Organ Failure and Prediction of Severity in Acute Pancreatitis

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KEYWORDS

• Acute pancreatitis • Organ failure • Predicted severe pancreatitis
• Systemic inflammation • Interleukin-6

KEY POINTS

- Acute pancreatitis with persistent organ failure (OF) has a very high mortality, and its prediction early in the disease course is crucial.
- Among various predictive biomarkers, persistent systemic inflammatory response syndrome plus interleukin-6 levels of 160 pg/mL or greater have a high predictive accuracy for the development of OF.
- Respiratory system is most common and usually the first organ system affected.
- OF can develop early in the disease course due to marked systemic inflammation (primary OF) or later due to infection of the necrosum (secondary OF).
- Management involves organ support measure in intensive care unit. A few therapeutic options are in pipeline to reduce systemic inflammation.

Video content accompanies this article at http://www.gastro.theclinics.com.

INTRODUCTION

Acute pancreatitis (AP) is one of the common causes of acute abdominal emergency resulting in significant morbidity and mortality. As per global estimates, the incidence of AP is 33.74 cases (95% confidence interval [CI]: 23.33–48.81) per 100,000 person years and a mortality of 1.60 deaths (95% CI: 0.85–1.58) per 100,000 person years due to AP.[1] In majority of cases, AP is mild, but it is moderate or severe in 20% to 30% of patients.[2,3] AP is associated with both local and systemic complications. Local complications include (peri)pancreatic necrosis and fluid collections while systemic complication manifests in the form of organ failure (OF), which usually occurs in patients with acute necrotizing pancreatitis. Thus, AP has been categorized as moderate

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and severe on the basis of local complications and persistent OF, respectively, as per the Revised Atlanta classification.[4]

OF is the primary determinant of mortality in AP.[5,6] OF may develop early during the first week of illness due to severe systemic inflammation resulting in a high mortality of 40% or greater. Secondary infection of the necrotic fluid collections may result in sepsis and consequent OF, that is, secondary OF occurring late in the course of illness.

Since OF portends poor prognosis and requires treatment in specialized centers, it is imperative to predict the development of OF. Many studies have evaluated various clinical and laboratory parameters to predict the development of OF during first 48 to 72 hours of onset of the disease to stratify the patients who require critical monitoring and care. In this review, we will be discussing predictors of OF, its pathophysiology, clinical course, and potential therapy in patients with AP.

DEFINITION OF ORGAN FAILURE

Organ dysfunction can be defined as the development of potentially reversible physiologic impairment of an organ system's function arising in the wake of a potentially life-threatening pathologic insult.[7,8] OF can be defined as significant functional impairment of an organ system that is critical to sustenance of life.[2]

CHARACTERIZATION OF ORGAN FAILURE IN ACUTE PANCREATITIS

Three organ systems are primarily affected in AP: respiratory, renal, and cardiovascular. Respiratory system is the most commonly affected organ. These 3 organ systems should be assessed to define OF in AP. OF is graded as per modified Marshall scoring system (**Table 1**). This system is preferred over other scoring systems such as sequential organ failure (SOFA) scoring system. A score of 2 or greater for any organ dysfunction in modified Marshall scoring is considered OF. OF persisting for 48 hours or greater is called persistent OF and that lasting less than 48 hours is taken as transient OF. Persistent OF defines severe AP and carries a high mortality.

OF should be characterized and evaluated in following ways as each aspect has a bearing on the clinical outcomes.

i. Grade of OF
ii. Type of organ system affected, that is, respiratory, renal, or cardiovascular
iii. Single or multi OF
iv. Duration of OF
v. Timing of OF from the onset of AP

Severity of each OF has a significant effect on the management of AP and its outcomes. Patients with higher grade of OF such as grades 3 and 4 generally require organ supportive measures such as noninvasive ventilation or mechanical ventilation for respiratory failure, hemodialysis for renal failure, and vasopressors for cardiovascular failure. Patients with higher grade have worse prognosis than lower grade OF.[9,10]

Patients with multi OF have a mortality of 24% to 48% as compared to 6% to 21% mortality in patients with single OF.[6,11–13] Patients with multi OF (MOF) having initial respiratory or cardiovascular system (CVS) failure had a higher mortality as compared to initial renal failure.[13] In terms of the duration of OF, the mortality in patients with persistent OF lasting less than 1 week, 1 to 2 weeks, 2 to 3 weeks, or more than 3 weeks was reported to be 43%, 38%, 46%, and 52%, respectively, in the Dutch multicenter study.[11] In another multicenter study, the mortality in patients with persistent OF lasting less than 1 week, 1 to 2 weeks and greater than 2 weeks was 15%, 32%, and 21% respectively.[13]

Table 1
Modified Marshall score[4]

	Score				
Organ System	**0**	**1**	**2**	**3**	**4**
Respiratory (Pao_2/Fio_2)	>400	301–400	201–300	101–200	≤101
Renal					
Serum creatinine (μmol/L)	≤134	134–169	170–310	311–439	>439
Serum creatinine (mg/dL)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)	>90	<90, fluid responsive	<90, fluid nonresponsive	<90, pH <7.3	<90, pH <7.2

For Nonventilated Patient, the Fio_2 can be estimated from below	
Supplemental Oxygen (L/min)	**Fio_2 (%)**
Room air	21
2	25
4	30
6–8	40
9–10	50

Abbreviations: FiO2, fraction of inspired oxygen; PaO2, partial presuure of arterial oxygen.

A score of 2 or more in any system defines OF.

From Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102111.

With regard to the timing, OF generally develops during the early phase of illness, that is, within first 2 weeks. This type of OF is due to sterile systemic inflammation as a result of release of damage-associated molecular patterns (DAMPs) from the necrotic pancreatic tissue, which activate immune cells to cause massive cytokine release into systemic circulation resulting in what is known as "cytokine storm syndrome" (CSS).[2] OF developing due to massive pancreatic injury and subsequent intense systemic inflammation has been referred to as "primary OF." Primary OF developing within first week of AP is called early severe AP (ESAP). Fulminant pancreatitis has been defined as a subgroup of patients with ESAP who develop one severe OF or multiorgan failure within 72 hours of onset of AP.[8] Such patients have a very high mortality.

OF can also develop during the later phase of illness due to infection of the necrotic fluid collections. This is called "secondary OF" as OF develops secondary to severe infection causing sepsis. In a series from a tertiary care center of 805 patients with AP of whom 274 patients had OF, mortality was 49.5% in patients with primary OF and was 36% in patients with secondary OF. Primary OF caused early mortality within 2 weeks in 15.8% of patients.[12] The Dutch multicenter study also reported a mortality of 42.8% in primary OF and 29.1% in secondary OF although the authors did not specifically referred OF as primary or secondary.[11]

Differentiation between primary and secondary OF is important for the following reasons: (1) it provides a mechanistic insight into the disease pathophysiology and dynamics and (2) management approach is different for both of them. Secondary OF is due to deep-seated abdominal infection. Early and aggressive treatment of infection may improve outcome in this group of patients and reduce mortality. Therapeutic window is large with relatively better prognosis. On the other hand, primary OF is due to severe pancreatic injury and dysregulated immune response leading to intense sterile systemic inflammation. Therapeutic window is small with dismal prognosis. The mortality in this group has been high varying from 40% to 49% over the last many decades despite improvement in organ support measures and intensive care. It is possible that potential therapy targeting systemic inflammation and minimizing pancreatic injury might improve outcome in this group.

PREDICTION OF SEVERITY OF THE DISEASE

Persistent OF lasting for 48 hours or greater is required for diagnosing severe AP. Thus, even if a patient develops OF on day 1 of illness, labeling severe AP will only be feasible on day 3. The median duration for the development of OF in early phase of illness is 4 to 5 days.[5,6,9] Prediction of severe disease is important for triaging and prioritizing care. The term, "predicted severe AP" is used to highlight patients who have a high likelihood of developing severe disease and thus require urgent referral. Prediction of severe AP is also important for an early inclusion of such patients in clinical trials.

Several scores have also been developed for severity prediction, but they do not have a high sensitivity or specificity, and some of these take 48 hours to complete (**Table 2**).

Various single biomarkers have been used on day 1 or day 2 of onset for prediction of severity. These include serum calcium, creatinine, albumin, C reactive protein (CRP), hematocrit, neutrophil to lymphocyte ratio (NLR), urinary trypsinogen-activated peptide (uTAP), polymorphonuclear cell elastase (PMN-E), procalcitonin, interleukin (IL)-6, and angiopoietin-2. In a systemic review and meta-analysis, angiopoietin-2 of greater than 1.9 ng/mL on day 3 had a pooled sensitivity of 0.93 (95% CI: 0.75–0.99) and specificity of 0.85 (95% CI: 0.75–0.92) with area under the receiver

Table 2
Biomarkers and scores used for prediction of severity of acute pancreatitis

Biomarker/Score	AUROC	Sensitivity (%)	Specificity (%)	Accuracy (%)	Comments
Calcium day 1 >1.9 mg/dL[82]	0.87	52–88	71–93	67–92	Serum calcium often decreases after onset of AP as calcium gets saponified in fat
Albumin day 1 <3–3.3 g/dL	0.83	55–83	71–88	68–87	Albumin is a nonspecific negative phase reactant; whole value decreases in inflammation and liver disease
CRP day 1 >150 mg/L	0.81	51–83	64–91	61–89	CRP is nonspecific marker of inflammation and increases in other inflammatory conditions apart from pancreatitis
HCT day 1 >44%	0.65	38–58	66–81	61–77	HCT is a marker of intravascular volume and gets elevated due to hypovolemia
Creatinine day 1 >70 μmol/L	0.65	60–71	61–85	61–85	Creatinine may get elevated on day 1 due to hypovolemia and fluid sequestration
NLR day 1 >10	0.79	73–83	46–72	56–76	Systemic inflammation in AP induces a neutrophilic response
uTAP day 1 >35 mmol/L	0.79	48–77	73–82	68–81	uTAP is a marker specific for AP though less sensitive
PMN-E day 1 >100 μg/L	0.9	65–94	60–93	62–93	PMN-E has modest sensitivity and specificity for AP severity prediction
PCT day 1 >0.5 ng/mL	0.81	50–90	60–86	56–88	PCT is a nonspecific marker of inflammation and more specifically infection
IL-6 ≥160 pg/mL day 3[16]	0.83	81–86	76–85	—	IL-6 is a very sensitive marker for severity prediction in AP and correlates well with outcome
Angiopoietin-2 day 3 >1.9 ng/mL[14]	0.95	75–99	75–92	—	It is very good marker with high diagnostic accuracy for AP severity prediction
Ranson's score >3	0.95	87–98	58–89	—	Requires 48 h for evaluation and has modest specificity
BISAP >3	0.94	27–92	85–98	—	Rapid bedside score for severity prediction

(*continued on next page*)

Table 2
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Biomarker/Score	AUROC	Sensitivity (%)	Specificity (%)	Accuracy (%)	Comments
Glasgow-Imrie score >2[83]	0.78	77	69	70	Requires 48 h for evaluation with modest diagnostic accuracy
APACHE II, day 1 ≥8	0.86	65–89	65–89	68–87	Can be evaluated daily and very good negative predictive value. Correlates well with clinical outcome
SIRS on day 1[21]	—	85–100	40–43	—	SIRS is a nonspecific marker as all patients with predicted severe will have SIRS and most of them resolve spontaneously; its PPV is low
Persistent SIRS ≥48 h	0.85	50–95	75	—	Persistent SIRS has higher specificity for development of OF
SIRS at admission + IL-6 >160 pg/mL on day 3[16]	—	79	95	—	This combination has much higher PPV as compared to persistent SIRS alone

Abbreviations: APACHE, Acute Physiological and Chronic Health Examination; AUROC, area under receiver operator curve; BISAP, bedside index for severity of acute pancreatitis; CRP, C reactive protein; HCT, hematocrit; IL-6, interleukin-6; NLR, neutrophil lymphocyte ratio; PCT, procalcitonin; PMN-E, polymorphonuclear cell elastase; PPV, positive predictive value; SIRS, systemic inflammatory response syndrome; uTAP, urinary trypsinogen-activated peptide.

Adapted from Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-111.

operating characteristics curve (AUROC) of 0.95 (95% CI: 0.92–0.96).[14] Inflammatory cytokines are released from proinflammatory cells such as neutrophils, monocytes, and lymphocytes due to pancreatic cellular injury and subsequent release of DAMPs. Severity of disease might correlate with the levels of these proinflammatory cytokines that precede the onset of OF and might be used as biomarkers for prediction. Among all proinflammatory cytokines, serum IL-6 and IL-8 have shown very good sensitivity and specificity for prediction of severe disease.[15,16] Serum IL-6 of 160 pg/mL or greater on day 3 correlates with the development of OF.[15] In a systemic review and meta-analysis, the pooled sensitivity of IL-6 was 81% to 83% and specificity was 76 to 86.%. The AUROC for IL-6 of day 1, 2, and 3 were 0.75, 0.88, and 0.85, respectively. The pooled sensitivity for IL-8 was 65.8% to 70.9% and specificity was 66.5% to 91.3%. The AUROC for IL-8 were 0.73 and 0.91 on day 1 and 2, respectively.[17]

The Acute Physiological and Chronic Health Examination (APACHE) II score, which was developed for critically ill patients, has been used for severity prediction in AP. Although the score requires 12 physiologic parameters, it has very good sensitivity and specificity for prediction of severity and fairly good sensitivity and specificity for mortality.[18] A cutoff value of 8 for admission APACHE II score could predict mortality with 75% sensitivity and 67.5% specificity (AUROC, 0.78).[19]

The bedside index of severity in AP (BISAP) is a simple index based on following parameters: BUN 25 mg/dL or greater, impaired mental status, systemic inflammatory response syndrome (SIRS), age greater than 60 years and the presence of pleural effusion. According to one study, a score of 0 had a mortality of less than 1% and score of greater than 5 had a mortality of 22%. A BISAP score of greater than 3 has a good specificity but a modest sensitivity.[20]

Persistent SIRS is a reliable clinical marker for prediction of severe disease. It has a very high sensitivity of up to 95% as almost all patients with OF have persistent SIRS but lower specificity of 64% to 75% and suboptimal positive predictive value (PPV) of 16% to 56%.[16,21] However, if IL-6 of 160 pg/mL or greater is added to persistent SIRS, it improves its specificity to 95% and increases the PPV to 85% for the development of OF.[16]

PATHOPHYSIOLOGY OF ORGAN FAILURE

The pathophysiology of OF is complex. In brief, initial events involve premature activation of pancreatic enzymes particularly trypsin within the pancreatic acinar cells. Intra-acinar trypsin leads to cellular injury. Intracellular Ca signaling is also involved in cellular perturbations. Trypsin has been the target for reduction in severity of AP for decades.[22] Intravenous trypsin infusion in experimental model resulted in shock and coagulopathy, which suggests its role in systemic injury.[23,24] Trypsin regulates protease-activated receptor 2, which acts on endothelial cells to cause hypotension.[25] Endothelial activation and stimulation of coagulation pathways subsequently may play a key role in the pathogenesis of acute necrotizing pancreatitis by causing microvascular thrombosis in the pancreatic microcirculation.[26] Nearly half of the patients with necrotizing AP have splenic or portal vein thrombosis.[27] Release of DAMPs from dying cells during AP such as high mobility group box 1 (HMGB1), DNA, histones, nucleosomes, extracellular matrix like hyaluronic acid, and ATP initiates an inflammatory cascade with the release of multiple cytokines and chemokines such as tumor necrosis factor (TNF)-α, IL-1β, monocyte chemoattractant protein-1(MCP-1), IL-6, IL-8, and IL-18.[28–30] Release of these proinflammatory cytokines by the immune cells results in cytokine storm syndrome (CSS), which is implicated in the pathophysiology of OF in AP. Neutrophils are recruited during the initial phase of sterile inflammation in AP as

evidenced by neutrophilic leukocytosis. Infiltration of neutrophils into organs, such as lungs, through the action of chemokines such as chemokine ligand 2 (CXCL2) and chemokine ligand 4 (CXCL4) results in lung injury, and neutralization of these chemokines improves lung inflammation in experimental models of AP.[31,32] Neutrophilic extracellular traps are released by neutrophils and have been implicated in increasing severity of AP.[33] Enzymatic digestion of peripancreatic visceral fat results in the production of unsaturated fatty acids, which can enter the systemic circulation and contribute to organ dysfunction. Inhibition of lipolysis has been shown to result in reduced systemic inflammation and cytokinemia in experimental AP.[34,35] Interestingly, cyclo-oxygenase-2 (COX-2) pathway activation has been implicated in pathophysiology of AP, and its inhibition reduces severity of AP in experimental models.[36] The pathophysiology of OF in AP is summarized in **Fig. 1**.

ORGAN FAILURE TYPE, CLINICAL TRAJECTORY, AND IMPLICATION FOR MANAGEMENT

Respiratory Failure

It is the most common type of OF in AP and usually the first organ to fail.[6,11,12] In 1977, Imrie and colleagues[37] first described hypoxemia (Pa_{O_2} <60 mm of Hg) in 38 out of 85 patients admitted in surgical emergency during the first week of illness. Clinical evidence of respiratory failure was uncommon, and the authors termed it as occult respiratory insufficiency. Patients may develop acute hypoxemic respiratory failure

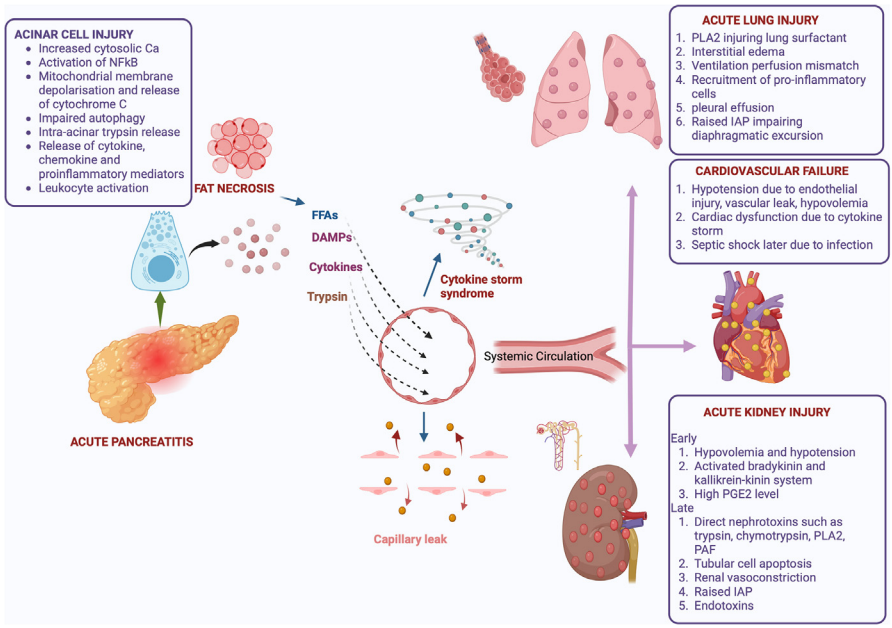

Fig. 1. Pathophysiology of organ failure in acute pancreatitis. Acinar cell injury releases damage-associated molecular patterns (DAMPs) that recruit inflammatory cells to produce cytokines. Free fatty acids (FFAs) from digestion of the peripancreatic fat by pancreatic enzymes enter systemic circulation and perpetuate systemic inflammation. Endothelial injury results in leaky capillaries and vascular leak. Excessive proinflammatory cytokine and chemokine release from immune cells results in "cytokine storm syndrome," leading to organ failure.

with minimal abnormalities on imaging. A chest radiograph usually shows mild-to-moderate effusion with relatively clear lung parenchyma. Ultrasound of the chest may show pleural effusion and acute interstitial syndrome characterized by Kerley's B lines in different lung fields (**Fig. 2**A, B and video 1). A few patients might show bilateral lung opacities suggestive of adult respiratory distress syndrome.

The pathophysiology of respiratory failure in AP is multifactorial as follows:

1. Injury to pulmonary vascular endothelium by circulating cytokines and possibly activated enzymes increases its permeability. This is known as interstitial alveolar syndrome. This results in leakage of fluid to interstitium and alveoli causing impaired gas exchange.[38]
2. There is ventilatory perfusion mismatch. Phospholipase A2 is activated by trypsin and its concentration in blood increases in patients with AP. Phospholipase A2 can damage pulmonary surfactant, dipalmitoyl phosphatidyl choline causing alveolar collapse, which leads to atelectasis and increased intrapulmonary shunt.[37]
3. Moderate-to-large pleural effusion
4. Patients with severe AP have CSS.[15,16,39] Activated cytokines lead to recruitment of neutrophil and macrophages in the lung and their degranulation, which also impairs gas exchange.
5. Raised intra-abdominal pressure (IAP) may result in impairment of diaphragmatic movement and contribute to respiratory failure.[40,41]

Hypoxemia without significant radiological abnormalities is the commonest presentation. Bedside monitoring of SpO_2 is useful to detect respiratory dysfunction in the early phase. Patients with hypoxemia should have regular monitoring of Pao_2/Fio_2 ratio to grade respiratory failure. Management of respiratory failure is discussed in the treatment section.

Renal Failure

Acute kidney injury (AKI) develops in patients with AP usually after the development of other OF. Kidney is the first organ to fail in 8.9% of all AP with AKI, and isolated AKI

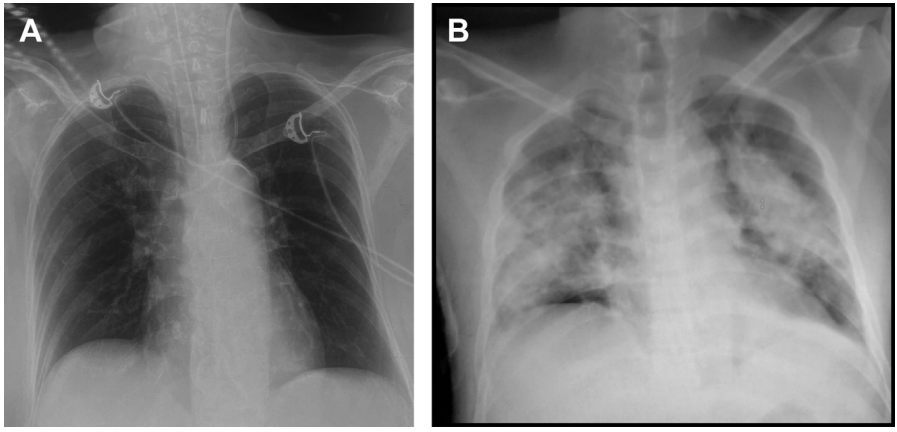

Fig. 2. (*A*) Chest radiograph of a patient with acute pancreatitis and respiratory failure with Pao_2/Fio_2 = 80. Lung parenchyma is relatively clear. (*B*) Chest radiograph of a patient with coronavirus disease 2019 infection and acute respiratory distress syndrome with Pao_2/Fio_2 = 80. There is diffuse parenchymal infiltrate in all the lung fields.

develops in a minority of patients.[42–44] The prevalence of AKI in severe AP is variable from 8% to 18.4%.[42–46] In a retrospective observational study using national inpatient sample, the prevalence of AKI among 3,466,493 patients with AP was 7.9%.[42] The mortality rate among AKI group was 8.8% as compared to 1.4% mortality in the whole population of AP.[42]

The pathophysiology of AKI in AP is poorly understood. The following mechanisms have been postulated:

1. During initial phase of AP, hypovolemia plays an important role. There is release of activated enzymes and proteases into systemic circulation, which may cause endothelial injury and vascular leak to interstitial space. In an experimental model of AP, glomerular filtration rate (GFR) fell by 40% and intravascular volume by 26% after 4 hours of induction of AP. It was prevented by plasma replacement. At 24 hours, however, the fall in GFR was unresponsive to plasma expansion.[47,48]
2. Toxic substances released from injured pancreas such as trypsin, chymotrypsin, bradykinin, histamine, prostaglandin E, and so forth cause endothelial injury and exudation of toxic substance into the peritoneal spaces. In a dog model of AP, peritoneal fluid was aspirated and 10 mL was injected into healthy dogs. The dogs developed hypotension without hypovolemia as evidenced by a normal hematocrit. There was a significant decline in renal blood flow, GFR and urine output, and increase in renal vascular resistance, which persisted after resolution of hypotension. Though hypovolemia may be the initial culprit but the toxic substances released from pancreatic injury and inflammation are the likely mediators of subsequent renal injury.[48]
3. Cytokines such as TNF-α act directly on glomeruli and tubular capillaries causing tubular injury. Other cytokines such as IL-1β, IL-6, and IL-8 act on endothelial cells causing ischemia and microthrombi. Phospholipase A2 is deposited in proximal tubular epithelial cells and hydrolyzes the epithelial membrane causing acute tubular injury.[49–51]
4. In patients with abdominal compartment syndrome, characterized by an increase in intra-abdominal pressure to greater than 20 mm Hg, renal blood flow may be compromised, which contributes to AKI.[52,53]
5. Occasionally, AP could be associated with thrombotic thrombocytopenic purpura, which might contribute to AKI.

To summarize, hypovolemia due to fluid sequestration in the initial phase of AP plays a key role, and it is usually fluid responsive. During later part of the illness, various other factors contribute to kidney injury such as toxic substances from pancreatic injury, endotoxins, intra-abdominal hypertension, renal vasoconstriction, microvascular thrombosis, tubular cell injury, and cytokine storm. Renal failure may improve gradually with improvement in AP.

Cardiovascular Failure

Circulatory perturbations are common in AP manifesting clinically as tachycardia in its milder form and hypotension in its severe form. Hypotension is uncommon during the initial phase of AP. It can develop as a result of hypovolemia due to endothelial injury and vascular leakage into the interstitial space. This is usually fluid responsive. One must be cautious during fluid resuscitation because excessive fluid administration may worsen respiratory failure.[54] Fluid nonresponsive hypotension might develop due to major circulatory disturbances such as peripheral vasodilatation and myocardial dysfunction. It portends poor prognosis. Hypotension in first week of AP is a risk factor for infected pancreatic necrosis (IPN).[55]

ORGAN FAILURE AND ITS IMPACT ON MORTALITY

OF accounts for almost all mortality in patients with AP. Patients who develop persistent OF during the early phase of illness have a mortality of up to 40% (**Table 3**).[11,12] The risk of mortality within 2 weeks of illness is high especially if they have a crescendo course with multiorgan failure, so called fulminant pancreatitis.[9,10,56] Most of the patients with persistent OF who survive the initial 2 weeks develop IPN, which contributes to late mortality. In a French study, 40 of 53 (75%) who survived the first 2 weeks of persistent OF developed infected necrosis.[57] Another study showed 76% patients with persistent OF developed infected necrosis after 2 weeks.[12] Mortality among patients with late onset OF and infected necrosis varies from 33.5% to 50%.[11,12,58] In the Dutch multicenter study, the mortality among patients with IPN and OF was 28% and was not different from mortality due to OF without IPN, which was 34% after excluding very early mortality within 10 days of hospital admission.[11] In an international multicenter study of 1544 patients with AP, persistent OF developed in 166 patients with a mortality of 20.4% at a median of 11.7 days from admission and 8.7 days after the onset of OF. The mortality was highest in patients with multi-OF involving 3 organs.[13]

To summarize, persistent OF during first week of illness is due to marked systemic inflammatory response with a mortality of up to 40%. A significant proportion of patients who survive the initial onslaught of massive systemic inflammation develop IPN and are prone to develop infected necrosis and secondary OF with a high mortality.

TREATMENT OF ORGAN FAILURE AND FUTURE DIRECTION

There has been an increase in the incidence of AP globally over last few decades but the overall mortality due to AP has reduced.[3,59,60] However, the mortality in patients with persistent OF is still high particularly in patients with early onset persistent OF.

Management of OF is largely supportive with organ support measures. Patients with predicted severe AP should be identified early and referred to a tertiary care center equipped with an intensive care facility. During the initial phase of illness, fluid and electrolyte balance plays a critical role. Lactated Ringer has been shown to reduce systemic inflammation as compared to normal saline.[61–64] Moderate fluid therapy should be given as aggressive fluid therapy is associated with fluid overload and worsening respiratory failure.[54,65] Aggressive fluid therapy did not prevent the development of moderate or severe disease.[65] Once OF develops, supportive measures should be provided like for any other critical illness such as mechanical ventilation for respiratory failure, dialysis for renal failure, and vasopressors for shock.

In case of worsening respiratory failure, patients should be provided respiratory support with positive pressure. Noninvasive positive pressure ventilation helps in opening up the collapsed airways and atelectatic lung, and thus augments respiration. In a recent randomized trial, patients with severe AP and acute hypoxemic failure who were treated with NIV required lesser need for a composite outcome of need for mechanical ventilation or hospital-acquired pneumonia compared to those treated with standard oxygen through face mask ($P = .04$) and lesser days of intensive care unit (ICU) stay (6 vs 10.5 days).[66] A recent retrospective study has shown comparative efficacy of respiratory support through high-flow nasal cannula as compared to NIV.[67]

Indications for renal replacement therapy in AP with AKI are not different from other critical illnesses with AKI. The choice of renal replacement therapy depends upon a patient's hemodynamic status. Intermittent dialysis, extended daily dialysis, or slow low-efficiency dialysis is reserved for hemodynamically stable patients. Continuous

Table 3
Studies summarizing organ failure and mortality in acute pancreatitis

Study	Total Patient with OF (N)	OF Type	Single OF Multi-OF	Mortality	Comments
Mofidi et al,[6] 2006	209	Respiratory: 192 Renal: 78 CVS: 114	SOF: 82 MOF: 125	N = 45 First week: 14 Second week: 9 Third week and beyond: 22	Included both transient and persistent OF
Padhan et al,[12] 2018	274	NA	SOF: 138 MOF: 136	N = 108 If OF develops in first 2 wk: 73 If OF develops third week and beyond: 35	Mortality was 49.4% in primary OF and 36% in secondary OF
Schephers et al,[11] 2019	219	Respiratory: 212 Renal: 100 CVS: 185	SOF: 53 MOF: 166	N = 83 If OF develops in first 2 wk: 60 If OF develops in third week and beyond: 24	Higher mortality in patients with OF and infected necrosis vs OF alone (44% vs 29%)
Machicado et al,[13] 2021	166	Respiratory: 145 Renal: 88 CVS: 40	SOF: 89 MOF: 77	N = 34	Risk of mortality higher in MOF and when CVS and respiratory failure first or concurrently
Sternby et al,[58] 2019	Transient: 121 Persistent: 113	NA	SOF: 141 MOF: 93	N = 68	Persistent OF was the most significant determinant of mortality

Abbreviations: OF: organ failure, CVS: cardiovascular system, NA: not available.

renal replacement therapy is preferred in patients with hemodynamic instability and has the advantage of lowering serum cytokines.[68–71] In a randomized trial, continuous veno-venous hemofiltration combined with peritoneal dialysis significantly improved serum cytokines such as IL-6, IL-8, and TNF-α and improved APACHE II score as compared to standard of care in patients with AP and AKI requiring renal replacement therapy.[69]

Specific therapy for OF is lacking. OF is a result of aberrant systemic inflammation in response to pancreatic injury. Various therapies have been tried to control an out-of-proportion systemic inflammation, and some are in pipeline for reducing systemic inflammation. Lexipafant, a platelet-activating factor antagonist was studied in 290 patients with AP and APACHE II score of greater than 6 in a double-blind randomized controlled trial (RCT) but had no effect on OF.[72] Probiotics to prevent gut transmigration of bacteria in AP were tried, but the trial was terminated prematurely due to increase in mortality in the probiotics arm.[73] Inhibition of cyclo-oxygenase-2 pathways by selective COX-2 inhibitor parecoxib and celecoxib resulted in a reduction in the development of OF in predicted severe AP in a randomized trial. The results appear promising but require subsequent validation in a larger trial.[74,75] A few trials have shown that inhibition of coagulation cascade by heparin resulted in improved survival and decrease in local and systemic complications.[76] However, a well-designed RCT is required to demonstrate the efficacy of heparin to prevent complications of AP. Cytokines such as TNF-α, IL-6, and IL-8 have been implicated in the systemic inflammation and development of OF in AP. In a small trial of 28 patients with predicted severe AP, pentoxifylline, a TNF-α antagonist, decreased the need for ICU admission and lessened hospital stay.[77] Subsequently, however, a larger trial failed to show any benefit.[78] A trial on the role of infliximab, a TNF-α antagonist, is currently ongoing in the UK (NCT03684278). Cytosorb therapy absorbs proinflammatory cytokines from blood. An uncontrolled trial in 16 patients has shown that cytosorb stabilizes hemodynamics in severe AP, decreases IL-6 levels, and improves OF score.[79] Systemic corticosteroids might reduce systemic inflammation in AP and improve OF. Two trials of systemic steroids are currently ongoing in patients with AP and persistent OF (NCT05160506, ChiCTR2300069365).

Tocilizumab, an IL-6 inhibitor, has been tried in patients with predicted severe AP in a small trial of 20 patients without any benefit on the development of severe disease or mortality.[80] Targeting intracellular cytosolic calcium signaling by specific ORAI1 inhibitors might result in reduction in the severity of AP and phase 2 trial is ongoing (NCT04681066).

Overall, we find that the mortality in patients with persistent OF has not shown a significant decline. The possible reasons for a failure to reduce mortality so far are (1) lack of a cohesive team approach to managing patients with AP and OF. A team comprising of an intensivist and a medical gastroenterologist should manage patients with severe AP right from the beginning. (2) There have been efforts to develop therapies for other aspects of AP such as optimal fluid therapy, effective and safe analgesic, and nutritional therapy but not many therapies to target systemic inflammation. (3) Our understanding of the pathophysiology of persistent OF is limited. When a patient with AP develops OF, it is usually too late for supportive therapies to work as the downstream inflammatory cascade plays the leading role. Previous efforts to mitigate the early pathophysiological events to prevent pancreatic injury such as by inhibiting activated pancreatic enzymes, for example, trypsin or by reducing pancreatic secretion did not succeed. Although, theoretically, such a strategy should work given the initial intracellular perturbations, the most likely reason for failure is that by the time a patient with AP presents clinically with abdominal pain, the series of events have

progressed with the involvement of inflammatory cells and their mediators that cause local and systemic inflammation and, therefore, the window of opportunity to intervene early is missed. (4) Lack of participation of pharmaceutical industries in developing effective drugs for AP.[81]

The question is how can we reduce mortality? We should focus our attention on identifying key molecular targets critical to the development of organ failure and develop directed therapy much like monoclonal antibodies for other inflammatory diseases such as autoimmune diseases and inflammatory bowel diseases.

In summary, persistent OF is the key determinant of mortality in AP. Over decades, improvement in our understanding of the pathophysiology of the disease and mechanistic pathways has provided potential therapeutic targets to treat the disease. Further intense research is needed to revolutionize the field of pancreatology and find a cure for AP.

CLINICS CARE POINTS

- Presence of organ failure is the most important determinant of outcome in patients with acute pancreatitis and carries a high mortality.
- Primary OF develops ealry in the disease course due to sterile systemic inflammation.
- Secondary OF develops later in the disease due to infection of the (peri)pancreatic necrosis and subsequent sepsis.
- Presence of systemic inflammatory response syndrome combined with high serum IL-6 within 72 hours of onset of illness predicts development of severe disease with fair accuracy.
- Management of organ failure is supportive in intensive care unit by multidisciplinary approach.

DISCLOSURE

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SUPPLEMENTARY DATA

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