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PANCREATITIS

Organ Failure Due to Systemic Injury in Acute Pancreatitis

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Acute pancreatitis may be associated with both local and systemic complications. Systemic injury manifests in the form of organ failure, which is seen in approximately 20% of all cases of acute pancreatitis and defines "severe acute pancreatitis." Organ failure typically develops early in the course of acute pancreatitis, but also may develop later due to infected pancreatic necrosis–induced sepsis. Organ failure is the most important determinant of outcome in acute pancreatitis. We review here the current understanding of the risk factors, pathophysiology, timing, impact on outcome, and therapy of organ failure in acute pancreatitis. As we discuss the pathophysiology of severe systemic injury, the distinctions between markers and mediators of severity are highlighted based on evidence supporting their causality in organ failure. Emphasis is placed on clinically relevant end points of organ failure and the mechanisms underlying the pathophysiological perturbations, which offer insight into potential therapeutic targets to treat.

Keywords: Acute Pancreatitis; Organ Failure; Pathophysiology.

Acute pancreatitis (AP) causes major morbidity and mortality. According to global estimates, the incidence of AP was shown to be 33.74 cases (95% confidence interval 23.33–48.81) per 100,000 person-years and a mortality of 1.60 (95% confidence interval 0.85–1.58) per 100,000 person-years due to AP.[1] The severity of AP can be mild, moderate, or severe, which depends on the extent of local injury in and around the pancreas, and more importantly systemic injury to remote organs.[2] Mild AP has no major local or systemic complications. A more severe form of the disease seen in approximately 20% of all patients with AP is associated with significant local complications in the form of necrosis and often systemic injury due to systemic inflammation.[3]

Systemic inflammation presents initially as systemic inflammatory response syndrome (SIRS). Patients with persistent SIRS are prone to develop systemic organ dysfunction and later organ failure (OF).[4,5] OF can develop either due to involvement of a particular organ system by a primary disease process or due to systemic effects of injury/inflammation at another site. Acute respiratory failure due to severe pneumonia is an example of the former and OF due to AP is an example of the latter. The most common cause of OF in clinical practice is sepsis. However, OF can develop due to noninfectious etiologies as well: AP and trauma are prime examples. OF is a *conditio sine quo non* of severe AP (SAP). SAP is defined by the presence of persistent OF as per the revised Atlanta classification of severity of AP.[2] OF largely governs the outcome and mortality in patients with AP, and therefore it is important to understand its epidemiology, risk factors, pathophysiology, potential mediators, impact on outcome, and management. This review focuses on relevant pathophysiological and clinical aspects of OF in patients with AP and identifies unmet needs.

Definition of OF

OF, as a generic term, can be defined as significant functional impairment of an organ system that is critical to sustenance of life. The severity of organ dysfunction can be quantified based on the parameter best defining the primary function of that particular organ (eg, partial pressure of arterial oxygen for pulmonary function or serum creatinine for renal function). In the case of AP, 3 organ systems are considered most important (ie, respiratory, renal, and cardiovascular), which are most commonly involved.[2] The severity of organ dysfunction is graded by the modified

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Abbreviations used in this paper: **AP, acute pancreatitis; DAMPs, damage-associated molecular patterns; HMGB1, high-mobility group box 1; ICU, intensive care unit; IL, interleukin; IPN, infected pancreatic necrosis; MPO, myeloperoxidase; NET, neutrophil extracellular trap; OF, organ failure; PAF, platelet-activating factor; PAR-2, protease activated receptor-2; PPV, positive predictive value; RCT, randomized controlled trial; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; TLR, Toll-like receptor; TNF, tumor necrosis factor; UFA, unsaturated fatty acid.**

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Marshall grading in AP,[2] which is preferred over the sequential OF assessment score used in sepsis. Any organ dysfunction of grade 2 or higher severity persisting for >48 hours is considered as persistent OF and defines SAP. Transient OF of <48 hours is considered a criterion for moderate AP.

How Common is OF in AP?

The proportion of patients with AP who develop OF varies in different studies and primarily depends on the setting. Data from population-based cohort studies show a lower proportion of patients with OF, whereas tertiary care hospital–based studies have shown a much higher frequency of OF. Population-based studies have shown the proportion of OF (severe AP) between 8% and 20%.[6–8] On the other hand, the proportion of patients with OF in a large series of patients from tertiary care hospitals may reach up to 40%.[9,10]

Risk Factors for OF

Why some patients develop OF and others do not is a matter of great importance. Host factors such as age, comorbid conditions, obesity, triglyceride levels, etiology, extent of local pancreatic injury, and genetic predisposition have been reported to predict the development of OF in patients with AP. Older age is a risk factor for OF and worse outcome, which also could be due to comorbidities.[11,12] Comorbidities, as measured by Charlson comorbidity index, may become worse due to AP and contribute to poor outcome but have not been directly related to another organ dysfunction.[13] Obesity is an established bad prognostic marker of outcome in patients with AP.[14] Visceral obesity predisposes to the development of OF.[15] Lipotoxicity causes multiorgan failure and exacerbates AP in obesity.[16] Peripancreatic visceral fat necrosis has been shown to worsen AP independent of pancreatic necrosis via unsaturated fatty acids (UFAs) resulting in OF.[17] Triglyceride levels at admission have been correlated with the severity of AP and even mild to moderate hypertriglyceridemia was found to be associated with the development of persistent OF.[18] Etiology has not been found to be an independent risk factor for OF, although patients with alcohol-induced AP may have a higher risk of early-onset OF.[19] Association between the extent of local pancreatic injury as measured by the extent of necrosis and development of OF has been reported, but the causality is not established.[3,20–22] The mechanisms of local tissue injury leading to pancreatic necrosis and systemic injury manifesting as OF are intimately linked.[23] The issue from the pathophysiology point of view is if the extent of necrosis is causally related to the development of OF or do they both signify the end result of a severe response to acute pancreatic injury. The association between extent of necrosis and OF could be bidirectional. A complex inflammatory network in which the extent of (peri) pancreatic necrosis influences the severity of OF and OF exacerbates the development of pancreatic necrosis might exist.[24,25]

Given the apparent similarities in the etiology and phenotype of patients with varying grades of severity of AP, differences in interindividual inflammatory responses might explain the variability in the severity of AP. It is conceivable that the highly variable inflammatory response might be related to an underlying genetic predisposition. However, the data regarding the role of genetic polymorphisms in determining the severity of AP are scant and equivocal. *TNF-α* gene polymorphism was associated with severity, but this finding has not been validated in other studies.[26–28] *MCP-1* gene polymorphism was associated with increased risk of severe AP with the G allele acting as the risk factor but the data were inconsistent.[29,30] One study has shown genetic polymorphisms of *IL-6* gene to alter the level of interleukin (IL)-6 but did not find any association with the severity of AP.[26]

Clinical Determinants/Characteristics of OF

There are various characteristics of OF that affect the clinical course and outcome. The important determinants are as follows: (1) grade of OF as per the modified Marshall score, (2) specific type of OF (eg, respiratory/renal), (3) number of organs affected (ie, single or multiorgan failure), and (4) the timing of OF from the onset of AP. A higher grade of OF naturally has a greater impact on outcome. Patients with grade 3 or 4 OF requiring organ assistance, such as mechanical ventilation, have a worse outcome.[31] Respiratory failure is the commonest OF.[10,32,33] Respiratory and renal failures are quite similar in their impact on the outcome, but cardiovascular failure leads to the worst outcome.[10] Multiorgan failure has a worse prognosis than single OF.[32] The timing of onset of OF has an important connotation regarding the likely cause of OF and possibly its impact on survival. Inflammation is the key pathological response both at the local and systemic levels in AP. OF may develop early within a few days of onset of AP, which is termed as early SAP and carries a high mortality.[19,31] This is primarily due to a sterile inflammatory response. OF also may develop late during the course of AP due to sepsis, as we discuss next.

Primary (Early) Sterile and Secondary (Late) Septic OF in AP

Although OF and its consequences are well recognized in AP, there is limited understanding about primary OF that develops early due to pancreatitis per se (sterile inflammation) and may precede/coincide with necrosis, and late secondary OF due to infected pancreatic necrosis (IPN)-induced sepsis (Figure 1). Infection of the necrotic (peri) pancreatic tissue is an ominous development during the course of AP. IPN is the cause of most of the late mortality during the course of AP. Although many studies have shown development of early and late OF in patients with AP, the relative contributions of primary OF and secondary OF to mortality have not been well studied. One recent study of 805 patients with AP has provided the concept of primary and secondary OF and shown several differences between

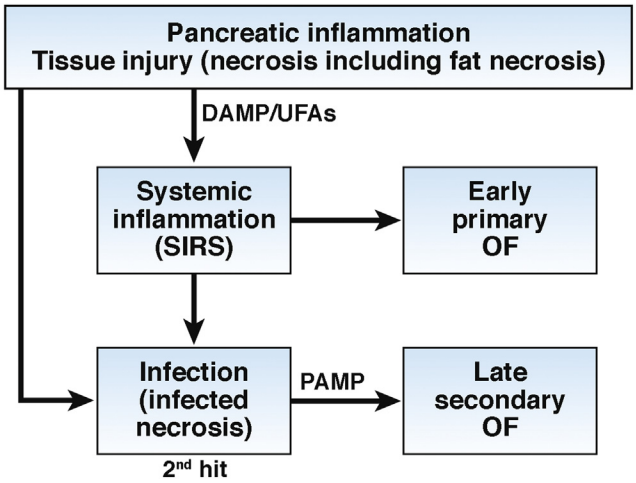


Figure 1. A conceptual model of early sterile injury and inflammation due to DAMPs/ UFAs, and late secondary septic inflammation due to pathogen-associated molecular patterns (PAMPs) that may lead to OF in AP.

the two (Table 1).[9] The window of opportunity is small in case of primary OF because it leads to early mortality, whereas temporally there is a larger window of opportunity to intervene in those with sepsis and secondary OF. The treatment is largely supportive for primary OF, whereas control of sepsis is the goal in secondary OF. Prognosis is poorer in primary OF and somewhat better in secondary OF.

Clinical Correlates of OF: Can We Predict Organ Failure?

By definition, persistent OF should last >48 hours. Therefore, it will take at least 3 days to document persistent OF even if a patient develops OF within a day of onset of pain. From triage and prognostic points of view, it is important to predict development of persistent OF in patients who present early to the hospital. Prediction of severe AP is largely based on several clinical scores, such as APACHE II (Acute Physiology and Chronic Health Evaluation II), which are multifactorial and somewhat tedious to use. BISAP (Bedside Index of Severity in Acute Pancreatitis) score has been developed and validated to predict development of severe AP and outcome.[34,35] Single prognostic markers are also used; C-reactive protein and IL6 being sensitive markers.[36,37]

Table 1. Differences Between Primary and Secondary OF

Characteristic	Primary OF	Secondary OF
Cause	Sterile inflammation	Sepsis
Timing	Early	Late
Therapeutic window of opportunity	Small	Large
Treatment	Supportive	Control of sepsis
Prognosis	Poor	Relatively better

Table 1 is adapted with permission from Padhan et al.[9]

Persistent SIRS is a reliable clinical marker to predict development of OF. However, despite a reasonably good sensitivity of 50% to 95%, SIRS has a lower specificity of 75% and suboptimal positive predictive value (PPV) of 16% to 56%.[5,38] Although almost all patients with persistent OF have persistent SIRS, a significant proportion of patients with nonsevere AP may also have persistent SIRS. PPV is an important attribute for a test variable, as a low PPV may lead to unnecessary and avoidable referrals from primary/secondary care centers, and increase monitoring and the overall cost of hospitalization. Recently, a study has shown that a combination of serum IL6 >160 pg/mL and SIRS at admission had a much higher PPV of 85% and a higher specificity of 95% for the development of severe AP.[39]

Clinical Trajectory of OF: Impact on Outcome

OF accounts for almost all the mortality in patients with AP. Patients who develop OF early on are at risk of having a severe course of the disease. In a population-based study of 1024 deaths due to AP, the median interval between the onset of AP and death was 6 days and from the onset of OF to death was 3 days.[33] The concept of transient and persistent OF was introduced in 2004.[4] Transient OF lasting <48 hours also has a negative impact on outcome.[4] The mortality in patients with transient OF was 1.4% to 10.0%, although the mortality was most likely due to other contributing factors such as IPN.[4,10,13] The overall mortality in patients with persistent OF is ~40% (Table 2). Patients with persistent OF have a high risk of early mortality within the first 2 weeks,[9,10,33] particularly those with very early onset high-grade single OF or multiorgan failure termed as fulminant pancreatitis.[19,31]

The mortality due to OF is high even after the first 2 weeks. Patients with persistent OF who survive the first 2 weeks are prone to develop infected necrosis, which accounts for the late mortality. In a French study of 148 patients, 40 (75%) of 53 patients with persistent OF developed IPN.[40] In another study, 76% of patients with persistent OF developed IPN after they survived the first 2 weeks.[9] Hypotension in the first week of AP was an independent risk factor for IPN.[41] There is not much difference between mortality due to early-onset OF and late-onset OF (Table 2). Two recent studies have focused attention on the issue of timing of onset of OF and outcome in AP. In a study of 614 patients, early-onset primary OF resulted in early mortality in 15.8% of patients and a further 42.8% late mortality due to development of infected necrosis.[9] In a Dutch study of 639 patients, 219 patients with persistent OF had a mortality of 38%. Mortality was not related to timing of onset of persistent OF. Mortality due to persistent OF developing within the first week, 1 to 2 weeks, 2 to 3 weeks, and >3 weeks from the onset was 42%, 46%, 36%, and 29%, respectively, in that study.[10] Patients with OF and IPN have a high mortality termed "critical AP" according to the Determinant-based classification,[42] but the data are inconsistent as to whether they have a higher mortality than those with early persistent OF without IPN. In the Dutch study, similar mortality rates were observed in patients with OF with and without IPN

Table 2. Summary of Results of Recent Studies Highlighting Mortality in Patients With Persistent OF

Study[a]	No. of patients with AP	No. of patients with POF	Mortality in patients with POF, n (%)	Mortality in patients with early-onset POF,[b] n/N (%)	Mortality in patients with late-onset POF, n/N (%)
Padhan et al 2018[9]	805	365	156 (42.7)	104/225 (46.0)	52/140 (37.0)
Schepers et al 2018[10]	639	219	83 (38.0)	47/112 (42.0)	36/107 (33.6)
Sternby et al 2018[13]	1655	113	59 (52.2)	47/89 (52.8)	12/24 (50.0)

POF, persistent OF.
[a]These are recent large studies, which had categorized patients according to revised Atlanta classification and the patients were treated as per current standard of care.
[b]Early OF defined by development of OF within the first week of onset of AP.

(28% vs 34%, $P = .33$) after excluding patients with mortality within 10 days of admission.[10]

In summary, the progression of an early systemic inflammatory response to OF defines severe AP and is associated with a high risk of mortality. Development of infected necrosis later in the clinical course exacerbates the initial injury and worsens the outcome.

Pathophysiology of Systemic Injury in AP

The pathophysiology of systemic injury in AP has remained enigmatic so far. The biggest hurdle has been the identification of mediators that are released locally in the pancreas and cause systemic injury. More so, as mentioned previously, the systemic severity can precede local severity and the extent of pancreatic necrosis may not correlate with systemic injury. It is to be noted that neither systemic involvement nor its severity are related to the etiology of AP. Figure 2 summarizes the potential pathophysiology of systemic injury. This is based on literature in pancreatitis, as well as where individual agents have been studied in their ability to cause systemic injury irrespective of pancreatitis. The endpoints relevant to human disease are summarized in lower panel of Figure 2 and more than 1 positive study showing that the agent can incite the endpoint is taken as positive.

It is to be noted that there are numerous and parallel steps involved in acinar cell injury induced by a single agent like caerulein, which itself does not cause systemic injury. Therefore, the role of other important factors in amplifying the signaling to become deleterious on a systemic level is essential. A clue to such factors that worsen pancreatitis lies in several reports showing hypertriglyceridemic AP to have a higher grade of severity than is usually reported.[43–45] This may be related to the fatty acids that compose the triglyceride, and is discussed in detail in the section "UFAs."

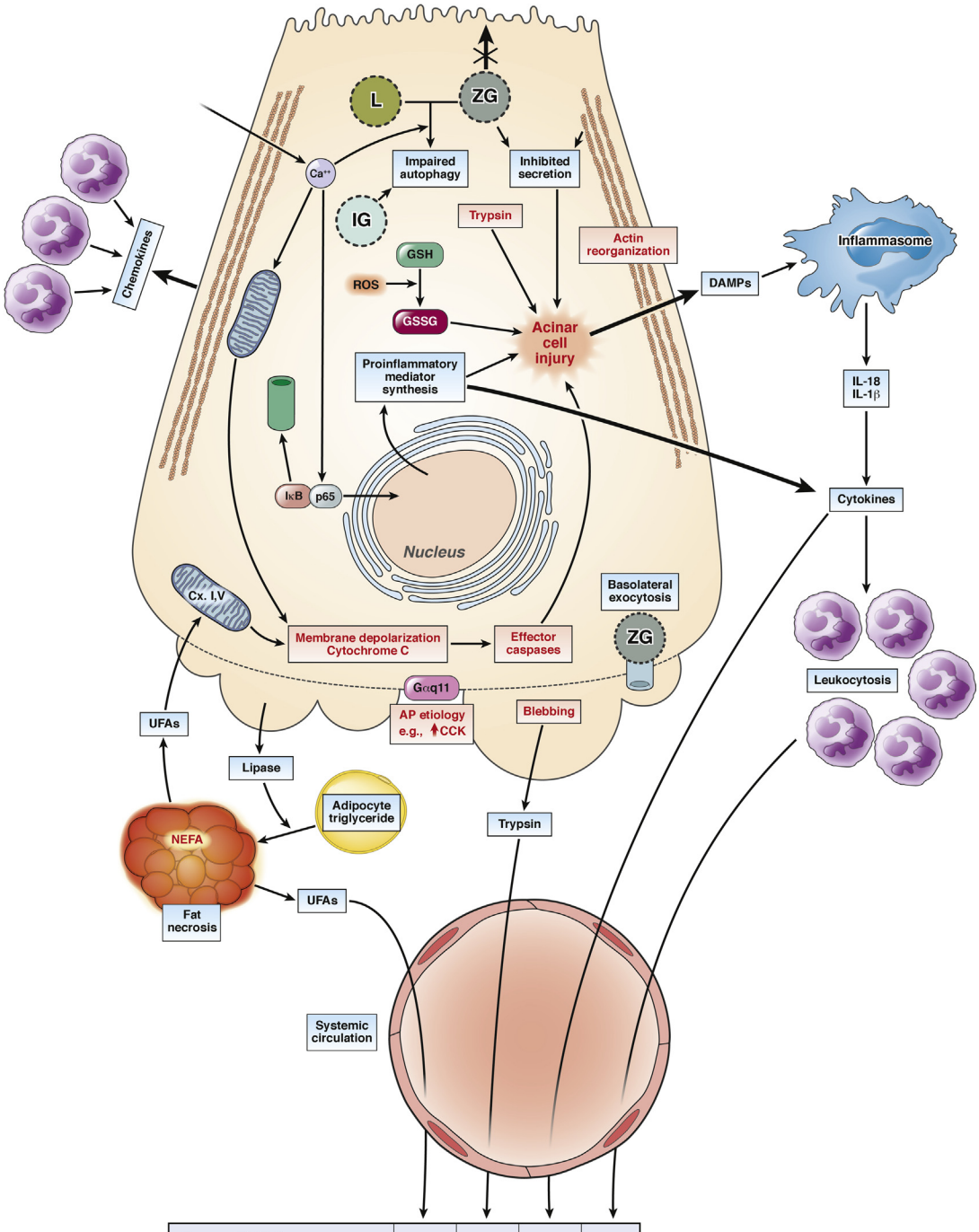
Distinction Among Markers, Mediators, and Endpoints of Systemic Injury

It is important to appreciate the difference between markers vs mediators vs endpoints of systemic injury. Markers of systemic injury, such as SIRS or serum cytokines, are distinct from the endpoints that determine the severity of systemic injury during pancreatitis. The clinical or biochemical clues do not themselves depict end organ injury, but may be markers or mediators of it. A marker in contrast to a mediator, when administered to an organism or when inhibited would not affect the endpoint of systemic injury. However, a mediator when administered would elicit an endpoint of systemic injury or when it is neutralized or inhibited the systemic injury would be ameliorated. As discussed previously, the endpoints of systemic injury during AP are renal, respiratory, and cardiovascular failure.

Animal Models and Systemic Injury in AP

Although there are several AP models, it is important to realize their limitations in measuring systemic injury. Most AP models have a strong emphasis on local pancreatic injury in the context of specific initiators or etiologies like caerulein. Recently, clinically relevant risk factors such as obesity have been shown to result in systemic injury by modifying the course of AP in animal models.[17,46–47] These studies have used clinically relevant endpoints such as renal failure. Thus, it is important to analyze whether the endpoints used in basic/animal models equate to human disease. For example, a common endpoint of lung injury used in animal models is the accumulation of myeloid inflammatory cells in the lung, shown as increase in lung myeloperoxidase (MPO) activity. Because pulmonary inflammation can be protective (please see section on neutrophils), it is important to realize the limitations of lung MPO as a parameter of lung injury. More relevant endpoints may be pulmonary microvascular permeability studied as the leakage into the alveolar space of an intravenously administered fluorescently tagged macromolecule such as albumin,[48–50] the oxygen saturation as determined by pulse oximetry,[17] or dead cells in the alveolar space,[16,17,46,47] which are relevant to pulmonary edema or adult respiratory distress syndrome in humans.[51] Similarly, clinically relevant endpoints for renal failure in animal models include a sustained increase in serum blood urea nitrogen,[46] like in sustained renal failure in humans.[46,52]

Although basic models typically cannot distinguish between primary and secondary OF due to their short course, we cover markers and potential mediators (Table 3) increased in early human AP independent of pancreatic necrosis, and where relevant distinguish these from those associated with infection in the following discussion.



Lung MPO increase	+	+	+	+
Lung TUNEL increase	+	±	-	-
Microvascular leak	+	+	±	-
Hypotension	+	+	±	-
Renal tubular injury	+	-	-	-
BUN increase	+	-	±	-

Table 3. Markers and Mediators of Systemic Injury in AP

Markers and mediators of systemic injury
Released from acinar cells
Trypsin
Inflammatory cells and their products
Neutrophils
NET
Inflammasome
Cytokines
IL6
IL1β
TNF-α
IL12
IL18
Adipokines
Resistin
Visfatin
Lipid mediators:
UFAs
PAF
DAMPs
HMGB1
Soluble receptor for advanced glycation end products
Double-stranded DNA
Histones/ nucleosomes
S100 proteins
ATP
Extracellular matrix (eg, hyaluronan)

Potential Mediators of Systemic Injury in AP

Trypsin

Trypsin generation is ubiquitous in AP[53–56] in both rodents and humans.[53,56] Being associated with the autodigestive hypothesis of pancreatitis for more than 100 years,[57] trypsin has been an attractive target to reduce pancreatitis severity. The most direct proof of the role of trypsin as a mediator of systemic injury early on came from its intravenous infusion resulting in hypotension, shock,[58,59] and coagulopathy, which is consistent with the coagulation cascade being a series of proteolytic steps. In support of this observation, elevated D-dimer, a fibrin degradation product, at admission has been shown to predict development of OF with a sensitivity, specificity, PPVs, and negative predictive values of 90%, 89%, 75%, and 96%, respectively.[60] Whether this coagulation cascade plays a role in splanchnic venous thrombosis, which is rare in the absence of necrosis, but occurs in approximately half of the patients with pancreatic necrosis,[61] remains unknown. Trypsin infusion also causes lung injury,[62] which is dependent on neutrophils (please see next section). More recent studies have identified the protease activated receptor-2 (PAR-2)[63] to be regulated by trypsin during pancreatitis. The most direct evidence comes from hypotension resulting from intravenous infusion of PAR-2 agonists, possibly via PAR-2 receptors on endothelial cells.[64] Whether trypsin actually plays a major role in systemic injury during clinical pancreatitis remains debated, because small molecule trypsin inhibitors have not shown conclusive benefit[65–74] in improving systemic injury during AP, and patients with hereditary pancreatitis due to trypsinogen gene mutations that result in its activation rarely develop systemic injury compared with other AP etiologies.[75] The interpretation of the role of trypsin is further complicated by circulating antiproteases such as alpha-2 macroglobulin,[76,77] which can inactivate it, and the inherent tendency of trypsin to auto-inactivate. Whether trypsin is indeed an initiator/mediator of systemic severity during pancreatitis, therefore, still remains inconclusive.

Neutrophils

Leukocytosis ($>12000/mm^3$) is part of the SIRS criteria,[78] and is an early predictor of severity of AP.[2] The leukocytosis in early pancreatitis is predominantly neutrophilic, and several studies have shown that depletion of neutrophils reduces inflammatory cell infiltration (eg, reduced MPO) into the lungs and improves microvascular

Figure 2. Pathophysiology of systemic injury in AP. The upper part of the figure describes the initiation of acinar injury by an AP etiology like high-dose CCK (↑CCK) during caerulein pancreatitis. The intra-acinar signaling events include the increase in cytosolic calcium (Ca^{2+}), which has a role in mitochondrial depolarization (Membrane depolarization) and cytochrome C leakage, along with activating nuclear factor-κB via dissociation and proteasomal degradation of IkB, nuclear translocation of p65. This upregulates inflammatory mediator synthesis, which include cytokines and chemokines, and thus leads to neutrophil infiltration into the pancreas. The trypsin generated due to impaired autophagy involving lysosomes (L) and zymogen granules (ZG) and increased oxidized glutathione (GSSG) (from its reduced form [GSH], due to reactive oxygen species [ROS]), along with concurrent deleterious mechanisms, cause acinar injury. These other mechanisms include the loss of apical microvilli, inhibition of apical secretion, the reorganization of F-actin, basolateral blebbing, release of DAMPs that can activate the inflammasome, and leakage of exocrine enzymes such as lipase, trypsin. The DAMPS can worsen local injury, and may also contribute to systemic injury. Similarly, cytokines can cause the leukocytosis associated with SIRS, which can enter the systemic circulation and are a part of systemic injury. The lower part of the figure describes the types of systemic injury that may occur due to these, along with the underlying mechanisms. The mechanisms include unregulated hydrolysis of adipocyte triglyceride by pancreatic lipase, resulting in fat necrosis, which generates UFAs, that inhibit mitochondrial complex I and V, which decrease ATP and worsen local injury. The effects of UFAs, trypsin, cytokine entry into the systemic circulation, and leukocytosis (from left to right) on endpoints of systemic injury are mentioned in the table in the lower part of the figure, with a + indicating 2 or more reports citing the agent in causing the endpoint. Unclear or weaker evidence is shown as ± or a –, respectively. BUN, blood urea nitrogen; TUNEL, TdT-dUTP terminal nick-end labeling.

permeability.[50,62,79,80] Neutrophil infiltration into an organ is dependent on their adhesion to the endothelium, mediated by P- and E-selectin on the surface of endothelial cells. These bind adhesion molecules like L-selectins and integrins on the surface of neutrophils. Blood levels of P- and E-selectin were elevated in rodent[81] and human[82] AP. These respectively correlated with severity of AP and lung injury. Interestingly, trypsin generation in the late phase of experimental pancreatitis has been shown to be neutrophil dependent,[62] and trypsin also can stimulate neutrophils to secrete matrix metalloproteinase-9. Based on these observations, trypsin-mediated lung injury has been hypothesized to be neutrophil dependent. Other studies have shown that neutrophil infiltration into the lungs is due to the chemokines CXCL2 and CXCL4, and that their neutralization reduces lung inflammation.[83] However, neutrophils also have physiologic roles and their accumulation in the lungs, such as by increasing KC/CXCL1[84–86] expression does not cause damage, but conversely protects from fungal and bacterial infections. Moreover, neutropenia predisposes to infections.[87–89] Therefore, it remains to be seen whether interference in neutrophil recruitment or their depletion during AP will improve systemic injury in human AP.

Neutrophil Extracellular Traps

Neutrophil extracellular traps (NETs) are web-like structures containing neutrophil granule proteins (eg, myeloperoxidase, elastase) and chromatin. These are released by neutrophils and are increased in the sera of patients with severe pancreatitis.[90] In addition, they occlude pancreatic ducts in human AP and may perpetuate pancreatitis.[91] NET formation in pancreatitis is catalyzed by the enzyme Protein Arginine Deiminase 4,[92] which causes histone modification of arginine residues to citrulline.[93] This modification weakens DNA-histone interactions and allows the neutrophils to expel the de-condensed chromatin. Protein Arginine Deiminase 4 inhibition reduces NET formation in humans[94] and rodents. Whether inhibition of NET formation will prove to be beneficial in reducing systemic injury in pancreatitis remains to be seen, more so because recent studies also show NET formation to wall off pancreatic necrosis from viable tissue in humans, and thus may play a role as a protective barrier to the progression of pancreatitis.[95]

Damage-associated Molecular Patterns

Damage-associated molecular patterns (DAMPs), which are released from dying cells during necrosis, correlate with human AP severity,[96–99] and are potential mediators of systemic inflammation based on animal studies.[100,101] DAMPs include small molecules such ATP, proteins, including S100 proteins, the soluble receptor for advanced glycation end products, and high-mobility group box 1 (HMGB1), nuclear components (eg, histones, DNA, nucleosomes), and molecules released from the extracellular matrix such as hyaluronic acid. Serum HMGB1 significantly correlated with AP severity in humans in a meta-analysis.[102] DAMPs can worsen inflammation by causing activation of the inflammasome,[100,103] as shown for soluble receptor for advanced glycation end products and HMGB1. DAMPs can also worsen the sterile inflammatory response[104] by disrupting the plasmalemma,[105] and further increasing DAMP release (eg, HMGB1[104]). However, it remains to be confirmed if DAMPs alone can induce the clinically relevant endpoints of OF or their inhibition during pancreatitis models, which induce OF, averts these endpoints.

Inflammasome

The inflammasome[106] is expressed in myeloid cells and has been implicated in systemic inflammation during pancreatitis.[100,107] Inflammasome activation results in production of IL1β,[108] IL18,[109–111] and HMGB-1,[101,112] all of which are associated with systemic injury during pancreatitis. Activation of the inflammasome is thought to be downstream of various receptors, some of which may be relevant to pancreatitis. These include nucleosomes (ie, DNA-histone complexes), double-stranded DNA, and RAGE activating the AIM2 (absent in melanoma 2) inflammasome[107,113] and extracellular ATP or NAD released from injured acinar cells activating the P2X7 receptor.[100] In addition, cell surface pattern recognition receptors, including Toll-like receptor (TLR) 4 and TLR9, may be activated by these DAMPs.[100] Interfering with nucleosomes activating the inflammasome or inhibiting RAGE signaling has been shown to reduce the severity of L-arginine and caerulein pancreatitis,[101,113] including lung inflammation. Interestingly, antagonism of TLR9 reduced lung inflammation, but not edema.[100] Similarly, although IL1β increased lung inflammation, it did not induce lung injury.[46] In addition, although IL18 (in combination with IL12) induces pancreatitis,[114] the systemic severity of pancreatitis these agents induce and the associated mortality are largely dependent on an increase in visceral fat[115] and its lipolysis to fatty acids.[51] In the absence of known genetic polymorphisms that govern inflammasome activation in pancreatitis, it is unclear how inflammasome activation variably affects the severity of pancreatitis in different individuals. This is further highlighted by early OF in pancreatitis occurring in the absence of extensive pancreatic necrosis and thus having a smaller source of inflammasome activators such as double-stranded DNA or nucleosomes than later in AP, when necrosis is progressing. Future studies are needed to clarify the role of the inflammasome in systemic injury during pancreatitis.

Adipokines and Cytokines

Previous clinical studies have shown that severe AP is associated with elevated serum levels of adipokines, including resistin and visfatin,[116,117] and cytokines including IL6,[118–121] IL1β,[108] IL8,[118,121,122] MCP1,[123] and tumor necrosis factor (TNF)-α.[119]. Serum cytokines are part of the criteria for severity stratification.[108,118–121,123–125] In a prospective study including 108 patients, IL6 was one of the best discriminators between mild and severe AP.[126] Another study showed that blood levels of IL6 correlated with OF and mortality. At a cutoff value of 122 pg/mL on

day 3, IL6 predicted OF and severe pancreatitis with a sensitivity and specificity of 81.8% and 77.7%, respectively.[37] Although the increase in their levels is associated with worse local and systemic complications, the evidence to support them as potential mediators of clinically relevant endpoints of OF in pancreatitis is so far lacking. For example, although IL1β induces fever and myeloid infiltration into the lungs, it does not induce respiratory failure.[46] Neutrophil infiltration mediated by cytokines, such as IL8, CXCL1, has been shown to protect from lung infections.[85,86,127] Similarly, IL6 infusion in humans inhibited endotoxin induced TNF-α increase,[128] and its long-term infusion led to hypoferremia and anemia,[129,130] but not systemic injury. IL6[131] and TNF-α[132] have also been shown to have a protective role in AP, and neither these or other cytokines have been shown to induce OF.[133–137] Therefore, targeting these cytokines alone may not improve outcomes in severe AP.

Coagulation Pathway

Vascular injury is an integral part of pancreatic inflammation and systemic injury. Endothelial activation, injury, increased vascular permeability, activation of coagulation, and increased leukocyte rolling, sticking, and transmigration to pancreatic tissue have been demonstrated in AP. The inflammatory process and proteases like trypsin may activate the coagulation system leading to microvascular thrombosis. Whether this coagulation cascade contributes to systemic injury is unknown. As mentioned before, portal or splenic vein thrombosis can occur in approximately half of the patients with pancreatic necrosis.[61] Similarly, although both antithrombin III and heparin have been shown to reduce the severity of AP in animal models, the clinical implications of this on systemic severity are unknown.[138]

Lipid Mediators

Platelet-activating factor (PAF). Apart from trypsin, PAF has been extensively targeted in pancreatitis. PAF is a phospholipid (acetyl-glyceryl-ether-phosphorylcholine) produced by myeloid cells, platelets, and endothelial cells. Intra-arterial delivery of PAFs into the pancreas causes AP.[139] PAF production in inflammation is mediated by phospholipase A2, and it is degraded by PAF acetylhydrolase.[140] Its receptor is a G-protein receptor.[141] PAF has a broad range of effects, including increasing vascular permeability, worsening inflammation, and initiating cell death.[142] Its levels are increased in severe biliary pancreatitis[143] in which it was thought to mediate shock and acute lung injury,[144] and the protective effect of antagonizing it was shown in multiple models, including biliary, choline-deficient ethionine-supplemented diet,[145] caerulein model in rats, and severe biliary pancreatitis in opossums.[49] Although initial clinical trials using lexipafant, a PAF antagonist, were promising,[146] the large definitive clinical trial did not show benefit in OF or mortality, even though local complications and sepsis were reduced.[147] Whether this was due to a limitation of targeting PAF or the high prevalence of early OF in the included patients remains to be studied (please see later in this article).

UFAs. The pancreas by its location is in proximity to visceral fat in humans. Several studies report an increased risk of severe pancreatitis to be associated with an increase in visceral fat,[148–151] which ranges from 1% to 10% of body weight.[152] This fat is composed of adipocytes, the mass of which is predominantly (>80%) triglyceride.[153–155] This triglyceride is predominantly composed of UFAs,[156,157] covalently linked to a glycerol backbone, which when released by unregulated lipolysis affect severity of AP. Interestingly, adipocyte triglyceride has become enriched in UFAs like linoleic acid over the past few decades,[158] which mirrors the 15% to 25% linoleic acid composition of necrosectomy samples from patients with severe AP.[46,51] Previous studies have shown pancreatic lipases to be present in the adipocytes, damaged during AP.[159] This results in a morphology known as fat necrosis, which can worsen pancreatic parenchymal necrosis,[47,51] but can also occur independently.[160,161] This lipolytic fatty acid generation can increase systemic injury during pancreatitis, in parallel with an increase in serum UFAs, such as linoleic and arachidonic acid,[162,163] which like visceral fat[46,47,51,156,157] are unsaturated. These UFAs when liberated in excess, inhibit mitochondrial complexes I and V,[51] and increase apoptotic cells in the lungs[17,46,47,51] (similar to patients with acute respiratory distress syndrome[52,164,165]), elevate serum blood urea nitrogen[46,47,51,166] due to renal tubular injury, and result in mortality. Interestingly, elevated serum levels of TNF-α, IL1β, MCP-1, and IL18 can all be induced during this fatty acid toxicity, perhaps due to the widespread release of DAMPs. Importantly, inhibition of this excessive lipolysis can result in prevention of systemic injury, hypercytokinemia, and mortality.[46,47,51] Although it remains to be seen if lipase inhibition will reduce systemic injury during human AP, it is encouraging to note that the cyclooxygenase inhibitor indomethacin, which is known to affect the metabolism of UFA products, may reduce progression of moderate-severe AP.[167]

Role of Intestine in Systemic Injury

The small intestine and colon may contribute to bacterial translocation and infected necrosis due to their close proximity to the pancreas, and thus to the pathophysiology of systemic inflammation. Another role may be played by mesenteric lymph from the gastrointestinal tract. In an experimental study, intravenous administration of mesenteric lymph from rats with intestinal ischemia exacerbated pancreatic microcirculatory disturbances and worsened the severity of pancreatitis in the recipient rats.[168] Similarly, profound vascular and coagulation changes can lead to ischemia of the pancreas[169–171] and bowel.[172,173] A lower gastric pH, which correlated with a higher mortality in AP, also supported the hypothesis of splanchnic ischemia.[174] In addition, ischemia-reperfusion can cause oxidative stress.[175] The major effect of such perturbations is gut barrier dysfunction with increased intestinal permeability,[176] as supported by human studies,[177] including a meta-analysis of

18 studies, which showed a pooled prevalence of gut barrier dysfunction of 59%.[178] However, parallel clinical observations question the gut as being the dominant player. These include patients with severe ulcerative colitis having a very low prevalence of sepsis[179] despite severe colonic ulcers being exposed to fecal matter for long periods. Similarly, although patients with fistulizing Crohn's disease do develop abdominal abscesses, the occurance of sepsis remains infrequent.[179] The translocation hypothesis as being the sole reason for developing infected necrosis is further challenged by the fact that bacterial translocation is common after dental[180] and endoscopic[181] procedures, but is transient. Thus, whether translocation of bacteria is the sole reason for infections of (peri) pancreatic necrotic tissue and collections, and the sepsis that ensues remains to be determined.

Mechanisms of Organ Dysfunction Due to Systemic Perturbations: Lessons From Sepsis-induced OF

Mitochondria are at the center of cellular perturbations from tissue hypoperfusion, which may result from hypovolemia, hypotension, and microvascular thrombi causing cellular hypoxia. Because mitochondrial energy production is oxygen dependent, their ability to generate ATP is severely compromised in such states, and can result in cellular dysfunction. OF may primarily be due to such mitochondrial dysfunction rather than cell death.[182] The following observations support this hypothesis: (1) cellular injury and death are minimal in postmortem examination of failed organs,[183] (2) functional recovery of the organ is swift once the underlying pathophysiological perturbations reverse, and (3) mitochondrial structural and functional changes have been documented in such patients. These observations are important from the point of prognosis and identifying targets for therapy.

Treatment of OF

Treatment for OF is largely supportive. Patients with predicted severe AP should be referred to a tertiary care center with intensive care unit (ICU) facility. Patients with OF must be managed in an ICU and often require organ support, such as dialysis, mechanical ventilation, and vasopressors.

Fluid and electrolyte balance is critical in the beginning of the illness. Ringer's lactate has been shown to be better than normal saline in reducing systemic inflammation.[184,185] Optimal amount of fluid administration remains a challenge.[186] Both under- and aggressive hydration can be detrimental. A randomized trial showed worsening of OF in patients given aggressive fluid therapy.[187] On the contrary, relative hypovolemia due to undercorrection of fluid deficit can lead to increased risk of necrosis. A recent trial showed benefit of aggressive fluid administration in mild AP,[187] but the results cannot be extrapolated to patients with severe AP because systemic events leading to OF develop rapidly and overzealous fluid therapy may exacerbate the clinical condition in those with impending respiratory and renal failure. One of the important points to consider is that normal homeostatic mechanisms are disturbed in patients with systemic injury due to abnormalities such as increased vascular permeability and thus the capability to deal with extra fluid being infused is compromised, unlike in patients with mild AP.

Enteral nutrition should be instituted as soon as possible and has been shown to reduce the length of hospital stay and possibly the risk of infected necrosis.[188] A multidisciplinary team composed of a critical care expert, gastroenterologist, intervention radiologist, and surgeon should look after the patient.

Specific Therapy for OF

Because the systemic injury is a result of dysregulated and out-of-proportion systemic inflammation in response to the local injury, specific treatment aimed at putative critical pathways has been tried. As mentioned previously, PAF antagonist, Lexipafant, failed in a randomized controlled trial (RCT) involving 290 patients with predicted severe AP having an APACHE II score of >6. However, the treatment failed to provide any therapeutic benefit mainly because the primary hypothesis was invalidated by the unexpected finding that 44% of patients had OF on entry and only 14% patients developed new OF.[147] Intravenous antioxidants too failed in an RCT of 43 patients, the primary endpoint, that is, OF, developed in 32% and 17% in antioxidant and placebo groups, respectively.[189] Probiotics were tried with an aim to prevent gut-derived infection, but unexpectedly increased mortality leading to premature termination of the trial.[190] TNF-α has been implicated as an important cytokine mediating systemic inflammation. In a proof of concept small study involving 28 patients with predicted severe AP, Pentoxifylline, an oral TNF-α antagonist, resulted in significantly fewer ICU admissions and shorter hospital stay.[191] A larger trial is currently in progress. Infliximab, a TNF-α antagonist, is being tested in an RCT involving patients with AP of all grades of severity (www.isrctn.com/ISRCTN16935761).

Unmet Needs and Potential Areas for Future Research

OF remains the proverbial Achilles heel of managing patients with severe AP. There is no specific therapy available either to treat or prevent the development of OF. The success of anti-cytokine therapy in chronic diseases such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis[192,193] may not translate to AP. Future approaches include targeting intermediary signaling, such as the increase in cytosolic calcium using ORAI1 inhibitors.[194] The benefits of this approach remain to be seen in human AP, because ORAI1 is involved in innate immunity as well.[195] Similarly, nuclear factor–κB has been shown to play a critical role in AP.[196–198] Pancreas-specific truncation of its trans-activating unit (RelA/p65) worsens pancreatic injury and lung inflammation. It would, therefore, be important to know whether clinically approved agents, such as Bortezomib[199] that interfere with nuclear factor–κB signaling affect

the course of human AP. Some other exciting potential targets include UFAs, lipase, DAMPs, inflammasome, and kynurenine,[200] which remain to be tested in human studies.

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Conflicts of interest
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