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NARRATIVE REVIEW

Acute pancreatitis: Translating early mechanisms to bedside management

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Abstract

Acute pancreatitis (AP) is a burgeoning challenge. The first week of the disease is generally considered early AP. Events that occur during this phase can determine the magnitude of subsequent events. Even after decades of research, there is still no curative therapy for early AP. One of the earliest events of clinical AP is the co-localization of zymogen and trypsinogen within autophagolysosome which is followed by trypsin activation. The resulting acinar injury releases damaged-associated molecular patterns (DAMPs) that trigger cytokine production by the resident immune cells. Concurrently, there will be neutrophil infiltration, endothelial dysfunction and capillary leak. The local intra-pancreatic inflammation will activate the circulating mononuclear cells traversing the inflamed pancreas and in turn, get activated and perpetuate the systemic inflammatory response syndrome (SIRS). This eventually triggers organ damage. Concurrently, another phenomenon called compensatory anti-inflammatory response syndrome (CARS) ensues, that makes the patient susceptible to infections including infected necrosis. CARS is characterized by the downregulation of human leukocyte antigen (HLA)-DR and results in immunosuppression. The intestine also has a substantial role in determining the severity progression of systemic events in AP. The three components of the intestine that have been implicated include gut mucosal barrier, the microbiota and intestinal lymph. Intestinal inflammation occurs as a part of SIRS and results in the loss of tight junctions and apoptosis of the intestinal epithelial cells thereby increasing the mucosal permeability. Meanwhile, there will be gut microbial dysbiosis resulting in the translocation of pathogens and pathogen-associated molecular patterns (PAMPS) into the circulation. This would result in infections, which was already facilitated by CARS. In addition, the intestinal lymph could also result in translocation of intestinal toxins to the systemic circulation thereby contributing to the severity of AP. This narrative review discusses the current understanding of the mechanisms of early AP and the clinical implications.

Keywords Acute pancreatitis · Compensatory anti-inflammatory response syndrome · Gut barrier integrity · Organ failure · Systemic inflammatory response syndrome

Introduction

Acute pancreatitis (AP) is a burgeoning challenge to clinicians and researchers alike. In spite of the description of the central dogma of intra-acinar trypsinogen activation by Hans Chiari over a century ago [1], there still does not exist a definitive cure for this disease. Over the years, several mechanistic and clinical management-related studies have flooded the literature. A substantial majority of the mechanistic studies were conducted on experimental murine models, in view of the limitations of such studies in humans. On the other hand, the clinical management studies were based on either cues derived from experimental studies, clinical observations or presumptions. No clinical studies have so far demonstrated a distinct causal association between mechanistic

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events and clinical outcomes. Even though several physiology and pathology-based predictors have been proposed and tested, we still do not have an ideal predictor of severity that stands out of the lot [2]. Even the more recent machine learning-based predictors have their own limitations [3]. These are clear indicators of our limited understanding of the mechanistic events of this disease, which has translated to the lack of a definitive curative therapy that can be initiated early in the natural course.

This narrative review delves into some of the recent studies that have addressed several mechanistic events using human and animal samples and the patient's pathophysiological parameters which potentially have a higher likelihood of being translated to drug development and clinical care.

Current status of management of early AP

AP is a dynamic condition. According to the Revised Atlanta Classification, the natural history of AP has been classified into an early (first week) and a late (second week and beyond) phase, that differs in pathophysiological processes and thereby, management approaches. However, it has also been observed that the first phase can often extend into the second week [4].

Several single and multi-parameter scoring systems had been developed and tested to predict severity of AP. However, head-to-head comparison failed to prove anyone to be better than the other and most of them had moderate discriminating capability.

The first line of treatment of AP is pain management, which might have to be repeated over the first few days. Recent randomized controlled trials (RCTs) have demonstrated efficacy on pentazocine and tramadol in pain management. There had been a long-drawn controversy on the long-term use of opiates in AP in view of the effects on sphincter of Oddi that could contribute to severity of the disease. However, a recent international multicenter study involving over a thousand patients failed to document any definite association of daily morphine equivalent doses with the severity of AP [5]. One of the foremost modalities in the management of the early phase of AP has been fluid therapy, the conceptual basis of which has undergone several reiterations over the years. The current dictum, based on the recent Waterfall trial, is a goal-directed moderate fluid management that has replaced the much-hyped earlier concept of aggressive hydration [6]. Even though lactated ringer's solution has been considered the ideal fluid of choice, results from meta-analyses suggest that further larger randomized controlled trials need to be conducted to achieve a clinically powerful effect size [7–9]. This issue is currently being addressed in the multicenter, multinational randomized controlled Waterland trial [10]. Early enteral nutrition per orally or by nasojejunal tube is essential [11]. This not only provides calories to the patient but also prevents intestinal bacterial dysbiosis and alteration of the gut mucosal barrier.

Protease inhibitors such as ulinastatin and antisecretory agents, namely octreotide and somatostatin, are often used in the early phase of AP. However, these agents have not been shown to confer high effect-sized clinical benefits and are not currently recommended by guidelines [12]. Similarly, even though prophylactic antibiotics during the first week of AP are not recommended by guidelines, they are often used in clinical practice[13–15]. Plasmapheresis is another modality that is used in hypertriglyceridemia-associated AP. However, studies have shown inconsistent beneficial effect on severity of AP and organ failure, with a recent meta-analysis showing no benefit and increase in healthcare cost [16–19].

Summary of experimental animal studies on early pathogenesis

Activation of trypsinogen to trypsin within the acinar cells has been considered the earliest event that triggers AP. Several experimental studies in murine models have demonstrated increased calcium fluxes within the acinar cells in response to alcohol metabolites (fatty acid ethyl esters), bile acids (sodium taurocholate), secretagogues (cerulein) and high doses of amino acids such as L-arginine and L-lysine. It was demonstrated by Saluja et al. in the early 1980s that calcium overload within the acinar cells results in redistribution of the proenzymes (including trypsinogen) from the apical zymogen to the lysosomal compartments within which lysosomal cathepsin B activates trypsinogen to active trypsin [20]. This occurred as early as 30 minutes after the initial injury. This was known as the co-localization hypothesis. Several years later, the same event was demonstrated with greater clarity where the different abnormal intracellular compartments were elegantly demonstrated and the concept of autophagy was introduced in AP [21]. At the same time, mitochondrial injury and endoplasmic reticulum stress were also implicated in the mechanistic landscape of AP [22]. While there were some debates regarding the role of cathepsin B in activating the redistributed trypsinogen to trypsin within the co-localized vacuoles, others questioned even the central dogma of the role of trypsin [23]. Dawra et al. [24] clearly demonstrated that pancreatic acinar destruction was less by 50% in trypsinogen and cathepsin B knock-out mice, indicating that activation of trypsin is responsible for only 50% of pancreatic injury. A subsequent study by Talukdar et al. using wild-type and knock-out animals clarified the role of trypsin and cathepsin B in the genesis of AP. The activated trypsin in the co-localized organelles or autophagolysosomes was shown to cause injury to the organellar membrane resulting in leakage of cathepsin B into the

cytosol. A low volume of cytosolic cathepsin B would result in acinar cell apoptosis via the mitochondrial mechanisms, while a larger volume would cause necrosis by activating the receptor-interacting protein (RIP) kinase pathways [25].

Why is there still no curative therapeutic modality of early AP?

As briefed above, a majority of the mechanistic studies in early AP had been conducted in experimental rodent models. More importantly, a majority of the studies evaluated the early acinar and pancreatic parenchymal event. These events occur rapidly to the tune of minutes to a few hours. However, in the real-world clinical scenario, these events have already occurred and systemic inflammatory response syndrome (SIRS) sets in by the time the patients present to the healthcare setting. An important knowledge gap is the fundamental understanding of how local pancreatic injury progresses to SIRS and multi-organ dysfunction syndrome (MODS). Furthermore, what predisposes patients with acute necrotizing pancreatitis (ANP) to infections in necrosed pancreatic/extrapancreatic tissues is also largely uncharted. A detailed understanding of these aspects in the context of clinical AP would perhaps pave the way for mechanism-specific curative therapeutic modalities.

Early acinar events in human acute pancreatitis

The early acinar injury resulting from bile acids such as taurolithocholic acid (TLCS) and alcohol metabolites, namely fatty acid ethyl esters (FAEE), in humans is similar to that observed in experimental models. The ryanodine receptor, which has been shown to be crucial in modulating calcium fluxes and acinar injury in experimental AP, has also been shown to be expressed in human acinar cells derived from cadaver pancreas. Its role in human AP was confirmed by the demonstration of over 80% reduction in the bile acid-stimulated human acinar cell injury when the ryanodine receptor was experimentally blocked [26, 27]. The other important route of calcium entry into the acinar cell is the calcium release-activated calcium channels (CRAC), of which the ORAI1 protein is an important component [28]. In more recent studies, we demonstrated that when healthy human pancreatic tissue slices were exposed to these compounds, there was redistribution of zymogens containing trypsinogen and cathepsin B containing lysosomes, akin to the co-localization phenomenon that was described in murine models. Transmission electron microscopy of the bile acid-treated pancreatic slices demonstrated the formation of vacuoles that were confirmed to be autophagolysosomes using specific markers of autophagy. These events translated to progressive morphological injury to the pancreatic tissue within a very short time [29].

Clinical implications: Since these are very early events that pass by the time the patient reaches the healthcare setting, use of agents such as protease inhibitors (e.g. ulinastatin) and antisecretory agents (e.g. octreotide) in the early stage is unlikely to be beneficial.

Initiation of systemic inflammatory response syndrome

SIRS is a response to both non-infectious and infectious stimuli that is triggered by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), respectively. SIRS is manifested by physiological alterations such as increased heart rate (> 90 bpm), increase or decrease in body temperature (< 36 or > 38 °C), increased respiratory rate (> 20/min) and also cause alteration in the total leukocyte count (< 4000 or > 12,000/cumm) [30].

In the context of early AP, injured acinar cells release DAMPs such as high mobility group box 1 (HMBG1) protein, histones and damaged deoxyribonucleic acid (DNA). These DAMPs, especially HMBG1, binds to the cell surface Toll-like receptor (TLR)−4 of immune cells, which triggers the intracellular nuclear factor-kappa B (NF-κB) pathways, eventually resulting in nuclear binding of NF-κB to the DNA and upregulates the translation of several cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)−1b, IL-2, IL-6 and IL-18, various chemokines such as IL-8, macrophage inflammatory protein 1 (MIP1), monocyte chemoattractant protein 1 (MCP1), platelet-activating factor and adhesion molecules. Most of these have been shown elaborately in experimental models of AP [31].

In our studies using human pancreatic tissues, we had shown that besides immune cells, human pancreatic acinar cells themselves produce cytokines in a time-dependent manner in response to injury with bile acids (TLCS) and alcohol metabolites (FAEE). The cytokines produced by the acinar cells along with the locally produced DAMPs together activate the circulating mononuclear cells that flow through the injured pancreas to produce more cytokines. This myriad of events results in SIRS. Simultaneously, the locally produced cytokines, especially TNF-α, can further injure adjacent acinar cells in a paracrine manner. The magnitude of the initial cytokine response could be one of the major determinants of progression to a severe form of AP [29, 32].

Clinical implications: Since local and systemic inflammation are the key mechanistic events that result in the early progression of AP, these are the appropriate therapeutic targets. Preliminary studies using ORAI1 inhibitors have demonstrated potential benefits in patients with AP. Besides the acinar cells, ORAI1 proteins are also present in the calcium channels in other cells such as neutrophils and T-cells [28, 33].

Progression of organ failure and impact on outcomes

Persistent organ failure (OF) is the single most important determinant of mortality in patients with AP. The development of OF results from a complex chain of events that is still not clearly understood. Based on the currently available literature, no single parameter can be ascribed independently to the pathogenesis of OF and what appears more likely is a convergence of discrete mechanistic alterations and their cumulative effect.

In the early phase of AP, OF is predominantly related to sterile inflammation (primary OF) while in the later phase, it results from inflammation secondary to infected necrosis (secondary OF), the prognosis of the former being worse than the latter. Figures 1 and 2 depict conceptual models and potential mediators for the development of early OF in patients with AP. While the lungs are the most common organs to dysfunction [34], the risk of mortality is determined by the combination and sequence of failed organs. One international multicenter study (22 centers, 1544 patients) reported extremely high odds of death if all three organs failed with the respiratory or cardiovascular system being the first to fail. On the contrary, if the kidneys fail first, then the risk of mortality is lower even if another concomitant organ failure follows [35]. A few clinical studies had attempted to predict development of OF in AP. For instance, one study demonstrated that baseline circulating IL-8 level of 105 pg/mL could predict acute kidney injury. However, while the sensitivity was 87.5%, specificity was 59.2%, with a modest area under the curve of 74.4% [36]. Another study suggested that a urinary neutrophil gelatinase-associated lipocalin (NGAL) level of 221.03 ng/mL on Day 1 could predict acute kidney injury (AKI). Contrary to that with IL-8 levels, the sensitivity and specificity of NGAL were shown to be 82% and 80% with an area under the curve of 90%. This appears promising and warrants further larger multicenter studies [37].

One of the earliest events that contributes to OF is the development of endothelial dysfunction and capillary leak syndrome. The endothelium is a dynamic organ. It regulates

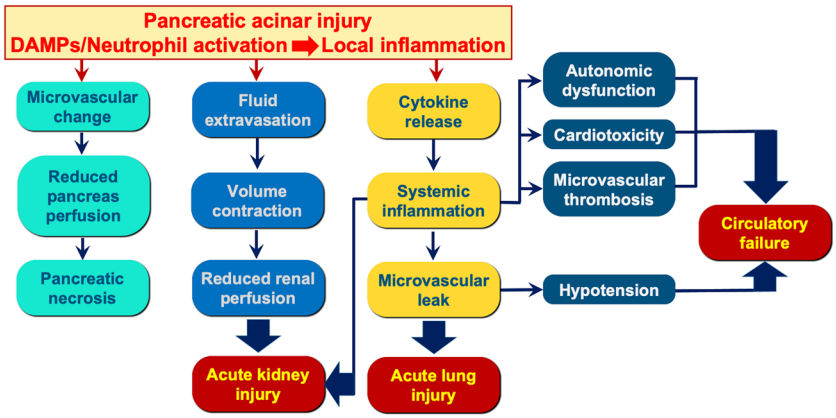

Fig. 1 Schematic representation of the temporal progression from local pancreatic inflammation to end organ dysfunction

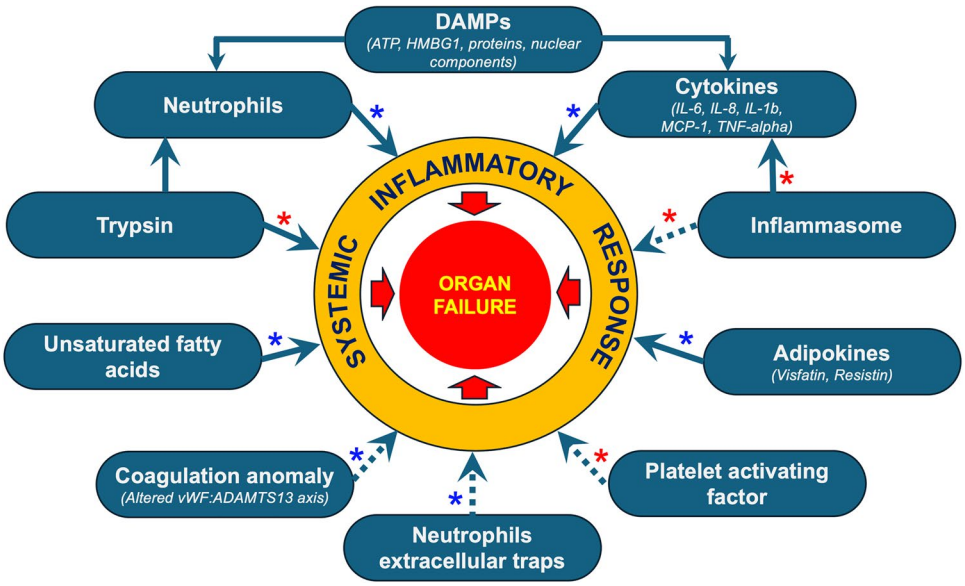

Fig. 2 Schematic representation of mediators that have been shown to be directly or indirectly involved in systematic inflammation and organ dysfunction in patients with acute pancreatitis (AP). Footnote: Red asterisk indicates data based on only experimental animal studies while blue asterisk indicates data based on human and animal studies. Solid arrow indicates clear association has been proven between the factor with systemic inflammation and organ dysfunction, while dotted arrow indicates that the association has not been conclusively established

the flux of molecules (including proteins) and fluids between the vascular and interstitial compartments and is regulated by local and systemic neurohumoral mechanisms [38]. Even though the precise mechanisms of endothelial dysfunction have not been demonstrated in human AP, based on mechanistic studies in experimental models, it appears that during the initiation of AP, the local intra-pancreatic cytokines increase vascular permeability by altering the function of gap junctions (zona adherens) [39]. In mild inflammation, the cadherin protein, which is an important component of the zona adherens, gets internalized thereby weakening the gap junction, while in severe inflammation there is actual disruption of the junction. In both cases, there will be leakage of fluids and proteins from the capillaries into the interstitial space to varying degrees. In mild pancreatic inflammation, the capillary leak rapidly resolves. In severe inflammation, with the progression of SIRS, the capillary leak also progresses to involve other viscera (especially the lungs). The earliest clinical manifestations of capillary leak include hypotension, hemoconcentration and compromised tissue perfusion due to third spacing. Eventually, several mediators, namely neutrophil products (e.g. myeloperoxidase), platelet activation factors, inflammasomes [40], neutrophil extracellular traps [41], altered von Willebrand factor-a disintegrin and metalloproteinase with thrombospondin motifs 12 (ADAMTS12) axis (that results in microvascular thrombosis) [42], activated coagulation cascade within the microcirculation, hypercytokinemia, trypsin and unsaturated fatty acid (UFA) [43], could act in concert to cause further pancreatic and distant organ injury. However, which of these mediators contributes to what proportion of pancreatic or systemic injury is not clear and studies have even shown variable results [43].

Clinical implications: Since fluid flux across the capillary barrier is one of the earliest events that initiates ischemia and OF, fluid replacement is the logical initial step in the management. However, in severe disease, since there are also impaired neurohumoral mechanisms that result in impaired restoration of the fluid dynamics, it could result in fluid overload and worsening of OF. Therefore, initial fluid therapy should be moderate and goal directed.

Susceptibility to infected pancreatitis necrosis

Up to 15% to 20% of patients with AP develop necrotizing pancreatitis and only around a third of these develop infections in the necrotic tissue [44, 45]. This implies that all patients with ANP do not progress to infected pancreatic necrosis (IPN) and there exist risk factors that would increase the likelihood of infections. Several studies have reported associations of various laboratory parameters (e.g. procalcitonin, systolic blood pressure (BP), blood urea nitrogen (BUN)) [46–49] as predictors for IPN. However, none of these markers is directly related to pathogenesis of infection. In fact, while one study reported that procalcitonin was not useful in early prediction of IPN [50], another recent meta-analysis concluded that PCT could predict IPN after 72 hours of admission [51]. Even though this study shows some promise in the predictive capability of procalcitonin, it did not consider the duration of illness in its predictive capability. This would have been more clinically relevant, thereby questioning the utility of the findings.

From a mechanistic perspective, IPN boils down to a fundamental molecular concept called compensatory anti-inflammatory response syndrome (CARS). Simplistically speaking, while SIRS in general mounts an immune reaction as a response to DAMPs or PAMPs, CARS follows SIRS to dampen the inflammation to prevent excess tissue damage. CARS is mechanistically a complex series of events characterized primarily by dampened type-1 T-helper cell-mediated immune response (proinflammatory cytokine production), an increase in anti-inflammatory cytokines (e.g. IL-10) and reduction in human leukocyte antigen (HLA)-DR expression on monocytes [52]. Physiologically, HLA-DR, an important component of innate immunity, is expressed by monocytes. Its role is to present bacterial and other foreign peptides/antigens to the T-cells, which are part of the adaptive immune response [53]. Therefore, in the context of infections, immunodepression (< 60% HLA-DR expression) or immunoparalysis (< 30% HLA-DR expression) can weaken the body's natural defense against microbial infections [54].

In the context of AP, it was indeed shown in earlier time course studies that HLA-DR expression comes down early in the course of AP, with the lowest level on Day 3, followed by a gradual recovery [55]. Low HLA-DR expression was associated with severity of AP. In a subsequent study, it was shown that patients in whom HLA-DR downregulation persisted beyond the second week of illness had over 10-folds elevated risk of developing IPN eventually [56]. This was further confirmed in a follow-up study involving patients with and without IPN, in which a significant negative correlation of HLA-DR expression with proinflammatory cytokines (IL-6 and IL-8) and procalcitonin was demonstrated beyond the second week of illness [57]. This implied a link between CARS and infected necrosis.

Alteration of the kynurenine pathway (KP), which is primarily responsible for tryptophan degradation, has been associated with immune dysregulation in inflammatory and autoimmune conditions. In the context of AP, studies on rodent models reported that a key enzyme of the kynurenine pathway, namely kynurenine-3-monooxygenase (KMO), could contribute to organ dysfunction [58]. In our clinical studies that included 134 patients with ANP (including those with and without infected necrosis), we observed a progressive reduction in plasma tryptophan levels, from

healthy controls to patients with AP without IPN and further in those with IPN. We also demonstrated an increased activity of the rate-limiting enzyme of the kynurenine pathway, namely indoleamine 2,3 dioxygenase (IDO), that was suggested by an increase in the kynurenine:tryptophan ratio, with the maximum being in patients with IPN [57]. It is known that the IDO enzyme is expressed in innate immune cells under the influence of proinflammatory cytokines during acute inflammation and it suppresses the immune response mediated by monocytes. We also observed that there was a significant positive correlation of plasma tryptophan with HLA-DR expression and a significantly negative correlation with TLR-4 expression (a marker for infection). This clearly implied associations between altered kynurenine pathway, immunosuppression and IPN [57]. These results also position plasma tryptophan in a potential biomarker role. Metabolomic studies further re-confirmed a significant reduction of tryptophan in patients with IPN compared to those without. Area under the receiver operating characteristic curve (AUROC) analysis showed that a plasma level of 9 µg/mL of tryptophan had the highest accuracy (area under curve [AUC] 91.9 [95% confidence interval {CI} 86.5–97.4]) to discriminate patients with IPN from those without IPN [57].

Figure 3 depicts a schematic representation of the sequence of events of the progression of AP from initial injury to the development of infected necrosis.

Clinical implications: So far, four RCTs have proven the futility of the use of prophylactic antibiotics in preventing IPN and are currently not recommended by most practice guidelines [13–15]. Several possibilities, namely heterogeneity in study design, antibiotic choice, selection criteria, treatment duration and outcome measures, have been suggested for the resulting inefficacy. These studies did not include only patients with definitive risks for IPN. Therefore, future studies should include high-risk features such as low HLA expression and/or tryptophan as an enrolment criterion to achieve more realistic outcomes.

Role of the intestine in the severity of AP

The intestine is an important component in the conundrum of AP and its importance is getting its due attention in recent years. Three components of the intestine that have been implicated in severity of AP, albeit with contradictions, are the gut mucosal barrier, intestinal microbiota and the mesenteric lymph. Figure 4 depicts a schematic representation of the involvement of the above three components.

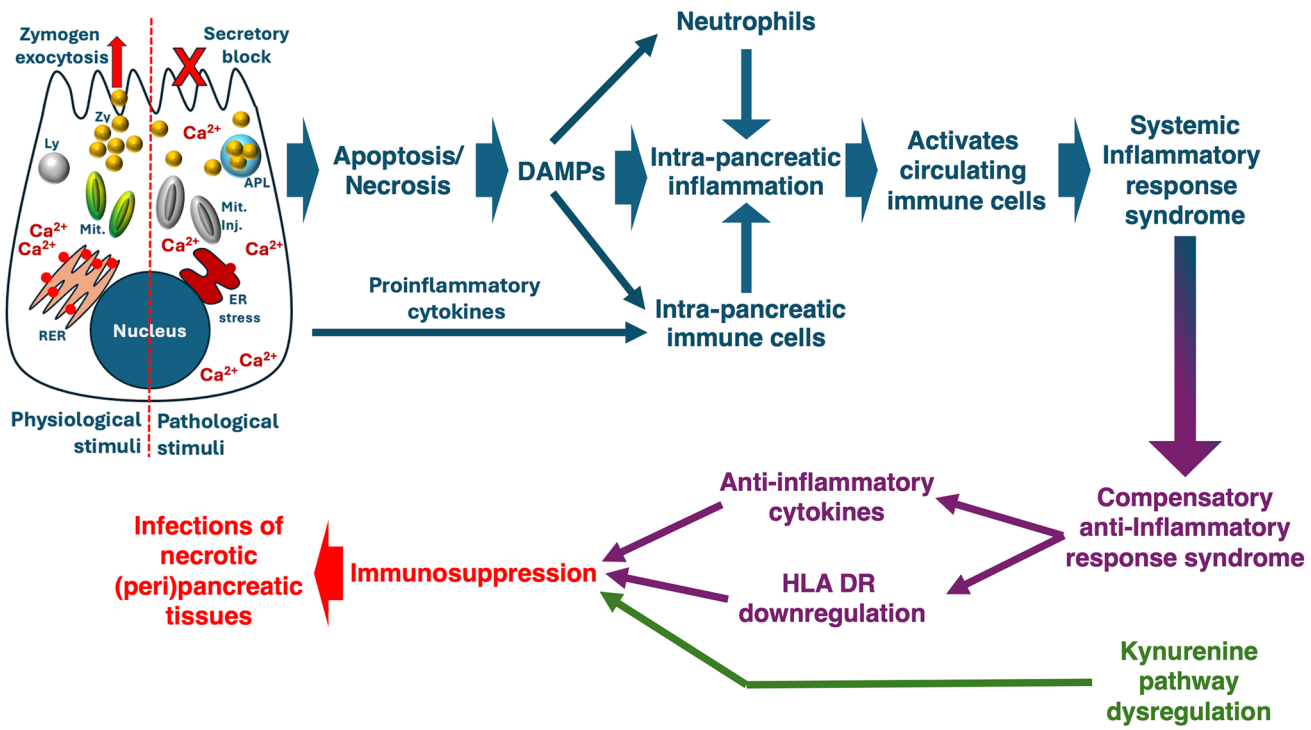

Fig. 3 Schematic diagram representing how healthy pancreatic acinar cells undergo intra-acinar molecular changes following an injury that eventually leads to local intra-pancreatic and systemic inflammation, followed by the development of susceptibility factors (compensatory anti-inflammatory response and kynurenine pathway alterations) for infected pancreatic necrosis. *Ly* lysosome, *Zy* zymogens, *Mit* mitochondria, *RER* rough endoplasmic reticulum, *APL* autophagolysosome, *ER* endoplasmic reticulum, Ca^{2+} calcium

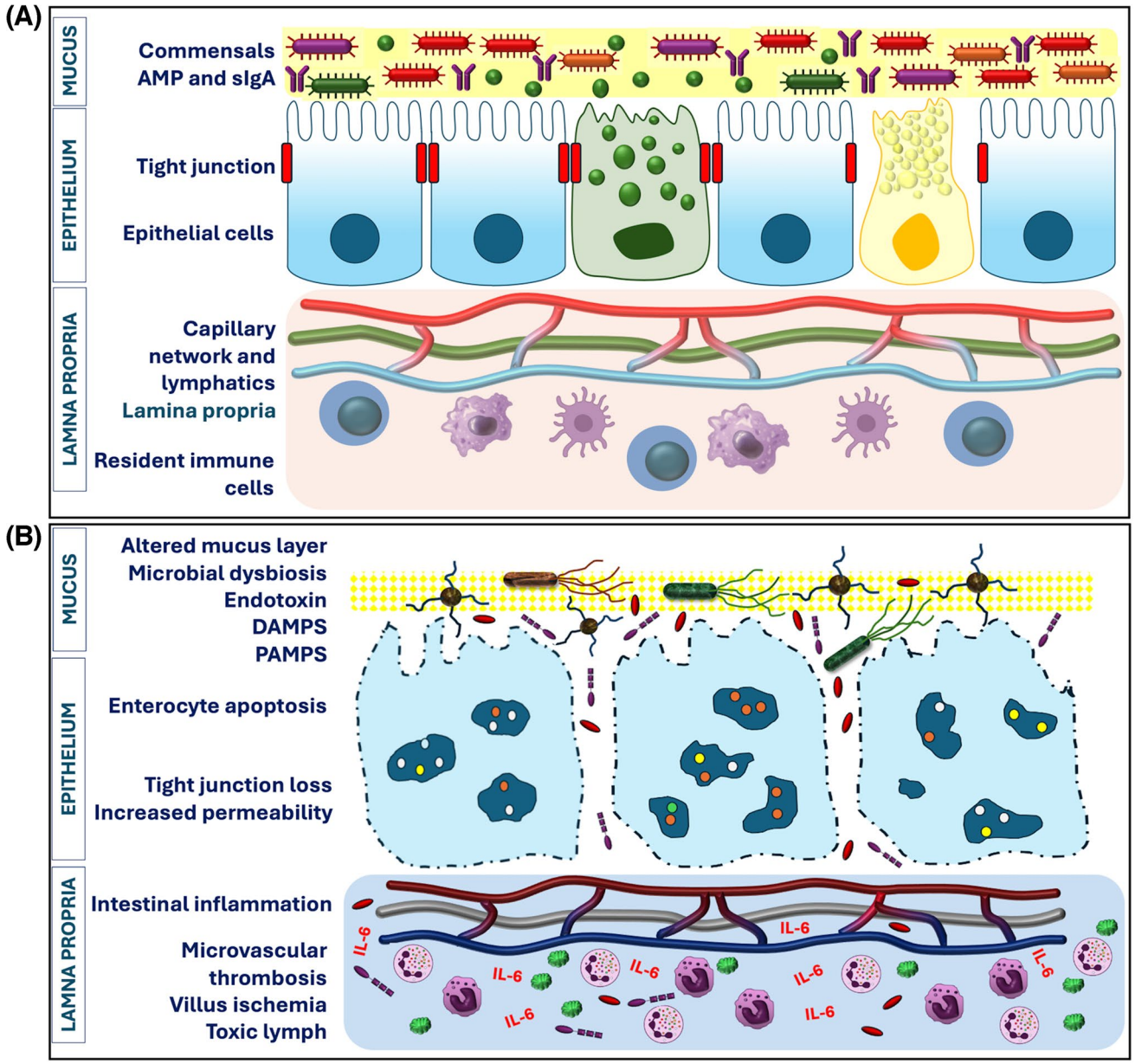

Fig. 4 Pictorial representation of the components of the gut barrier in health and acute pancreatitis. **A** A normal mucosal barrier with an intact mucous layer populated with healthy commensal bacteria, antimicrobial peptides and secretory IgG; cellular monolayer comprising epithelial cells (blue) with tight junctions, paneth cells (green) and goblet cells (yellow) and lamina propria with intact capillary system and lymphatics and resident immune cells (macrophages, dendritic cells and T regulatory cells). **B** The alterations that occur during acute pancreatitis (AP) characterized by alteration of the mucus layer with the growth of pathogenic organisms, the release of pathogen-associated molecular patterns (PAMPS), endotoxins; epithelial cells apoptosis and loss of tight junctions; lamina propria with inflammatory cells (neutrophils, mononuclear cells), cytokines, translocated endotoxins, damage-associated molecular patterns (DAMPS), an altered capillary system that results in mucosal ischemia and lymphatics that carry DAMPS and other inflammatory mediator to the systemic circulation

1. The gut mucosal barrier

The gut barrier consists of various structural and functional components, with the single layer of columnar epithelial cells being the most crucial. Two major components contributing to this barrier are the microvilli, which possess an electrostatic charge in the apical region of the columnar cells and the zona occludens (tight junctions), which surround the apical regions and connect adjacent cells to the cellular cytoskeletons [59, 60]. The former prevents microbial adhesion due to the small intervillous area and electrostatic repulsion, while the latter prevents intercellular entry

of molecules, including endotoxins and other PAMPs, with a radius greater than 11.5 angstroms [61].

A meta-analysis from 2014 that evaluated 44 studies demonstrated a 59% (95% CI 48–70%) prevalence of gut barrier dysfunction in AP [62]. However, gut barrier dysfunction was not found to be associated with the disease severity or the day of hospitalization when testing for barrier dysfunction was performed. Additionally, although nine out of 13 studies reported improvement in gut barrier function after following nutritional intervention, only three of the six studies that used standard enteral nutrition showed improvement. A subsequent prospective clinical study linked increased gut barrier permeability (using the lactulose:mannitol ratio) and to bacterial overgrowth (detected by 16SrDNA sequencing) early in the disease course [63]. A mechanistic explanation for this was proposed based on the observed downregulation of mucosal barrier proteins claudins and zona occludens 1 in the duodenal crypts and villi. These occurrences were observed within the first two weeks of AP.

A major cellular factor that impacts the intestinal epithelial barrier is the activated neutrophils [64]. These cells increase the inflammatory response by releasing a host of vasoactive and proinflammatory mediators (e.g. lysozymes, IL-6, IL-8). Activated neutrophils also release proteases, generate free radicals and contribute to intestinal ischemia by activating the coagulation cascade and inhibiting fibrinolysis. The intestinal villi, particularly the apex, are especially susceptible to ischemia due to the arrangement of the villus microcirculation which facilitates arteriovenous shunting of blood and ischemia of the villus tip [65]. This results in enhanced intestinal epithelial cell apoptosis and disruption of the barrier. This injury is enhanced by prolonged fasting which further results in epithelial cell injury. The intestinal ischemic injury receives a second hit when there is restoration of blood flow (reperfusion) during which the enzyme xanthine oxidase converts hypoxanthine to xanthine with the release of superoxide that further generates oxygen-free radical resulting in lipid peroxidation injury to the epithelial cell membrane [66]. Intestinal ischemia results in the lowering of the intestinal pH, which was shown to be associated with MODS and death. It was shown that an intestinal pH of 7.25 or lower in patients within 48 hours of intensive care unit (ICU) admission was significantly associated with mortality [67].

However, the direct role of altered intestinal permeability and bacteremia as a cause for infected necrosis and OF gets somewhat weakened by observations that patients with severe ulcerative colitis and fistulizing Crohn's disease (both known to be associated with gut barrier dysfunction) seldom develop distant infections and bacterial sepsis.

2. Gut microbial dysbiosis

The healthy gut microbiota forms an important component of the protective intestinal barrier. In the physiological state, while the intestinal paneth cells release antimicrobial peptides (AMPs) such as defensin and cathelicidins to protect from gut pathogens, the healthy microbiota produces short-chain fatty acids (SCFAs), especially butyrate, among other important metabolites [68]. Butyrate contributes significantly to the maintenance of the intestinal epithelial barrier.

Gut microbial dysbiosis in patients with AP has been shown in several clinical studies [69, 70]. The most consistent findings were a reduction in alpha diversity and an increased abundance in proinflammatory organisms such as *Enterobacteriaciae*, *Enterococcus*, *Escherichia-Shigella* and *Veilonella.* There was also a parallel reduction in the abundance of some of the health-promoting organisms, namely *Faecalibacterium*, *Bifidobacterium* and *Prevotella.* Dysbiosis was also implicated in the severity of AP as demonstrated by a positive correlation of IL-6 with *Enterobactereciae* and *Enterococcus.* However, this kind of observational data might not necessarily imply a cause-effect relationship. It is a common practice to prescribe prophylactic antibiotics early on in AP despite guidelines recommending against it [71]. Many of these patients who are initially kept nil per oral are given proton pump inhibitors (PPIs). Both antibiotics and PPIs can also cause dysbiosis in these patients irrespective of severity [72]. Furthermore, even though experimental studies that evaluated the impact of gut microbial manipulation on the severity of AP had demonstrated benefit [73–75], clinical studies had demonstrated heterogeneous results. For instance, while randomized controlled trials by Pan et al. and Olah et al. demonstrated clinical improvement of AP with probiotics, the PROPATRIA trial by the Dutch group reported an increase in mortality in the treatment group [76–78]. All these studies used *Lactobacillus*-dominant strains with or without various combinations of prebiotics. A follow-up study on the PROPATRIA trial showed that in the patients with OF, there was early enterocyte damage and gut barrier dysfunction that resulted in bacteremia, infected necrosis and increased mortality [79].

Based on the current body of evidence, even though the presence of gut barrier dysfunction and microbial dysbiosis is strongly demonstrated, it may not be apt to ascribe these events to a direct causal association. Experimental and clinical studies with robust designs that would address the temporal progression of these events and their interrelations (whether inflammation and intestinal barrier dysfunction result in dysbiosis or vice-versa) would be required to evaluate the precise role.

Table 1 Therapeutic modalities for early acute pancreatitis

Targets	Agents	Likelihood of benefit	Status
ACINAR EVENTS	Protease inhibitors (e.g. gabaxate, aprotinin, ulinastatin)	**Uncertain**	• Retrospective studies showed benefit [12, 86] • Require high-quality multicenter RCTs
	Antisecretory agents (e.g. octreotide)	**Unlikely**	• No benefit demonstrated in clinical trials [12]
LOCAL AND SYSTEMIC INFLAMMATION	Steroids	**Has potential for benefit**	• Earlier meta-analysis showed benefit [87] • Require better quality clinical trials • Clinical trial currently ongoing (NCT05160506)
	TNF-α inhibitor (infliximab)	**Uncertain**	• Require high-quality clinical trials • 1 RCT (RAPID I) currently ongoing in UK (NCT03684278)
	Single anti-cytokine therapy (e.g. IL-6 inhibition)	**Uncertain**	• Require high-quality clinical trials
	Multiple anti-cytokine therapy	**Likely**	• Require high-quality proof-of-concept studies
	Calcium entry inhibitor (CRAC channel inhibitor)	**Likely**	• Demonstrated benefit in dose–response/efficacy RCT [28, 88] • Require multicenter validation studies
	COX 2 inhibitor (parecoxib followed by imrecoxib)	**Likely**	• Demonstrated benefit in RCT [89] • Require multicenter validation studies
	Orlistat	**Uncertain**	• Experimental studies show variable results [90, 91] • Require high-quality clinical trials
	Extra-corporeal removal of cytokines (CytoSorb)/toxins/plasma exchange/plasmapheresis	**Uncertain/ Unlikely**	• Require high-quality RCTs
	Pentoxifylline (TNF-α inhibition)	**Unlikely**	• No benefit demonstrated in an RCT [92]
	Lexipafant (PAF receptor antagonist)	**Unlikely**	• No benefit demonstrated in a phase 3 multicenter RCT [93]
ORGAN DYSFUNCTION	Early goal-directed moderate fluid therapy	**Beneficial**	• Suggested by RCT
	Early enteral feeding	**Beneficial**	• Suggested by RCT
	Omega-3 fatty acid supplementation	**Has potential for benefit**	• Meta-analysis has shown benefit, but study size small [94] • Require well-designed RCTs
INFECTED NECROSIS	Gut bacterial manipulation (antibiotics/FMT/probiotics/prebiotics)	**Has potential for benefit**	• Require proof-of-concept studies and well-designed RCTs with the right modalities
	Supplementations (butyrate/tryptophan)	**Has potential for benefit**	• Require proof-of-concept studies and well-designed RCTs • A trial on butyrate going on (NCT06147635)

IL interleukin, *TNF* tumor necrosis α, *RCT* randomized controlled trial, *FMT* fecal microbial transplantation

3. Mesenteric lymph

In the context of systemic inflammation and sepsis, mesenteric lymph has been implicated in the delivery of gut-derived toxins and inflammatory mediators [80]. A similar concept has also been evolving, albeit not widely studied, in the context of AP. One of the earliest studies to report the involvement of mesenteric lymph in the severity of AP demonstrated that rodents with experimental AP had a more severe pancreatic injury, reduced pancreatic microcirculation and increased intra-pancreatic lymphocyte adhesion in rodents, which were additionally treated with mesenteric lymph derived from animals with AP [81]. Subsequent studies have confirmed the role of mesenteric lymph in OF in experimental AP by demonstrating severe cardiac dysfunction in the animals with intact mesenteric lymphatics compared to those with thoracic duct ligation or external diversion of mesenteric lymph [82]. It was also shown that

specific ligation of the mesenteric lymph duct resulted in a milder form of lung injury along with lower concentration of endotoxin, nitric oxide, IL-1 and TNF- α in the plasma and lung tissue, further indicating its role in systemic inflammation and organ dysfunction [83]. Earlier, it was not known what component in the lymph contributed to the inflammation. However, more recent studies have implicated DAMPs such as HMGB1 and histones derived from the injured intestine that flow into the systemic circulation via mesenteric lymph in contributing to systemic inflammation [84, 85]. It is to be noted that all these studies were in experimental models and clinical validation is needed from human experiments, which are challenging to carry out.

Clinical implications: Based on the aforementioned premises, it becomes prudent to maintain the intestinal perfusion and gut barrier integrity. Even though studies have shown inconsistent results, it would still be worth keeping the gut functioning with early oral feeds. If the patient does not tolerate orally, they should be fed through a nasojejunal (NJ) tube. In sick patients who do not tolerate oral or tube feeding and complain of post-prandial abdominal pain and/or vomiting, the possibility of mesenteric ischemia should be considered and evaluated accordingly.

Novel molecules

Table 1 shows several molecules that have been used or have the potential for use in early AP based on the mechanisms [86–93].

To conclude, no definitive, curative or preventive strategies exist for early AP, despite a huge gamut of experimental and clinical studies. However, some of the mechanistic events do appear to offer promising targets that need to be explored with more rigor and robustness. Even though acinar events are important, emphasis should be given to the understanding of the temporal progression of AP from SIRS to organ dysfunction, which is the predominant determinant of mortality.

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Declarations

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