis could significantly influence the success rate of PCD. Higher values indicate them less appropriate for PCD; and because of that it should be considered seriously before the treatment decision [78].

Endoscopic necrosectomy is another emerging therapeutic avenue. Unlike surgical and percutaneous approaches that can be used before or after organized necrosis formation, endoscopic therapy is usually reserved for the treatment of organized necrosis only. Endoscopic ultrasonography is used to guide the site of puncture through the gastric or duodenal wall, to avoid injury to the blood vessels and to enter the cystic structure accurately. Multiple pigtail catheters are inserted to create a drainage pathway from the cyst to the stomach or duodenum. Endoscopic therapy has the advantage of being less invasive than surgery, but it requires considerable expertise. The main limitation of the endoscopic treatment is the difficulty to achieve a complete evacuation of the necrotic tissue, with the possible persistence of infection within the cavity.

c. Imaging guided approach to treatment of complications of pancreatitis

The most frequent complications treated by percutaneous image guided procedures are pancreatic pseudocyst and pancreatic abscess, followed by embolisation of pseudoaneurysms and debridement of liquefied necrosis.

Pancreatic pseudocyst would require drainage if more than 5 cm at time of diagnosis, enlarging over time, painful, infected or causing local mass effect exempli gratia biliary obstruction. Transperitoneal approach with utilization of CT guidance is most commonly used. Alternatively, transgastric approach can be used, especially when pseudocyst is communicating with the pancreatic duct. Presence of such a communication would require prolong drainage up to 6-8 weeks, but the duration can be decreased with the use of somatostatin analog octreotide. The success rate of percutaneous drainage currently stands at approximately 90%.

Pancreatic abscess drainage by percutaneous approach is overall challenging given its generally multilocular nature and extremely viscous content, thus large bore catheters (14 to 26 French) are preferred. CT guided procedure is the common approach since the ileus associated with the condition in most cases renders US imaging unsuitable.

Pseudoaneurysms of peripancreatic arteries is a well recognized late complication of SAP being a result of erosion by pancreatic enzymes. The most commonly affected arteries are: splenic artery, gastroduodenal artery, and arteries comprising pancreaticoduodenal arcades. Rapture of a pseudoaneurysm is life threatening event and carries a mortality rate of approximately 37%. Percutaneous intervention in a form of embolization can serve as a temporary (till surgery) or permanent solution.

Complications of severe acute pancreatitis

Elevated intra-abdominal pressure (IAP) with progression to abdominal compartment syndrome (ACS) has been described in a wide variety of clinical conditions [79, 80] including SAP [81]. Intra-abdominal hypertension (IAH) may develop due to pancreatic and retroperitoneal inflammation, paralytic ileus and peripancreatic fluid collections with third-space loss. De Waele et al. [82] had shown a 51% frequency of IAH in a group of 44 patients with SAP. This prompts earlier, more aggressive monitoring of IAP to facilitate the institution of corrective/preventive measures before full-blown ACS develops. Percutaneous drainage of fluid collections represent a less invasive abdominal decompression option [83], while the definitive treatment for fully manifested ACS is surgical decompression via laparotomy [84, 85].

Conclusions

The majority of patients admitted with acute pancreatitis have a benign course, however approximately 20% will develop SAP with significantly increased mortality. Supportive care, including fluid management, analgesia, and nutritional support, ideally via the enteral route remains the cornerstone of therapy. Repeated clinical, radiological and biochemical assessment is
essential for the timely diagnosis of pancreatic necrosis and infection. Patients with confirmed pancreatic necrosis should receive prophylactic antibiotics. For biliary pancreatitis, early ERCP should be performed and infected pancreatic necrosis should be evacuated.

Although the overall incidence of acute pancreatitis is rising, recent data suggest that the mortality associated with SAP is falling. Large scale trials could help to further elucidate the pathophysiology and management of SAP and further lead to improvements in outcome.

**Conflict of interest**

Nothing to declare

**References**

New developments in understanding of pathophysiology, diagnosis and treatment of severe acute pancreatitis


Progrese în descifrarea fiziopatologiei, diagnosticului și tratamentului pancreatitei acute severe

Rezumat
Pancretita acută severă rămâne o provocare clinică, întrucât creează o mare responsabilitate în privința relației dintre morbiditate, mortalitate și costuri impuse de starea pacientului. În general, pancreatita acută poate varia în severitate, de la o inflamație pancreatică ușoară, auto-limitantă, la necroza pancreatică cu risc vital. La adulți, cele mai frecvente cauze ale pancreatitei sunt litiaza biliară și abuzul de alcool. Interesul în creștere pentru noi markeri biologici și posibilitățile de identificare în timp util a pancreatitei acute severe subliniază importanța clinică a predicii precoce a severității bolii. Dintre acești markeri, IL-6, IL-10, procalcitonina, peptida activatoare a tripsinogenu sunt cel mai utilizate în practica clinică. Deși toate scorurile prezic cu o mare acuratețe severitatea și evoluția pancreatitei, scorul SOFA este utilizat cel mai frecvent. Tratamentul pancreatitei ușoare este mai ales de susținere, în timp ce episoadele severe necesită ca tratamentul să fie efectuat de o echipă multidisciplinară care să includă gastroenterologi, radiologi intervenționali, specialiști în terapie intensivă și chirurgi. Scopul acestei prezente este de a trece în revistă progresele recente în domeniul fiziopatologiei, diagnosticului și tratamentului pancreatitei acute severe.

Cuvinte cheie: pancreatită acută severă, fiziopatologie, diagnostic, tratament