Pancreas (C Forsmark, Section Editor)

Management of Severe Acute Pancreatitis

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Abstract

Purpose of review There have been significant advancements in different aspects of management of severe acute pancreatitis (SAP). Our review of the most recent literature focuses on severity prediction, fluid resuscitation, analgesic administration, nutrition, and endoscopic intervention for SAP and its extra-pancreatic complications.
Recent findings Recent studies on serum cytokines for the prediction of SAP have shown superior prognostic performance when compared with conventional laboratory tests and clinical scoring systems. In patients with established SAP and vascular leak syndrome, intravenous fluids should be administered with caution to prevent intra-abdominal hypertension and volume overload. Endoscopic retrograde cholangiopancreatography improves outcomes only in AP patients with suspected cholangitis. Early enteral tube-feeding does not appear to be superior to on-demand oral feeding. Abdominal compartment syndrome is a highly lethal complication of SAP that requires percutaneous drainage or decompressive laparotomy. Endoscopic transmural drainage followed by necrosectomy (i.e., "step-up approach") is the treatment strategy of choice in patients with symptomatic or infected walled-off pancreatic necrosis.
Summary SAP is a complex clinical syndrome associated with a high mortality rate. Early prediction of SAP remains challenging due to the limited accuracy of the available prediction tools. Early fluid resuscitation, organ support, enteral nutrition, and prevention of/or prompt recognition of abdominal compartment syndrome remain cornerstones of its management. A step-up, minimally invasive drainage/debridement is the preferred approach for patients with infected pancreatic necrosis.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease that results from pancreatic injury via various mechanisms [1••]. Its incidence is increasing worldwide, and it continues to be among the top causes of GI-related hospitalizations in the USA [2]. Several key pathophysiologic mechanisms of organ injury in AP have been recently identified [1••]. These include intra- and peripancreatic fat lipolysis, exaggerated immune response, and microvascular dysfunction leading to vascular leak syndrome [1••]. AP- and ischemia-conditioned mesenteric lymph is being explored as another potential mediator of severe acute pancreatitis (SAP) [3–6]. Approximately half of all AP patients develop a systemic inflammatory response, which can then progress to organ failure and even death [7, 8]. Two major determinants of morbidity and mortality include pancreatic necrosis and presence of end-organ injury, respectively [9]. SAP, defined by presence of persisting organ failure [9, 10•], represents a relatively small subgroup of all AP patients (10–20%), in whom the risk of death is particularly high. The majority of mortality occurs within the first 2 weeks of presentation, making early prediction an important part of management of SAP [11•]. Pancreatic necrosis often accompanies end-organ failure; however, development of pancreatic necrosis *in the absence of* organ failure does not lead to increased mortality [12].

Early prediction of SAP continues to be limited by lack of accurate prognostic tools [13]. Measurement of serum cytokines such as IL-6, IL-8, angiopoietin-2, and resistin appears to predict SAP more accurately than laboratory tests and clinical scoring systems, but head-to-head comparison studies are lacking and cytokine measurements are not available in clinical practice [14–16]. Recently there have been several advancements in defining the timing and type of endoscopic therapy in AP patients with infected walled-off pancreatic necrosis and the role of endoscopic biliary decompression in biliary AP [17••]. There continues to be paucity of data on the optimal strategies for intravenous fluid resuscitation, administration of analgesia, and management of intra-abdominal hypertension. This review will summarize the most recent literature covering the above aspects of SAP management.

Definition

What constitutes SAP had been a subject of debate until recently [10•]. In the past, presence of acute fluid collections, and necrosis independently qualified subjects as having severe pancreatitis until a new definition of severe pancreatitis was proposed by the Revised Atlanta Classification experts [9]. The distinguishing feature of SAP from mild and moderately severe pancreatitis is presence of persistent organ failure (organ failure persisting for 48 h or longer; see Table 1). Recent data indicates that in the absence of organ failure, prognosis of AP patients is favorable even in the presence of necrosis and fluid collections [18]. Before the advent of minimally invasive drainage techniques, patients with infected pancreatic necrosis carried a significant mortality even in the absence of persistent organ failure [19], but its prognosis has improved largely in the recent years [11•, 17••]. Therefore, while infected walled-off pancreatic necrosis is an indication for intervention, it is not classified as SAP by the Revised Atlanta Classification.

Pathophysiology

Pathogenesis of organ failure in AP is still not clearly delineated [6]. However, several hypothesized mechanisms have recently been developed:

Table 1. Revised Atlanta Classification

	Mild	Moderately severe	Severe
Determinants	No acute fluid or necrotic collections, No exacerbation of a comorbid condition, No organ failure	Transient organ failure (organ failure lasting 24 hours or less) and/or Presence of fluid or necrotic collection and/or Exacerbation of a comorbid condition	Presence of persistent organ failure*
	Type of local complication	<4 weeks	>/= 4 weeks
Local complications	Fluid collection without necrosis	Acute fluid collection	Pseudocyst
	Fluid collection with necrosis	Acute necrotic collection	Walled off pancreatic necrosis

*Organ failure is defined according to the Modified Marshall Scoring System [9]

Adipose tissue lipolysis

Obesity has long been identified as a risk factor for SAP [20]. Recent evidence from animal models has suggested that unsaturated free fatty acids produced from peri- and intra-pancreatic parenchymal fat upon lipase mediated lipolysis, are toxic and lead to mitochondrial dysfunction in end-organs [5, 21, 22•]. This hypothesis is supported by clinical studies showing that increased visceral adiposity is associated with higher risk of organ failure [23]. In contrast, pancreatic parenchymal fibrosis, which limits the lipolytic flux, appears to protect against SAP [24].

Severe innate immune response

Exaggerated immune response to local parenchymal injury has long been observed to precede organ dysfunction in AP. For example, pro-inflammatory cytokines are markedly elevated early in the disease course. These include interleukin 6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1), and TNF-α [6]. Based on the above findings, a randomized controlled trial (RCT) was recently initiated assessing a TNF-α inhibitor as a potential treatment option in AP (NCT03684278). Supporting the central role of exaggerating innate immune response in mediating SAP, a recently completed RCT showed that administration of COX-2 inhibitors in AP subjects reduced the incidence of SAP by an absolute difference of 19% compared to placebo [25]. Additionally, disease-associated molecular patterns (DAMPs) have been found to be elevated in AP and their levels appear to predict SAP. DAMPs are intra-cellular contents that are released upon cell death and can cause a potent immune response [26]. This suggests the amount of DAMPs released may also have a key role in exaggerated innate immune response.

Microvasculature dysfunction

Systemic microvascular dysfunction is one of the pathways leading to SAP. Vascular leak results in marked third space fluid sequestration and may lead

to abdominal compartment syndrome similar to other critical illnesses [27]. Endothelial integrity, maintained by the Tie2 pathway under physiologic conditions, is markedly downregulated in SAP and sepsis [28]. Angiopoietin-2 is a paracrine peptide that destabilizes endothelial cells and increases vascular permeability via inhibition of the Tie2 pathway. Angiopoietin-2 levels are increased in patients with SAP and predict SAP with high accuracy [14, 29]. Nonetheless, a therapeutic agent targeting microvascular dysfunction has not yet been tested in AP; such mechanistic studies are underway for sepsis models [30].

Mesenteric lymph

There is preliminary evidence supporting that ischemia-conditioned and AP-conditioned mesenteric lymph mediates cardiac dysfunction. In a recent animal study in rats, cardiac output, contractility, and relaxability decreased significantly upon infusion of mesenteric lymph conditioned by AP into rats [31•]. Cardiac dysfunction could then be reversed upon external drainage and thoracic duct ligation [31•]. Specific mediators of organ dysfunction in the mesenteric lymph have not yet been elucidated. Ongoing studies are evaluating the impact of thoracic duct diversion in other disease models, such as sepsis. This is a novel research area in the field of SAP; once the mechanism is delineated, it will have a potential impact in the management of SAP.

Management

Severity prediction

The majority of organ dysfunction in AP occurs within the first week of presentation and its development can be rapid [11•]. For appropriate assignment of care, organ support, and future therapeutic studies, prediction of SAP has been a major focus of many studies [32, 33]. Over a dozen laboratory tests and clinical scoring systems have been proposed; however, their predictive accuracies have only been suboptimal for meaningful clinical application [13, 32, 34]. Serum cytokine measurements and machine learning may lead to developing tools with higher predictive accuracies [35–37]. Promising cytokines as candidates for accurate prediction of SAP include angiopoietin-2, resistin, and interleukin-6 [36–38] (Table 2). With the development of point of care assays for interleukin-6, its integration for use in SAP may be possible in the near future [38]. However, further studies are needed to explore the optimal cytokine utility for AP prediction in clinical practice.

Most widely used, routinely available laboratory tests and clinical scores include hematocrit, BUN, systemic inflammatory response syndrome (SIRS), and Bedside Index of Severity of Acute Pancreatitis (BISAP) [39, 40]. Hemoconcentration, BUN elevation greater than 20 mg/dL with an upward trend, SIRS score of 2 or more, and BISAP score of 3 or more are all validated predictors of AP severity, but with only modest sensitivity and specificity [13]. Our clinical practice is to calculate the SIRS score daily, which is easy to measure requiring only vital signs and white blood cell count; the score ranges from 0 to 4. We closely monitor SIRS positive patients, especially with a score of 3 or 4, for signs of organ failure.

Table 2. List of cytokines and their accuracy in predicting severe pancreatitis or mortality

Name of cytokine	Function	AUC
Interleukin-1β (IL-1β)	Pro-inflammatory cytokine: stimulates macrophages, causes lymphocyte maturation; induces acute phase protein production; facilitates leukocyte trafficking	74–82%
Interleukin-6 (IL-6)	Pro-inflammatory cytokine: regulates T lymphocyte activation and differentiation; induces acute phase protein production; facilitates neutrophil trafficking	75–88%
Interleukein-8 (IL-8)	Pro-inflammatory cytokine with function similar to IL-6	73–76%
Tumor Necrosis Factor-α (TNF-α)	Pro-inflammatory cytokine: induces acute phase protein production; activates neutrophils and macrophages	81%
Angiopoeitin-2	Autocrine peptide regulator of vascular permeability	74–81%
Resistin	Adipokine: induces production of IL-1β, IL-6, and TNF-α	76–80%
Visfatin	Adipokine: induces production of IL-1β, IL-6, and TNF-α	74%
Monocyte chemotactic protein-1 (MCP-1)	Chemokine secreted early in the disease course; induces recruitment of monocytes, lymphocytes, mast cells, and eosinophils	88%

TNF-α, Tumor Necrosis Factor-α; AUC, area under the curve
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Fluid resuscitation

Aggressive fluid resuscitation for prevention of necrotizing and severe pancreatitis has long been regarded as the cornerstone of early management of AP [41], but controversy persists in matters of the type, rate, and duration of fluid administration [42]. There has been promising evidence to support the role of early aggressive fluid resuscitation with Lactated Ringers in mild AP [43]; however, in subjects with predicted SAP, prolonged aggressive volume administration may be harmful [44]. Specifically, in SAP patients with systemic vascular leak syndrome, aggressive fluid resuscitation may increase third-spacing and intra-abdominal pressure, which can lead to the development of abdominal compartment syndrome and respiratory failure [44–46]. Thus, after initiation of fluid therapy, endpoints such as urine output, mean arterial pressure, oxygen saturation with respiratory rate, and intra-abdominal pressure should be closely monitored early in the disease course. Persistent aggressive fluid administration should be avoided if these endpoints suggest impending volume overload (i.e., decreasing saturation with tachypnea and increasing intra-abdominal pressure) without improvement in end-organ perfusion (i.e., persistent low urine output and/or hypotension).

Experts advocate to assess patients' fluid responsiveness before administering fluid therapy and then monitor intra-abdominal pressure [47]. The fluid resuscitation strategy should be goal-directed and determined by patient's fluid responsiveness, time elapsed since disease onset (benefits of aggressive fluid resuscitation may be marginal beyond 24 h after onset of disease [48, 49]), and patient's propensity for fluid sequestration and risk for abdominal compartment syndrome. Our clinical practice is to initiate early fluid resuscitation as soon as the AP diagnosis is established in the Emergency Department by

administering 1–2 L of Lactated Ringers bolus. Subsequently, we recommend administration of Lactated Ringers at a rate of 3 cc/kg/h (~ 200 cc/h for a 70-kg patient) and reassess patient's fluid responsiveness at 12 and 24 h.

Enteral nutrition

The gut barrier dysfunction is a common and well-recognized phenomenon in SAP [50]. Enteral feeding has a clear benefit in reducing morbidity and mortality over parenteral nutrition [51]. However, it is controversial whether early nutrition through a nasoenteric feeding tube is better than "on-demand" oral feeding. In a large RCT in predicted severe pancreatitis patients, early enteral tube-feeding did not appear to confer significant morbidity or mortality benefit [52••]. In patients with established SAP, however, there is insufficient evidence for or against early enteral feeding [53]. Additionally, the comparative effectiveness of the route of enteral nutrition and specifically nasogastric versus nasojejunal feeding needs to be investigated further [54]. Based on the available evidence, we recommend offering an oral diet (a low fat solid diet) and assessing patients' tolerance. In intubated patients, enteral feeding should be pursued with a nasogastric feeding tube unless there is evidence of gastric outlet obstruction from peri/pancreatic edema and fluid, in which case endoscopic placement of nasojejunal feeding tube can be pursued. In most tertiary care centers, there are non-invasive tools that guide enteral tube placement into the post-pyloric location. Where this tool is available, nasoduodenal tube placement is also acceptable.

Pain management

Pain in subjects with SAP is typically managed with opioids in the USA; however, there are significant geographical variations in AP pain management worldwide, which highlights the need for additional evidence in this domain [55]. In animals with AP, morphine worsens the severity of AP and inhibits pancreatic regeneration [56•]; also codeine, a different opioid, has been implicated as a risk factor for AP among patients who undergo cholecystectomy [57]. Postulated mechanisms include increased bacterial translocation due to intestinal dysmotility, increased sphincter of Oddi pressure, and delay in regenerative immune response [56•]. Nevertheless, these hypotheses have not been tested in clinical studies.

Non-steroidal anti-inflammatory drugs (NSAIDs), such as COX-2 inhibitors, have recently shown encouraging results in prevention of SAP. However, due to their propensity for nephrotoxicity, they may not be a feasible option in patients with established SAP, many of whom are in renal failure [25]. Recognizing this limitation, researchers have investigated the benefit of administering epidural analgesia containing non-opioid agents. In patients with SAP requiring intensive care unit, there is early evidence for mortality benefit [58•]. A randomized clinical trial is underway to investigate the benefits of thoracic epidural analgesia in AP patients requiring intensive care unit admission [59]. In our clinical practice, opioids remain the most effective short-term analgesic agents for alleviation of pain in SAP; however, they should be administered judiciously, especially in the presence of ileus.

Role of ERCP in biliary pancreatitis

Patients with predicted SAP resulting from gallstones commonly develop abnormal liver function tests and jaundice, due to the extensive pancreatic head edema that causes obstruction at the intrapancreatic portion of the common bile duct and/or co-existing choledocholithiasis. In this subgroup of patients, biliary decompression with biliary sphincterotomy had been postulated to confer morbidity and mortality benefits. However, in a recent randomized clinical trial, early decompression of the bile duct in this population did not reduce the composite endpoint of mortality or major complications within 6 months [60]. As such, our clinical practice is to reserve ERCP for AP patients of biliary etiology with evidence of choledocholithiasis on imaging or clinical suspicion of cholangitis with prompt biliary drainage within 24 to 48 h.

Intra-abdominal hypertension

Due to extensive intra-abdominal edema that occurs from fluid extravasation secondary to third-spacing and potential aggressive fluid resuscitation, intra-abdominal hypertension (IAH) is relatively common in SAP patients [61]. IAH is defined by intra-abdominal pressure higher than 12 mmHg and is a precursor to intra-abdominal compartment syndrome (ACS; > 20 mmHg), which carries a poor prognosis [62]. It is unclear whether IAH is an epiphenomenon or a distinct entity that requires prompt recognition and treatment. If ACS ensues, decompressive laparotomy should be considered urgently for prevention of worsening end-organ failure. Percutaneous drainage represents an alternative decompressive modality in ACS when feasible [45]. Further studies are needed to clarify the type and timing of decompressive techniques that can lower intra-abdominal pressure and their impact on morbidity and mortality in SAP. Our clinical practice is to measure intra-bladder pressures in AP patients in the ICU with respiratory failure when they develop increased ventilator requirements. When IAH is confirmed, we then proceed with cross-sectional imaging to assess for any drainable large pancreatic fluid collections.

Role of endoscopic cystenterostomy with/without necrosectomy

Necrotizing pancreatitis accompanies commonly SAP. In patients with SAP and coexisting acute necrotic collections or walled-off pancreatic necrosis, drainage with/without necrosectomy is indicated in several instances. The most rigorously studied population is those with infected walled-off pancreatic necrosis [17••]. In this population, drainage should be considered when the medical condition does not improve with maximum medical therapy. A "step-up" to minimally invasive necrosectomy should be considered in patients in whom drainage does not lead to a significant improvement with 72 h. We recommend percutaneous drainage as the modality of choice when the necrotic collection is less than 4 weeks old, whereas, for walled-off pancreatic necrosis (mature necrotic collections older than 4 weeks),transmural endoscopic drainage followed by necrosectomy appears to be superior to percutaneous drainage with video-assisted retroperitoneal debridement based on lower rates of pancreaticocutaneous fistula formation [63••]. In SAP patients with
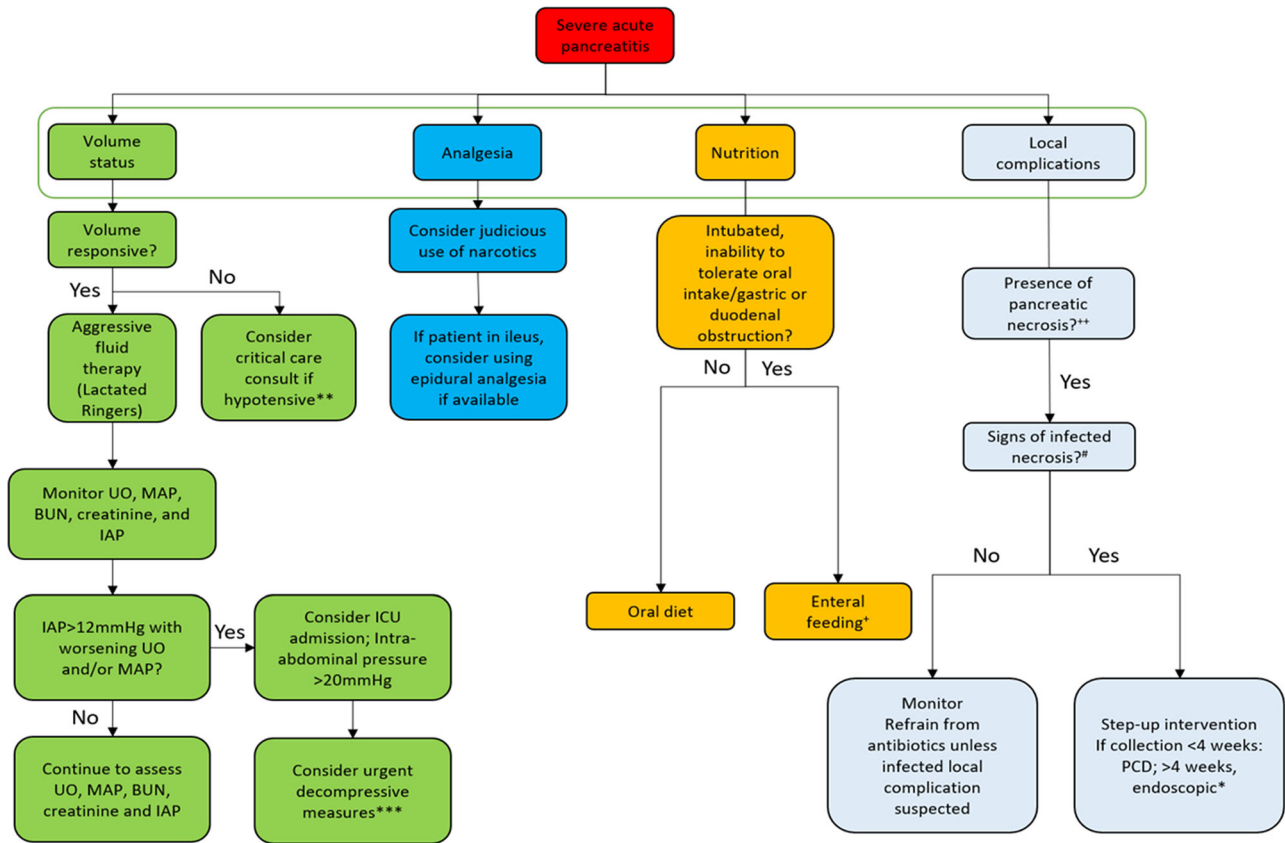
Fig. 1. Management algorithm of severe acute pancreatitis according to separate domains. UO, urine output; MAP, mean arterial pressure; BUN, blood urea nitrogen; IAP, intra-abdominal pressure; ICU, intensive care unit; PCD, percutaneous drainage. +Nasojejunal route in patients with gastric or duodenal obstruction; ++presence of necrosis is best established with a contrast-enhanced cross-sectional imaging; #signs of infected necrosis include gas within a necrotic collection, or worsening organ failure in a patient with necrotic collection despite maximum medical therapy in the intensive care unit, or new onset fevers in patients with established necrotic collection; *endoscopic step-up intervention: endoscopic ultrasound guided transmural drainage, followed by endoscopic necrosectomy if there is no clinical improvement in 72 h; **in hypotensive SAP patients who are not fluid responsive, intensive care unit admission needs to be considered to prevent volume overload; ***decompressive measures include decompressive laparotomy or percutaneous drain placement.

symptomatic, sterile necrotic collections, data on the optimal management strategy is sparse [40].

Conclusions

SAP is defined as AP complicated by persisting organ failure. It is a complex clinical syndrome, which is challenging to manage and carries a significant mortality. There have been significant advancements in understanding the underlying pathophysiology of SAP, including intra- and extra-pancreatic fat lipolysis, severe innate immune response, and microvascular dysfunction. However, therapeutic pharmaceutical targets have not yet been identified for

clinical trials, with the exception of TNF-α and COX-2 inhibition. Serum cytokine measurements appear promising for early accurate prediction of SAP, but they are not readily available in clinical practice. In addition to supportive therapy for end-organs, management strategies should address 4 main domains of SAP including (1) volume status: with fluid resuscitation guided by assessment of fluid responsiveness, intra-abdominal pressure, and markers of intravascular volume status; (2) analgesia with administration of non-steroidal anti-inflammatory drugs, opioids, or epidural analgesia in expert centers; (3) gut-barrier dysfunction: with nutritional support via on-demand oral or enteral feeding; and (4) infected necrotic collections: with minimally invasive drainage approaches and necrosectomy in a step-up manner (Fig. 1).

Compliance with ethical standards

Conflict of interest
Peter J. Lee declares that he has no conflict of interest. Georgios I. Papachristou declares that he has no conflict of interest.

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