A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management

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\textbf{Abstract:} Acute pancreatitis (AP) is an inflammatory disease that can progress to severe acute pancreatitis (SAP), which increases the risk of death. AP is characterized by inappropriate activation of trypsinogen, infiltration of inflammatory cells, and destruction of secretory cells. Other contributing factors may include calcium (Ca\textsuperscript{2+}) overload, mitochondrial dysfunction, impaired autophagy, and endoplasmic reticulum (ER) stress. In addition, exosomes are also associated with pathophysiological processes of many human diseases and may play a biological role in AP. However, the pathogenic mechanism has not been fully elucidated and needs to be further explored to inform treatment. Recently, the treatment guidelines have changed; minimally invasive therapy is advocated more as the core multidisciplinary participation and “step-up” approach. The surgical procedures have gradually changed from open surgery to minimally invasive surgery that primarily includes percutaneous catheter drainage (PCD), endoscopy, small incision surgery, and video-assisted surgery. The current guidelines for the management of AP have been updated and revised in many aspects. The type of fluid to be used, the timing, volume, and speed of administration for fluid resuscitation has been controversial. In addition, the timing and role of nutritional support and prophylactic antibiotic therapy, as well as the timing of the surgical or endoscopic intervention, and the management of complications still have many uncertainties that could negatively impact the prognosis and patients’ quality of life. Consequently, to inform clinicians about optimal treatment, we aimed to review recent advances in the understanding of the pathogenesis of AP and its diagnosis and management.

\textbf{Keywords:} Acute pancreatitis (AP); diagnostic criteria; pathogenetic mechanism; management; complications; prognosis

Submitted Jun 19, 2020. Accepted for publication Nov 26, 2020.

doi: 10.21037/atm-20-4802

\textbf{View this article at:} http://dx.doi.org/10.21037/atm-20-4802

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Introduction

In recent years, the incidence of acute pancreatitis (AP) has increased globally to approximately 34 cases per 100,000 persons annually (1). Although gallstones and alcohol consumption are the most common causes of AP, hypertriglyceridemia, drugs, endoscopic retrograde cholangiopancreatography (ERCP), trauma, obesity, diabetes, and infection are also well-known triggers of local and systemic inflammation (2,3). In recent years, the treatment concept of AP has undergone considerable changes, more advocacy is given to minimally invasive therapy as the core multidisciplinary participation and step-up approach (4). The surgical procedures have gradually changed from open surgery to minimally invasive surgery that mainly includes percutaneous catheter drainage (PCD), endoscopy, small incision surgery, and video-assisted surgery (4). Open surgery involves abdominal and/or retroperitoneal necrosectomy (RN). Due to the complexity and diversity of its conditions, AP is no longer limited to a single treatment, as a variety of therapies have been combined and the degree and scope of necrosis, which is the so-called step-up approach. In such treatment, a multidisciplinary team is formed, focusing on surgical, endoscopic and radiological interventions and critical care medicine. Individualized treatment plans should be formulated according to the patients with specific conditions, and the step-up approach should be further applied to the treatment concept of AP to improve the cure rate and reduce the incidence of complications, so as to improve patient quality of life and long-term prognosis (5,6). Owing to timely and accurate diagnosis and treatment, the population mortality and morbidity of AP have decreased over the past decade (7); nonetheless, the sequelae of AP has remained severe (8). Impaired pancreatic endocrine and/or exocrine function due to massive necrosis of pancreatic parenchymal cells is identified in approximately 20% of patients after an episode of AP (9). Moreover, chronic pancreatitis (CP) develops in approximately 10% of patients after a first episode of AP and in about one-third of patients with recurrent AP, with men and patients who abuse alcohol being at a specifically higher risk of transition from AP to CP (10). Of further clinical significance, prediabetes or diabetes mellitus develops in approximately 37% of patients after an initial episode of AP; overall, patients are at a two-fold higher risk of diabetes development over the subsequent 5 years after an episode of AP than the general population (11).

In the past decade, considerable advancements have been made in the research on the pathogenesis of AP related to the mechanism of calcium (Ca$^{2+}$) overload, trypsinogen activation, impaired autophagy and ER stress have been elucidated, which is helpful to further understand the occurrence and development process of AP. Recently, it has been found that exosomes, as transport and storage tools for proteins, nucleic acids, and lipid substances, are widely involved in the pathophysiological processes of a variety of diseases, and may play a biological regulatory role in the evolution of AP (12). Because related research remains relatively rare and the pathogenesis is not fully clear, research related to the exosomes in the pathogenesis of AP has become a popular research topic for scholars. Therefore, exosomes may be a new biomarker or target for the diagnosis and treatment of AP in the future. However, no effective guidelines for AP treatment exist; as such, there is a need to better understand the pathogenesis of pancreatitis to identify potential novel therapeutic targets. Hence, we aimed to review recent advances in the understanding of the pathogenesis of AP as well as its diagnosis and management to better inform treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4802).

Methods

We conducted a literature search for published manuscripts on AP up to April 2020 in PubMed, Web of Science, and EMBASE databases and employed the following search terms: “acute pancreatitis”, “pancreatitis”, “diagnostic criteria”, “pathogenetic mechanism”, “clinical management”, “complication”, and “prognosis”. Qualitative and quantitative data were extracted by interpreting each paper in cycles to avoid missing potentially valuable data.

Discussion

Diagnostic criteria and classification of AP

The 2012 Atlanta Classification was revised to better and more accurately diagnose AP, requiring two of the following three diagnostic criteria to be fulfilled (13): (I) persistent and severe abdominal pain, often radiating to the back; (II) a threefold increase in serum lipase and/or amylase above the upper limit of the normal value; (III) and typical imaging manifestations of AP. We note, however, the limited diagnostic value of serum lipase and amylase in hyperlipidemic pancreatitis and alcoholic pancreatitis, as
well as acute cholecystitis, gastrointestinal perforation, and intestinal obstruction as other causes of elevated amylase and lipase levels. Therefore, imaging is generally necessary for AP diagnosis.

An enhanced computed tomography (CT) scan is the most effective method to diagnose AP and pancreatic necrosis, with typical features on cross-section imaging including enlargement of the pancreas, pancreatic edema, uneven density, peripancreatic fat stranding, and fluid collection. Necrotizing pancreatitis should be considered when multiple “soapy” density-reducing regions of varying sizes appear in an enlarged pancreas (13). However, these features are not apparent in the early stage of AP, with evidence of pancreatic necrosis typically developing about 72 hours after onset of clinical symptoms (14). Consequently, for patients presenting with typical clinical symptoms of AP corroborated by laboratory tests, imaging may not be necessary during the first 72 hours after admission (15–17). However, if the possibility of necrotizing pancreatitis is suspected, an enhanced CT scan or CT perfusion should be performed to monitor and manage adverse outcomes on an emergent basis to prevent irreversible pancreatic necrosis and to reduce the risk of death (18,19). Several scoring systems are also available to evaluate the severity of AP, including the Acute Physiology and Chronic Health Examination II score, the CT severity index (CTSI), the Harmless Acute Pancreatitis Score, and the Ranson score (20,21). Of these, the CTSI has good prognostic value, with a score <3 being predictive of a better prognosis (22).

AP can be classified as mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) (13). MAP is mainly characterized by interstitial edematous pancreatitis without organ failure and local or systemic complications. In contrast to MAP, MSAP and SAP are mainly necrotizing pancreatitis. MSAP often results in transient organ failure, lasting for <48 hours, with or without local or systemic complications. Local complications typically include fluid collection.

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**Figure 1** (a) Cholecystokinin, alcohol, and bile acids activate the ER to release stored Ca\(^{2+}\) via the InsP3 receptor pathway. ORAI1 promotes Ca\(^{2+}\) to enter the cell from the extracellular space, further increasing the Ca\(^{2+}\) overload. (b) Sustained Ca\(^{2+}\) overload increases the permeability of MPTP, which determines the sensitivity of cyclophilin D. (c) Change in the membrane potential, leading to ATP depletion and cell necrosis. (d) ATP depletion damages acinar cells by blocking SERCA and PMCA, which aggravates the intracellular Ca\(^{2+}\) overload. (e) Ca\(^{2+}\) overload can activate trypsinogen and inflammatory signaling pathways. (f) Ca\(^{2+}\) overload can also cause mitochondrial dysfunction, leading to impaired autophagy. ER, endoplasmic reticulum; Ca\(^{2+}\), calcium; MPTP, mitochondrial permeability transition pores; ATP, adenosine triphosphate; SERCA, smooth ER Ca\(^{2+}\) channels; PMCA, plasma membrane Ca\(^{2+}\) channels.
around the pancreas, formation of a pancreatic pseudocyst, and sterile or infected pancreatic necrosis (IPN) (23,24), whereas systemic complications, which develop in 20% of AP cases, are characterized by intermittent organ failure and deterioration in disease status (25). SAP, on the other hand, is characterized by persistent organ failure, lasting for >48 hours, and is associated with poor prognosis and death in approximately 30% of cases (13,26).

**Intracellular pathogenetic mechanisms of AP**

AP is a common disease of the digestive system, with a multifactorial pathogenesis, including Ca\(^{2+}\) overload, trypsinogen activation, impaired autophagy, endoplasmic reticulum (ER) stress, and exosomes. Among them, Ca\(^{2+}\) overload and trypsinogen activation are both equally important intracellular pathogenetic mechanisms of AP. In addition, other factors affect the development of AP, to a certain extent.

**Ca\(^{2+}\) signaling and mitochondrial dysfunction**

Ca\(^{2+}\) overload is a common mechanism that leads to cell damage in the body. Under a normal physiologic state, cholecystokinin activates the ER to release stored Ca\(^{2+}\) via the InsP3 receptor and ryanodine receptor pathways, with the former playing a major role in this process (27,28). The resultant Ca\(^{2+}\) influx stimulates the mitochondria to produce adenosine triphosphate (ATP). Simultaneously, the activated secretory granules in the apex of acinar cells release protease (29). An overload of intracellular Ca\(^{2+}\) and mitochondrial dysfunction, triggered by cholecystokinin, alcohol consumption, and bile acids, have been shown as key steps in SAP development caused by acinar cell dysfunction (27,30,31). Moreover, Ca\(^{2+}\) release-activated Ca\(^{2+}\) channel protein 1 (ORAI1) promotes extracellular Ca\(^{2+}\) to enter the cell, which further increases the Ca\(^{2+}\) overload (32). Sustained intracellular cytosolic Ca\(^{2+}\) overload results in mitochondrial membrane damage, increasing the permeability of mitochondrial permeability transition pores (MPTP), which determines the sensitivity of cyclophilin D and changes the membrane potential, leading to a decrease in ATP production (31,33). ATP depletion damages acinar cells by blocking the ATP-dependent smooth ER Ca\(^{2+}\) channels (SERCA), which transfer Ca\(^{2+}\) from the intracellular to the ER, and ATP-dependent plasma membrane Ca\(^{2+}\) channels (PMCA), which transfer Ca\(^{2+}\) from the intracellular to the extracellular space (27,34). This process causes dysfunction of the Ca\(^{2+}\)-Na\(^{+}\) pump on the cell membrane and the Ca\(^{2+}\) pump and ATP-dependent channels on the ER, which aggravates intracellular Ca\(^{2+}\) overload. Finally, Ca\(^{2+}\) overload activates intracellular and pericellular enzymes, resulting in pancreatic self-digestion (27,35). Mitochondrial dysfunction impairs cell autophagy, with a resultant production of reactive oxygen species (ROS) and cytokines, thereby aggravating pancreatic cell damage. Damaged pancreatic cells produce damage-related molecules, such as tissue factor, DNA, and heat shock protein, which activate NF-kB, MAPK, STAT3, and PI3K inflammatory signaling pathways, extending local inflammation to systemic inflammation (36,37). Mitochondrial injury aggravates ER stress and lysosomal damage, as well as the release and activation of cathepsinogen and trypsinogen, leading to cytoplasmic protein degradation and cell necrosis (Figure 1) (30). Based on the study of the mechanism of Ca\(^{2+}\) overload, blocking Ca\(^{2+}\) channels to prevent AP from progressing to necrotizing pancreatitis might warrant further investigation. ORAI1 channel inhibitors can prevent extracellular Ca\(^{2+}\) ions from entering acinar cells and effectively relieve intracellular Ca\(^{2+}\) overload. Studies have shown that ORAI1 channel inhibitors can effectively prevent necrosis in AP in animal models and human acinar cells and can significantly alleviate the degree of local and systemic inflammation (38). Furthermore, MPTP inhibitors may become a potential target for AP treatment, which can effectively prevent the reduction in ATP production, maintain the transport of intracellular Ca\(^{2+}\) ions by ATP-dependent SERCA and PMCA channel proteins, and reduce the probability of intracellular Ca\(^{2+}\) overload. As a MPTP inhibitor, TRO40303 can effectively maintain the cell membrane potential and prevent necrosis in animal models of alcoholic pancreatitis and human acinar cells (39). TRO40303 is effective and well tolerated in the treatment of acute myocardial infarction and hepatitis and may be an effective way to treat AP (40,41). A multicenter clinical trial is underway to evaluate the effectiveness of high-calorie parenteral nutrition (PN) to maintain sufficient ATP consumption during AP (42).

**Trypsinogen activation**

Trypsinogen activation is another important, widely studied pathogenetic pathway of AP. Trypsinogen cannot be activated due to the presence of trypsin inhibitors and zymogen granule exocytosis at the apex of acinar cells (43); hence, it cannot trigger AP. Alcohol consumption, bile acids, and pancreatic toxic substances stimulate acinar cells, resulting in the increased synthesis of lysosomal and digestive enzymes in...
these cells. Furthermore, pancreatic toxic substances inhibit the release of zymogen granules from the apex of acinar cells, leading to an increase in the content of zymogen granules. The lysosome and zymogen granules become fused, a process known as colocalization (43,44). Cathepsin B in lysosomes activates trypsinogen, causing the release of cathepsin B and trypsin into the cytoplasm following lysosomal membrane rupture (45). Cathepsin B in lysosomes also acts on the RIP3-RIP1-MLKL signaling pathway to promote RIP3-RIP1 necrosis complex formation. (c) The RIP3-RIP1 complex acts on the MLKL, causing MLKL phosphorylation and oligomerization, which then translocates to the plasma membrane, ultimately leading to acinar cell necroptosis. (f) The cathepsin B released after lysosomal membrane rupture leads to the release of cysteine-c from the mitochondria, which activates caspase-3 and mediates cell apoptosis.

**Figure 2** (a) Alcohol, bile acids, and pancreatic toxins stimulate acinar cells, increasing lysosome synthesis. (b) Pancreatic toxins inhibit the release of zymogen granules from the apex of acinar cells, which leads to an increase in the content of zymogen granules. (c) The lysosome and zymogen granules become fused, a process known as colocalization. (d) Cathepsin B causes trypsinogen activation, resulting in the release of cathepsin B and trypsin into the cytoplasm. The released cathepsin B acts on the RIP3-RIP1-MLKL signaling pathway to promote RIP3-RIP1 necrosis complex formation. (e) The RIP3-RIP1 complex acts on the MLKL, causing MLKL phosphorylation and oligomerization, which then translocates to the plasma membrane, ultimately leading to acinar cells necroptosis. (f) The cathepsin B released after lysosomal membrane rupture leads to the release of cytochrome-c from the mitochondria, which activates caspase-3 and mediates cell apoptosis.
Impaired autophagy

Autophagy is a central mechanism for cell protection, allowing cells to remove damaged, aged, and nonfunctional organelles as well as denatured protein macromolecules to provide energy for cellular regeneration and recycling (30, 57). The process of autophagy includes four main steps (58). The first step is autophagy induction, in which cells stimulated by autophagy signals form an autophagy precursor, an open circular double membrane comprised of ER, Golgi apparatus, and plasma membrane. In the second step, mediated by the autophagy-related gene (ATG), the autophagy precursors gradually enclose aged organelles to form vesicle-like structures, which develop into autophagosomes. In the third step, mediated by the lysosomal associated membrane protein (LAMP), the autophagosomes transfer their encapsulated contents to the lysosome cavity and subsequently fuse with lysosomes, under the mediating influence of LAMP. In the fourth step, after the autophagosomes are fused, they are degraded by lysosome hydrolase and the degradation products are recycled into the cell (Figure 3).

Figure 3 (a) After being stimulated by autophagy signals, cells form a circular open double membrane from the ER, with the Golgi apparatus and plasma membrane, to form an autophagy precursor. These autophagy precursors elongate aged organelles. (b) Autophagy precursors gradually enclose aged organelles to form vesicle-like structures, subsequently developing into autophagosomes. (c) The autophagosomes transfer their encapsulated contents to the lysosome cavity and subsequently fuse with lysosomes, under the mediating influence of LAMP. (d) Aged organelles are degraded by lysosome hydrolase (cathepsin B), and the degradation products are recycled in the cell. ER, endoplasmic reticulum; LAMP, lysosomal associated membrane protein.

Physiological autophagy can respond to various metabolic stresses, removing unwanted or aged organelles, and, thus, providing a defense mechanism to maintain homeostasis. Excessive autophagic activity can lead to autophagy stress or defective autophagy, aggravating damage to organelles and leading to cell death. Studies have shown that physiological autophagy does not trigger the pathological process of AP (60). However, once acinar cells are activated by pancreatic toxins, alcohol consumption, and/or bile acids, the process of autophagy is impaired, promoting inflammation and cell death. Studies have shown that impaired autophagy is a prominent pathological event in AP that is associated with the abnormal activation of pancreatic enzymes (30, 61). Of note, a few studies have reported that the extent of autophagy vacuoles formed in acinar cells and trypsinogen activation are significantly decreased in AP mouse models with knock-out ATG5, which significantly lowers the severity of AP (57, 62). This research confirms that autophagy in the early stage...
of AP activates trypsinogen, which aggravates AP disease progression (57,62). Consequently, clarification of the process of impaired autophagy early in AP could provide a new target for clinical exploration for novel AP drugs. Oxidative stress is also increased due to bacterial translocation, which further aggravates AP-associated lung injury, this process may be related to decreased autophagy level (63). The AP models of IL-22 transgenic mice and IL-22 recombinant adenovirus mice induced by caerulein confirmed that IL-22 can prevent the formation of autophagosomes through the Beclin-1 pathway, thereby reducing the severity of AP (64). Additionally, impaired autophagy leads to trypsinogen activation, ER stress, and mitochondrial dysfunction, which eventually leads to acinar cell damage and death. Therefore, how AP can restore acinar cell autophagy is an important topic for future research. Furthermore, previous studies have reported that trehalose can reduce the severity of pancreatic injury in AP animal models, which may be related to increased autophagy levels; nonetheless, the specific protective mechanism is still unclear (65).

**ER stress**

ER stress can be triggered by hypoxia, alcohol consumption, Ca\(^{2+}\) overload, and oxidative stress and results in impaired post-translational modification and increased protein synthesis (66). As pancreatic acinar cells have abundant ER, the pancreas is specifically vulnerable to ER stress (67,68). Basic cell biology studies have shown that ER over-activation may be an important mechanism that triggers and exacerbates pancreatic injury (69). ER stress is caused by an increase in unfolded or misfolded proteins in the ER. The stress signal is transmitted to the nucleus via the ER membrane, which in turn causes a series of specific target transcription and protein translation levels to

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**Figure 4** (a) ER stress can be triggered by alcohol, bile acids, pancreatic toxins, and increased protein synthesis. UPR is caused by an increase of misfolded or unfolded proteins in the ER. (b) ATF6 is transferred to the Golgi apparatus and is cleaved by S1P and S2P. The N-terminal transcription activation domain is released and transferred to the nucleus as a transcription factor to promote transcription of the target gene. (c) PERK-mediated phosphorylation of eIF2\(\alpha\) shuts off mRNA translation, decreasing the protein folding load and preventing misfolded proteins from being accumulated. ATF4 upregulation can result in CHOP expression, inducing cell apoptosis. (d) When the IRE1 signaling pathway is activated, IRE1 excises a 26 nucleotide intron to form the XBP1s. The protein encoded by the XBP1s is rapidly degraded (ERAD), relieving ER stress. ER, endoplasmic reticulum; UPR, unfolded protein response; ATF, activating transcription factor; PERK, PRK-like ER kinase.
be downregulated, allowing the cell to survive, known as the unfolded protein response (UPR). In the early stage of ER stress in acinar cells, the UPR is activated to restore ER homeostasis and allow cell survival (70). UPR is regulated by three ER transmembrane proteins: inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (71). When unfolded proteins accumulate in the ER, BiP/GRP78 dissociates with three transmembrane proteins and binds to unfolded proteins, thereby activating the UPR signaling pathways (72). PERK can be activated by self-dimerization and phosphorylation of the cytoplasmic domain, which promotes eukaryotic translation initiation factor-2α (eIF2α) phosphorylation. This process can rapidly reduce the initiation of mRNA translation, slow or suspend protein synthesis, and reduce the pressure on the ER to fold newly synthesized proteins. This is important as upregulation of ATF4 can increase the transcription of factor C/EBP homologous protein (CHOP), which induces cell apoptosis. PERK-mediated phosphorylation of eIF2α may shut off mRNA translation, decreasing the protein folding load on the ER and preventing accumulation of misfolded proteins and, thus, CHOP-induced cell apoptosis (73). ATF6 is transferred to the Golgi apparatus and is cleaved by site-1 (S1P) and site-2 (S2P) proteases. The N-terminal transcription activation domain is released and transferred to the nucleus as a transcription factor to promote the expression of the ER molecular chaperones XBP1 and CHOP (71,74). ATF6 can increase the protein folding capacity of the ER. When the IRE1 signaling pathway is activated, the IRE1, in two specific positions, excises a 26 nucleotides intron of unspliced X-box binding protein 1 (XBP-1) mRNA to form the spliced XBP-1 mRNA (XBP1s). The protein encoded by the XBP1 is rapidly degraded, relieving ER stress (71,72). UPR is a sophisticated signaling network, which can activate the PERK, ATF6, and IRE1 signaling pathways that block protein translation and synthesis. Meanwhile, the UPR pathway can also increase protein folding and increase the degradation of misfolded proteins,
both of which relieve ER stress (Figure 4). When the ER disorder exceeds the regulatory capacity of the cell, ER homeostasis cannot be restored and the resultant prolongation in ER stress causes inflammation and cell death or apoptosis (75). The occurrence and development of AP are closely related to ER stress (67,69). UPR activates the NF-κB inflammatory pathway through three signaling pathways, leading to progressive exacerbation of acinar cell inflammation and cell necrosis. The process eventually leads to AP exacerbation. Therefore, NF-κB inhibitors (IL-10 and cAMP) can block ER stress, down-regulate pro-inflammatory factors, such as TNF-α, IL-1 and IL-6, and delay the progress of inflammation (76). Meanwhile, several studies have demonstrated that peroxisome proliferator activator receptor gamma (PPAR-γ) ligand, pyrrolidine dithiocarbamate (PDTC), proteasome inhibitor, and calpain I inhibitor have inhibitory effects on NF-κB activation in experimental AP (77). Another study revealed that 4-phenylbutyric acid (4-PBA) can inhibit the activation of trypsinogen and UPR, thus alleviating the pro-apoptotic pathways associated with ER stress and reducing systemic inflammation and cell apoptosis (78). In an observational study, HMG-CoA reductase inhibitors were found to promote UPR, with long-term use of statins reducing the severity of AP. Therefore, HMG-CoA reductase inhibitors help prevent the recurrence of AP (79).

Exosomes and AP

Exosomes are vesicles secreted by various living cells, including RNA and proteins (30–100 nm in size). Considering the significant increase in exosomes in the peripheral blood of patients with AP, exosomes may play an important regulatory role in the progression of pancreatitis, which has now become a popular topic of research. In the AP model of rats, the content of the exosomes, which is released to the peripheral blood by the pancreas, was significantly increased. Some of the contents of the exosomes can directly reach the liver through the portal system and can be retained in the liver tissue, while the remaining contents of the exosomes can be degraded by the high hydrolytic activity of pancreatitis-associated ascitic fluid (PAAF) and then transferred to the hepatic tissue. Subsequently, the liver may generate and release new exosomes. When the exosomes labeled with fluorescent dye were observed, it was found that exosomes from the circulatory system could effectively reach alveolar tissues and be absorbed by alveolar macrophages. Exosomes from the circulatory system of the AP model can activate alveolar macrophages cells by converting the phenotype from M2 to M1, which in turn aggravate the degree of lung injury caused by AP (80). Meanwhile, another study found that plasma-derived exosomes can activate NOD-like receptor protein 3 (NLRP3) inflammasomes to induce pyrolysis of alveolar macrophages, thereby causing AP-related lung injury. On the contrary, inhibition of exosome release or uptake by inhibitors can suppress the pyroptosis of alveolar macrophages cells, thereby reducing the extent of AP-induced lung injury (81) (Figure 5). In addition, abundant exosomes visible in the culture medium of acinar cells during AP may be a vital condition for the activation of macrophages. Analysis of microRNA (miRNA) and target genes in exosomes confirmed that acinar cells activate macrophages mainly through the MAPK pathway in AP, which contributes to acinar cell injury via apoptosis, necrosis, and autophagy (82). These findings are of great importance in support of research on exosome-miRNA in AP. Exosomes can activate the CaN/NFAT signaling pathway via miRNA-23a, activating the transcription of various chemical factors and ATGs. This causes trypsinogen to be excessively secreted in interstitial tissues, causing local inflammation that can expand to a systemic inflammation response (83). In addition, exosome-miRNA can transfer to other organs, such as the lungs, kidney, and intestinal tract, via the circulatory system. Once activated by exosomes-miRNA, these organs begin to release new exosomes, promoting cell apoptosis and organ injury (84,85). However, exosomes derived from different cells may play different roles in the pathogenesis of AP. For example, exosomes derived from bone marrow mesenchymal stem cells (MSCs) have a healing effect on AP (86). In addition, exosomes-miR-223-3p from MSCs can also attenuate cerebral injury via inhibiting M1 polarization mediated pro-inflammatory response, which may be related with a negative effect on exosomes-miR-223-3p for CysLT$_2$R (87). Therefore, there is a need to further investigate the similarity and specificity of exosomes in different cells, tissues, and organs, the targeting mechanism of exosomes, as well as the gene regulation mechanism of target organs. As exosomes can protect RNA or protein from being damaged, it may be a promising treatment in the future (12). Hence, drug trials focusing on exosome-related targets could improve the success rate of AP treatment.

Management of AP

Fluid resuscitation

Several types of fluids are currently used for fluid
resuscitation, which mainly include crystalloid and colloidal solutions. An increased risk of mortality and kidney failure requiring renal replacement therapy has been observed when using hydroxyethyl starch instead of crystalloid solution (88,89). At present, the use of crystal fluids for fluid resuscitation is generally preferred, with colloidal fluids playing an auxiliary role (90,91). Wu et al. (92) compared lactated Ringer’s solution to normal saline with respect to C-reactive protein (CRP) levels after a 24-hour infusion. CRP levels were lower with the lactated Ringer’s solution (51.5 mg/dL) than with the normal saline solution (104 mg/dL) (P=0.02). Moreover, the systemic inflammatory response improved to a greater extent in patients treated with Ringer’s solution (84%) than in those treated with normal saline (0%) solution (P=0.035) (92). Of note, previous research has also reported a higher rate of morbidity and mortality when using saline compared to other crystalloid fluids for the treatment of SIRS (93,94). A large amount of normal saline intake can cause perchloric acid poisoning, which is associated with an increased probability of kidney injury. In this sense, Ringer’s solution provides an advantage over normal saline in terms of acid-base metabolism balance (95). Therefore, the IPA/APA guideline suggests that lactated Ringer’s solution is superior to normal saline for AP treatment (17). However, this suggestion is based on limited evidence from small-sample randomized controlled trials (RCTs); hence, further research on fluid resuscitation for AP is required (96), including large-sample, multicenter RCTs.

Pancreatitis increases the demand for fluids, with the volume of fluid replacement needed determined based on clinical disease status and the principle of balancing the intake and output fluid volume. Insufficient or slow fluid replacement will adversely affect organ function and inflammation control (97), prolonging the duration of hospitalization. However, a RCT from China is important in this regard, having found that, compared to relatively slow hemodilution (hematocrit ≥35%), rapid hemodilution (hematocrit <35%) is associated with a higher incidence of sepsis and mortality within 48 hours of hospitalization (98). Another study compared two rates of fluid infusion (10–15 vs. 5–10 mL/kg/h) among patients with SAP, with the higher rate (10–15 mL/kg/h) having been shown to be associated with a higher incidence of infectious complications and mortality (99). Based on available evidence, the American Gastroenterological Association (AGA) suggested that early goal-directed fluid therapy is important for the management of AP, being cognizant of the potential harm of blindly pursuing rapid and massive fluid resuscitation (15). Although both the ProCESS and ARISE trials showed that early goal-directed fluid therapy has no effect on the long-term mortality of patients (28 vs. 90 days), it can reduce short-term mortality and still has significance for the treatment of patients with SAP (100-102).

In addition to the issues noted above, there is a need to monitor clinical indicators to determine if treatment goals have been reached. Non-invasive indicators can be used in most cases to monitor whether fluid resuscitation goals have been achieved, including an increase in the mean arterial pressure to 65–85 mmHg, a heart rate <120 beats/min, and urine volume >0.5–1 mL/kg-h (17). Invasive indicators such as central venous pressure and cardiac output can be used to assess the effects of fluid infusion (103). Several other parameters can be utilized to evaluate the effects of fluid infusion, including BUN, hematocrit, and serum creatinine. Previous studies have reported that a hematocrit level <44–47% and an increase in BUN were predictive of pancreatic necrosis (92,104). The above-mentioned indicators need to be comprehensively evaluated together to avoid misjudgment of the clinical diagnosis, which can lead to serious adverse consequences.

Use of analgesics
Pain is the main symptom of AP, requiring appropriate analgesic treatment (105). Several types of analgesics can be used, including non-steroidal anti-inflammatory drugs, fentanyl, and meperidine. Basic research using an animal model indicated that morphine might have an adverse effect on pancreatitis, causing spasm of the Oddi sphincter, which aggravates the disease status (106). Of note, however, a Cochrane review did not find that opioids caused serious complications (107). A meta-analysis revealed similar outcomes, with no evidence of a negative effect of using morphine for pain control in AP (108). As current evidence is unclear, the use of morphine should be avoided for the control of pain in AP, with high-quality multicenter RCTs being required to clarify this issue. Considering the addictive effect of opioids, non-steroidal anti-inflammatory drugs can be selected as the first line pain management for AP without acute kidney injury and peptic ulcer (109).

Nutritional support
Patients with MAP only need short-term fasting without additional nutritional support. Nevertheless, nutritional support is an important component of comprehensive SAP treatment and provides sufficient caloric intake,
which can improve the clinical prognosis to some extent (110,111). Patients with SAP are in a state of high catabolic metabolism, resulting in a large consumption of protein and glycogen. If nutrition is not adequately supplemented in a timely fashion, it may lead to malnutrition and an immunocompromised state. Lack of enteral nutrition (EN) has been proven not only to change the composition of the intestinal epithelial barrier function, but to cause bacterial translocation, and promote the occurrence of infectious complications such as pancreatic infection and peripancreatic necrosis, which aggravates the patient’s systemic inflammatory response to a certain extent. Therefore, active and effective nutritional support is of vital importance for maintaining and improving the nutritional status of AP patients, maintaining intestinal barrier function, inhibiting bacterial translocation, and reducing systemic inflammatory response (3,112,113).

Compared to PN, EN or oral intake does not increase the risk of adverse events and may shorten the length of hospital stay in patients with AP (114,115). A review of 18 RCTs comparing EN to PN provides evidence that EN confers a benefit in reducing the rate of complications associated with infection and the length of stay in an intensive care unit, but did not have an effect on overall mortality (116). Other studies reported a superiority of EN over PN or delayed EN in reducing the rate of complications due to severe pancreatitis infection (117,118). However, it is important to note that research evidence is not consistent with regard to EN, with two studies reporting that EN did not reduce the risk of mortality and infectious complications compared to PN (119,120). This difference may be because that the patients enrolled in the above two studies were all SAP combined with septic shock, and the systemic inflammatory response was severe. Therefore, early EN support could not effectively reduce the occurrence of infectious complications and suppression of systemic inflammatory response. Overall, further research is warranted to determine the benefit, if any, of EN over PN.

Meanwhile, the optimal timing of early nutritional support for AP also remains controversial. Wu et al. (121) reported an incidence of organ failure in 81% of patients with AP in whom EN was delayed, compared to a rate of 21% among patients provided with early EN. A meta-analysis comparing delayed EN or PN (>24 hours) with early EN (<24 hours) decreased the rate of multi-organ failure and pancreatic-related infections among patients with SAP (118,122). A review of three meta-analyses indicated that, compared to delayed EN or PN, early EN (<24 hours) significantly reduced the rate of mortality, surgical intervention, multi-organ failure, and SIRS among patients with AP (123-125). In summary, compared to delayed EN or PN, EN provided within the first 24 hours of AP may be of benefit (15).

EN can be provided via a nasogastric or a nasojejunal tube. The first RCT regarding the effects of EN route was conducted in 2005, with findings indicating that there is no difference between nasogastric and nasojejunal feeding with regard to mortality, tolerance to EN, and length of hospital stay (126). Several studies reported similar outcomes, including no difference in the rate of infectious complications, gastrointestinal discomfort, and the need for energy supplementation between the two routes of EN feeding (127-129). Therefore, both nasogastric and nasojejunal feeding are feasible for EN in patients with the AP. However, the above research does not solve the problem of safety (130). Generally, nasojejunal feeding would be useful for patients at high risk of aspiration, with nasogastric feeding useful for patient with a low risk of aspiration (15).

Although clinical benefits of EN have been shown, oral feeding (OF) retains several advantages over EN, such as avoiding the pressure of a nutrient tube on the nasopharyngeal and esophageal mucosa, as well as discomfort and diarrhea caused by tube feeding (131). Consequently, several studies have compared EN to OF. A meta-analysis of five RCTs showed that early OF (within 24 hours) can shorten the length of hospital stay, while avoiding abdominal pain and bloating (132). Two RCTs also reported that most patients can tolerate OF without increased risk of complication, infection rate, and mortality (133,134). Based on this evidence, AGA recommends initiation of early OF instead of EN (15).

**Antibiotic prophylaxis**

The academic community has continued to debate the utility of antibiotic prophylaxis in the management of AP (7). Two decades ago, antibiotic prophylaxis was recognized as an important component of the clinical management of AP (7). Since then, multicenter prospective RCTs and meta-analyses have shown that prophylactic antibiotic is ineffective to prevent infections and does not lower the rate of complications and mortality among patients with SAP (135,136). Nakahara et al. (137) reported that routine use of prophylactic antibiotics might, in fact, increase the risk of hospital-acquired infections, rather than being of any benefit to patients with AP. Consequently, guidelines for AP treatment indicate that intravenous antibiotics are not recommended for the prevention of infections among patients with AP (15,17). However, patients with AP clearly...
accompanied by an infection, infection-related shock, organ dysfunction, and systematic inflammatory response need to be treated with antibiotics (17,138,139).

**Etiological treatment**

**Acute biliary pancreatitis**

The optimal timing and method for the treatment of biliary stones in patients with acute biliary pancreatitis remain controversial (140,141). For patients with MAP, laparoscopic cholecystectomy is recommended during the initial period of hospitalization (142) and may shorten the length of hospital stay and decrease the risk of gallstone recurrence, without an increased risk of conversion to open cholecystectomy, complication, or increase in procedural time (143-145). Therefore, laparoscopic cholecystectomy should not be delayed for 2 or more weeks (144,146). ERCP should be performed urgently (i.e., within 24 hours) for SAP associated with acute cholangitis, as a delay is associated with an increased risk of mortality (16,17,147-149). However, for patients with an inflammatory response, delaying cholecystectomy for ≥6 weeks is recommended until regression of the inflammatory response is achieved (110,150). For elderly patients who cannot tolerate surgery, endoscopic sphincterotomy (EST) provides a temporary option to ERCP and can decrease the risk of biliary pancreatitis recurrence (151,152). Definitive cholecystectomy can be performed once the patient’s physical condition has improved (153). However, EST does carry the risk of introducing bacteria into an otherwise sterile pancreatic necrosis, as well as increasing the risk of other complications. As such, the pros and cons of EST need to be weighed on a patient-by-patient basis.

**Hyperlipidemic AP (HLAP)**

A key point in the treatment of HLAP is the rapid reduction in the blood triglyceride (TG) level to <5.65 mmol/L to alleviate disease progression, with possible treatment including plasmapheresis and anti-hyperlipidemic drugs, often in combination with the clinical use of heparin and/or insulin, as needed (152,154). For mild HLAP, fasting and routine treatment can significantly reduce blood lipids and achieve clinical cure. However, for severe HLAP, routine treatments cannot reduce blood lipids to the normal level or the level of blood lipid decline is very slow, requiring plasmapheresis. Several studies have reported that plasmapheresis can effectively decrease serum TG, remove inflammatory lipoproteins, and shorten the length of hospital stay (155,156). Furthermore, the long-term use of anti-hyperlipidemic drugs in combination with lifestyle and dietary changes is a key component of HLAP management (157). Additionally, administration of heparin or insulin can reduce the TG level within a short time, accelerate the hydrolysis of chylomicron and TG, and achieve the purpose of reducing TG. Heparin or insulin administration can also control the patient’s blood sugar and improve the local blood circulation of the pancreas. He et al. (158) reported that treatment using low-molecular-weight heparin and insulin provides a better outcome, at a lower healthcare cost, than early high-volume hemofiltration. Serum TG levels should be monitored after discharge in these patients to prevent recurrence (159,160).

**Complications**

**Acute fluid collection (AFC)**

AFC occurs in the early phase of AP (<4 weeks), located inside and/or around the pancreas, without a cystic wall, which can be diagnosed by imaging (161). In most cases, AFC is sterile and is naturally reabsorbed without surgical intervention.

**Symptomatic pseudocysts**

When AFC persists beyond 4 weeks, there is the possibility of surrounding fibrous tissue forming a pseudocyst, with a round or ellipse shape; enlargement of the cyst may cause symptoms of compression, while infection of the cyst can induce an inflammatory response (162). For a pancreatic pseudocyst with an immature cystic wall, conservative therapy is generally recommended, including the use of antibiotics, physiotherapy, and regular follow-up examination using abdominal ultrasound, enhanced CT, and MR imaging (163). For pseudocysts >6 cm that persist for >6 weeks, surgical or endoscopic intervention is recommended when symptomatic, as the cyst wall is mature and, thus, cannot resolve spontaneously (164,165). Several approaches can be used to drain pseudocysts, including surgical, percutaneous, and endoscopic approaches. Several studies have confirmed endoscopy as one of the most common and effective approaches for fluid drainage, being associated with a lower rate of mortality and complications compared to surgical and percutaneous approaches (166,167). Based on this evidence, endoscopic techniques, such as trans-mural drainage, trans-papillary drainage, and stenting, are best choice for the treatment of symptomatic pseudocysts (168).

**Infected acute necrotic collection and walled-off necrosis**

IPN refers to the collection of acute necrotic by-products or walled-off necrosis secondary to infection (13). Imaging has a high diagnostic value for IPN, with characteristic features including the “bubble sign” (i.e., a gas/liquid level)
and morphological features of cellulitis observed on CT in the area of necrosis (13,169). Clinical symptoms, such as SIRS and organ dysfunction, can provide auxiliary indicators for diagnosis (5,16,170). Bacterial culture from pancreatic tissue, obtained by percutaneous fine needle aspiration (FNA), may also assist in the diagnosis of IPN (171), although Japanese guidelines recommend against the routine use of FNA, indicating that FNA should be used for patients with suspected fungal infection or an infection that has not been effectively controlled using multiple antibiotics (172). For patients with clinically confirmed or highly suspected IPN, surgical intervention is an important treatment method (173) and should follow the “3D” principles, namely delay, drain, and debride (174). Specifically, the surgery should be delayed to 4–6 weeks after the onset of IPN. Necrotic tissue is sufficiently liquefied to form an envelope, providing a clear boundary relative to surrounding tissues, which maximizes retention of normal functioning pancreatic tissue. Surgery can be effective in lowering the occurrence of intestinal fistula, bleeding, and infection-related complications. Studies have reported an incidence rate of complication of 34–95% using traditional open abdominal debridement, with an associated mortality rate of 5.6–39% (175). In recent years, the treatment of IPN has been expanded beyond a single approach, with the approach selected based on the patient’s health status, degree and extent of necrosis, and other relevant clinical measures. To this end, a “step-up” approach has gradually become the gold standard treatment for IPN (176–178). Two 10-year follow-up studies have reported on the benefits of a step-up approach relative to open necrosectomy, without an increased risk of mortality, re-intervention, and long-term complications (179,180). The step-up approach uses PCD or endoscopic necrosectomy as the initial treatment with the purpose of alleviating the systematic inflammatory response of IPN (181,182). With IPN progression, laparoscopic necrosectomy (LN), or RN can be performed, with the use of the sinus tract created by PCD being a good approach for these two surgical procedures (183). The surgical goal of the step-up approach is to control the systemic inflammatory response, rather than to remove the necrotic tissue completely, thereby reducing the rate of postoperative complications and mortality (4,184). Due to the complexity and variability of presentation of SAP, multidisciplinary collaboration is required, with the focus being on minimally invasive treatment (185). In this way, the step-up surgical approach can include the full scope of treatment possible for IPN.

**Summary**

AP is a common disease of the digestive system, with its pathogenesis being multifactorial, including trypsinogen activation, Ca\(^{2+}\) overload, ER stress, mitochondrial dysfunction, impaired autophagy, and exosomes. AP can progress to SAP, with a high risk of mortality, without effective control. Therefore, there is a need for clinicians to regularly evaluate patients’ disease status, determine the severity of the disease, and provide active treatment, as needed, including fluid resuscitation, nutritional support, analgesics, and etiological treatment. For patients with local complications, appropriate treatment for SAP is necessary, including drainage, ERCP, cholecystectomy, and necrotic tissue debridement. Although we may take positive measures to treat AP, these complications can still significantly reduce life quality and prognosis. Consequently, the pathogenesis of AP needs to be further explored to identify effective therapeutic targets and improve therapeutic effect and patients’ quality of life.

**Acknowledgments**

**Funding:** This work was supported by the Beijing Municipal Science & Technology Commission, Capital Research and Demonstration Application of Clinical Diagnosis and Treatment Technology (No. Z191100006619038 and No. Z171100001017077), the Capital Health Research and Development of Special (No. 2020-1-2012), and Capital Medical University Clinical Medicine Advanced Sophisticated Subject Construction Project (No. 1192070312).

**Footnote**

**Reporting Checklist:** The authors have completed the Narrative Review reporting checklist. Available at [http://dx.doi.org/10.21037/atm-20-4802](http://dx.doi.org/10.21037/atm-20-4802)

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/atm-20-4802](http://dx.doi.org/10.21037/atm-20-4802)). The authors have no conflicts of interest to declare.

**Ethics Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are
appropriately investigated and resolved.

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Cite this article as: Zheng Z, Ding YX, Qu YX, Cao F, Li F. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management. Ann Transl Med 2021;9(1):69. doi: 10.21037/atm-20-4802