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Review Article

A narrative review of the mechanism of acute pancreatitis and recent advances in its clinical management

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Abstract: Acute pancreatitis (AP) is a common gastrointestinal disease with a high risk of mortality. Recently, the exosome and its potential regulatory role in the progression of AP has garnered the interest of researchers. However, effective drug interventions and therapeutic targets for AP remain to be established. Treatment approaches for AP have undergone considerable changes in the recent years: there is a greater preference for minimally invasive therapy (as primary treatment), multidisciplinary participation and the step-up approach. We aimed to discuss AP mechanism and the recent advancement in its treatment strategies to manage AP better in clinical practice.

Keywords: Acute pancreatitis, exosome, mechanism, clinical practice, follow-up

Introduction

Acute pancreatitis (AP), an inflammatory disorder, is a common cause of hospitalization and has a high morbidity rate with approximately 34 cases per 100,000 persons annually worldwide [1]. Although gallstones and alcohol consumption are the most common causes of AP, hypertriglyceridemia, drugs, endoscopic retrograde cholangiopancreatography (ERCP), trauma, auto-immune, genetic, and infectious diseases are also well-known triggers of local and systemic inflammation [2]. Mild AP is mostly a self-limiting disease and recovery can be obtained within a week. However, about 20% of patients will go on to develop moderate or severe AP, which is combined with organ failure and impaired pancreatic endocrine and/or exocrine function due to massive necrosis of pancreatic parenchymal cells and peripancreatic tissue with a mortality rate of approximately 30% [3]. Moreover, chronic pancreatitis (CP) develops in approximately 10% of patients after an initial episode of AP and in about one third of patients with recurrent AP, which has a serious impact on a patient's long-term quality of life [4].

The current treatment guideline for AP has undergone considerable changes; where minimally invasive therapy as the core, with multidisciplinary participation, and the step-up approach being more highly advocated [5]. However, there is still a lack of effective drug interventions and potentially novel therapeutic targets for treating AP. Hence, we aimed to review the recent progress in the mechanism and clinical practice of AP in order to inform treatment options.

Methods

We conducted a literature search for published manuscripts on AP up to October 2020 in PubMed, Web of Science, Cochrane Library, and EMBASE databases. We used the following search words and terms: "acute pancreatitis", "pathogenesis", "exosomes", "diagnostic criteria and classification", "etiology", "initial treatment", "surgery or intervention", "local complication management", "follow-up", and "prevention". Qualitative and quantitative data were extracted by interpreting each paper in cycles to avoid missing potentially valuable data.

Discussion

Diagnostic criteria

A diagnosis of AP(2) required two of the following three criteria to be fulfilled [6]: (1) upper

abdominal pain, which radiated to the back; (2) serum lipase and/or amylase usually three times higher than the upper limit of normal; however, the limited diagnostic value of serum lipase and amylase in both hyperlipidemic and alcoholic pancreatitis, and the quantity of amylase, was not associated with the severity of AP; (3) typical imaging manifestations of AP. We noted, however, that these features were not apparent in the early stage of AP, with evidence of pancreatic necrosis typically developing about 72 hours after the onset of clinical symptoms [7]. Consequently, if patients had typical clinical symptoms and laboratory tests, imaging examinations were not necessary within first 72 hours after admission to hospital [8-10]. Otherwise, patients required a further abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) to verify AP [11]. Thus, it was necessary to identify which situation required further evaluation [12].

Classification and prediction of severity

AP classification

AP can be divided into three categories according to the revised Atlanta classification (RAC) based on the organ failure and local or systemic complications, which include mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) [6]. Among these, local complications include fluid collection around the pancreas, sterile or infected pancreatic necrosis, and pancreatic pseudocyst [13, 14], while systemic complications are characterized by intermittent or persistent organ failure and/or deterioration in disease status [15]. MAP is mainly characterized by clinical presentation and biochemical changes associated with AP without organ failure and local or systemic complications. It usually resolves within 1-2 weeks without the need for repeated pancreatic imaging examination, and the mortality rate is lower. In contrast to MAP, MSAP often results in transient organ failure, lasting <48 hours, with or without local or systemic complications. For AP patients with severe predisposition, vital signs should be regularly monitored and continuously evaluated. In addition, SAP refers to persistent organ failure, lasting for a minimum of 48 hours, and is associated with poor prognosis and death in about 30% of co-infected cases [16, 17].

Moreover, a determinant-based classification (DBC) of AP severity has also been proposed in 2012, which includes four categories and is similar to the RAC. The DBC was divided into mild, moderately severe, severe, and critical according to the two risk factors for organ failure (transient or persistent) and pancreatic or peripancreatic necrosis (sterile or infected) [18] (**Table 1**). However, there is still no consensus on whether AP should be classified into three (RAC) or four categories (DBC) [19]. The latest evidence showed that only multiple organ failure is a risk factor directly related to mortality; however, the number of critical AP (CAP) patients are small in this study, therefore the DBC principle has not yet shown a significant advantage in the judgement of AP severity [20].

Prediction of severity

As the etiology of AP is complex and there have been many uncertainties, scholars have sought to establish an effective evaluation system in the hope of accurately predicting the development trend of AP. Currently, there are several clinical and biochemical scoring systems that are used to predict the severity of AP, including the Acute Physiology and Chronic Health Examination II score (APACHE II), the modified CT severity index (MCTSI), the bedside index for severity in AP (BISAP), the Harmless Acute Pancreatitis Score, and the Ranson score [21-23]. Of these, the MCTSI has good prognostic value, with a score <3 being predictive of a better prognosis [21]. A prospective study showed that the BISAP scoring system was similar to MCTSI and APACHE II in terms of AP severity prediction [23]. However, there is still no consensus on which scoring system can accurately predict the trend of AP severity. It is therefore necessary to determine this in further studies (**Figure 1**).

Recent progress on the exosome pathogenetic mechanism of AP

AP is a common digestive system disease, with its pathogenesis being multifactorial, including calcium overload, trypsinogen activation, impaired autophagy, endoplasmic reticulum (ER) stress, and exosomes. Among them, calcium overload and trypsinogen activation are the most important intracellular pathogenetic mechanisms of AP [24]. Meanwhile, considerable advancement in research has been made on

Table 1. The revised Atlanta classification and the determinant-based classification of acute pancreatitis

Classification	Revised Atlanta classification (RAC)	Determinant-based classification (DBC)
Mild	AP without organ failure and local or systemic complications*	AP without organ failure# and pancreatic or peripancreatic necrosis
Moderately Severe	AP with transient organ failure (lasting for <48 hours) and/or local or systemic complications	AP with transient organ failure (lasting for <48 hours) and/or sterile pancreatic or peripancreatic necrosis
Severe	AP with persistent organ failure, lasting for ≥48 hours	AP with persistent organ failure (lasting for ≥48 hours) or infection pancreatic or peripancreatic necrosis
Critical	NA	AP with persistent organ failure and infection pancreatic or peripancreatic necrosis

*Local complications: fluid collection around the pancreas, sterile or infected pancreatic necrosis and pancreatic pseudocyst, disconnected duct syndrome, venous thrombosis, arterial and/or venous pseudoaneurysms. *Systemic complications: intermittent or persistent organ failure, systemic inflammatory response syndrome, abdominal compartment syndrome, and deterioration in disease status. #Organ failure: The diagnostic criteria for organ failure are based on the modified Marshall scoring system, which defined the presence of organ failure as organ score >2. NA: not available.

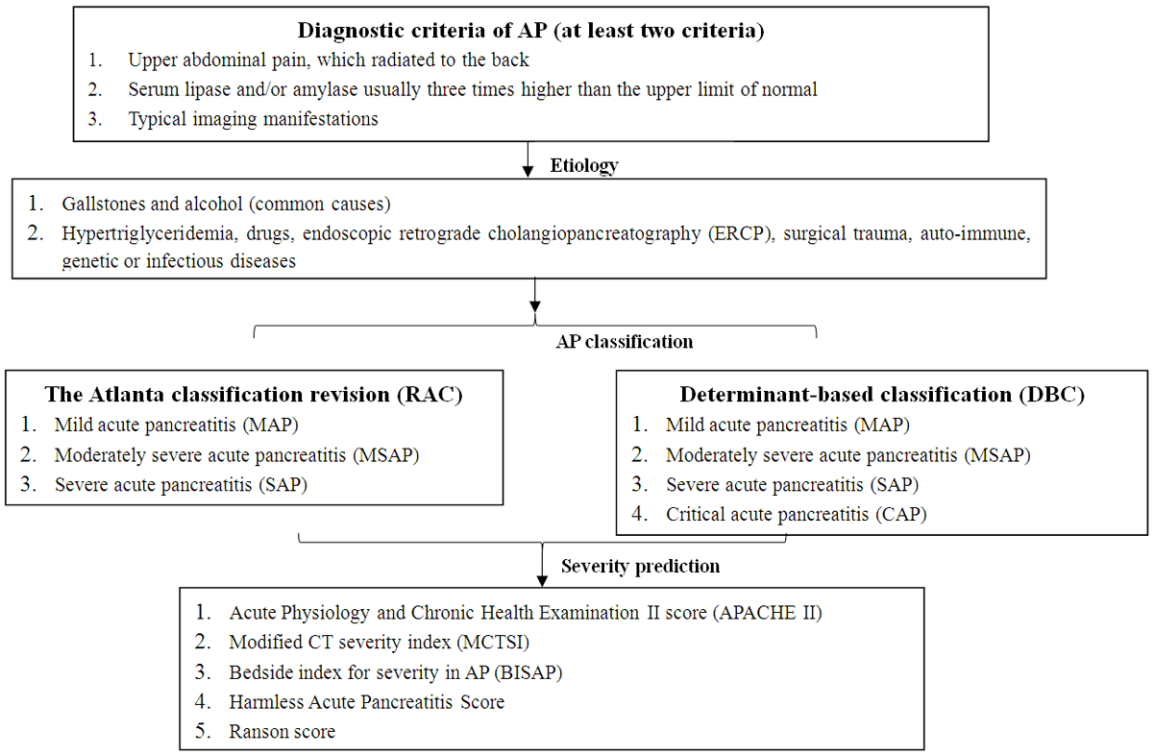

Figure 1. The diagnostic procedure and severity assessment of AP.

the pathogenesis of AP in the past decade, and the mechanisms of calcium overload, trypsinogen activation, impaired autophagy, and ER stress have been elucidated, affording us a greater understanding of the occurrence and development process of AP. Recently, exosomes, as a transport and storage tool for proteins, nucleic acids, and lipid substances, have been reported to be widely involved in the pathophysiological processes of a variety of diseases, and may play a biological regulatory role in the evolution of AP [25]. However, the exosomal pathogenesis of AP is not fully understood. Thus, it has gradually become a research hot topic for scholars. Therefore, exosomes may be a new biomarker or target for the diagnosis and treatment of AP in the future.

A recent study reported that the content of exosomes, which is released into the peripheral blood by the pancreas, was significantly increased in an AP rat model [26]. Some exosomes can reach the liver directly through the portal system and are then retained in liver tissue, while the remaining exosomes can be degraded by the increased hydrolytic activity of pancreatitis-associated ascitic fluid (PAAF) before being transferred to the liver tissue. The liver can then generate and release new exosomes. When exosomes labeled with fluorescent dye were observed, it was found that those from the circulatory system could effectively reach alveolar tissues and be absorbed by alveolar macrophages. It was confirmed that the exosomes from the circulatory system of the AP model could activate alveolar macrophages by converting the phenotype from M2 to M1, which in turn aggravated the degree of lung injury caused by AP [26]. 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 (**Figure 2**). In addition, 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 [27]. These findings are of great importance for research on exosome-miRNA in AP. Moreover, exosome-miRNAs can transfer to other organs, such as the kidney and intestinal tract, through the circulatory system. Once activated by exosome-miR-

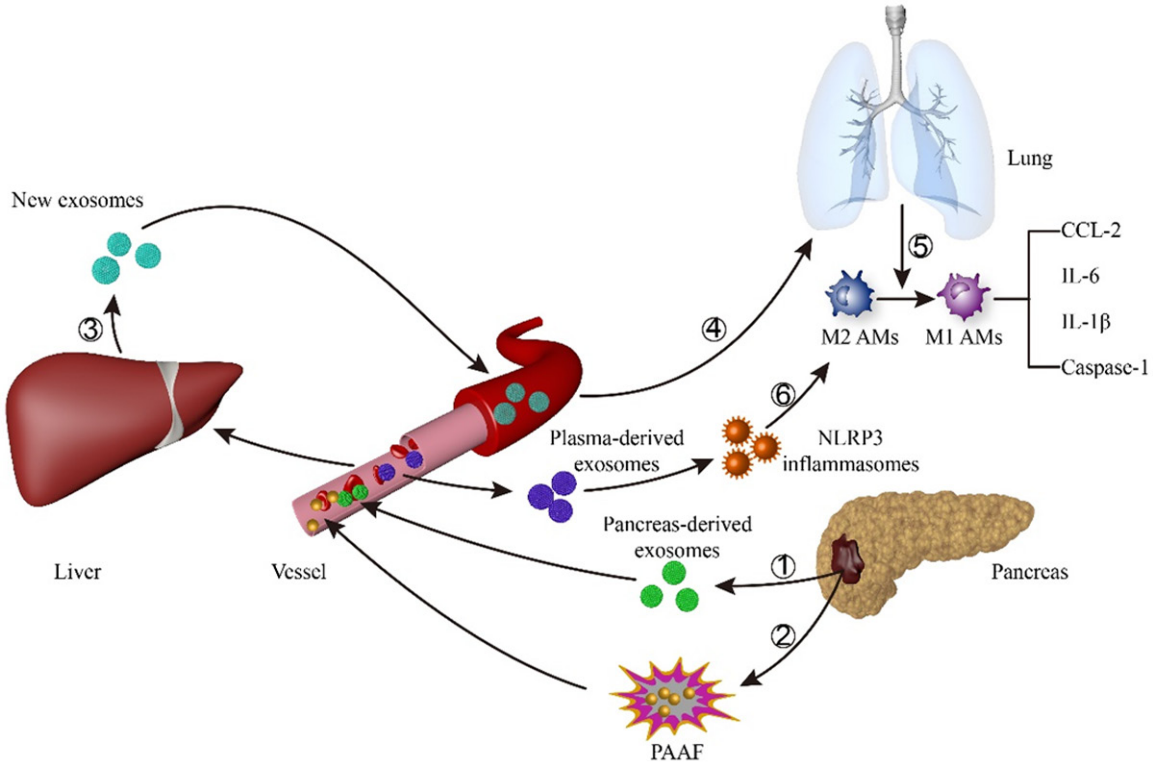

Figure 2. The biological regulatory role of exosomes in AP. ① During AP, the pancreas can release the exosomes into peripheral blood. Some of the exosomes (green circles) can reach the liver via the portal system and can retained in the liver tissue. ② The remaining exosomes (yellow circles) can be degraded by the high hydrolytic activity of pancreatitis-associated ascitic fluid (PAAF) and then transferred to the hepatic tissue ③ The liver can generate and release the new exosomes (blue circles) to the circulatory system. ④ The new exosomes reach alveolar tissues and can be absorbed by alveolar macrophages (AMs). ⑤ Exosomes from the circulatory system of the AP model can activate alveolar macrophages (AMs) by converting the phenotype from M2 to M1, which in turn worsens the degree of lung injury. ⑥ Plasma-derived exosomes (purple circles) can activate NOD-like receptor protein 3 (NLRP3) inflammasomes to induce pyrolysis of alveolar macrophages, thereby causing AP-related lung injury.

NAs, these organs begin to release new exosomes, promoting cell apoptosis and organ injury [28, 29]. 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 have a healing effect on AP [30]. Therefore, there is a need to further investigate the similarity and specificity of exosomes in different cells, tissues, and organs, the targeting mechanisms of exosomes, as well as the gene regulation mechanisms of target organs. As exosomes can protect RNAs or proteins from being damaged, this may be a promising treatment in the future [25]. Hence, drug trials focusing on exosome-related targets could improve the success rate of AP treatment.

Management of AP

Accurate diagnosis and assessment of disease severity is necessary in the early phase of AP. Active-support therapy, including monitoring of organ function and early identification of complications, plays a crucial role in the management of patients with AP. Research on the etiology of AP, as well as evaluation of the effectiveness of current treatments, are important to prevent short-term disease progression and improve patients' quality of life (**Figure 3**).

Fluid resuscitation

Hypovolemia and/or shock caused by severe inflammatory responses results in organ hypoperfusion and impairment in microcirculation, which can eventually exacerbate local pancreatic damage and result in multi-organ failure. Fluid resuscitation is an effective treatment to prevent hypovolemia and organ hypoperfusion in the management of AP [31]. However, excessive and rapid fluid infusion can adversely affect AP patients, such as increasing the incidence of respiratory complications and abdom-

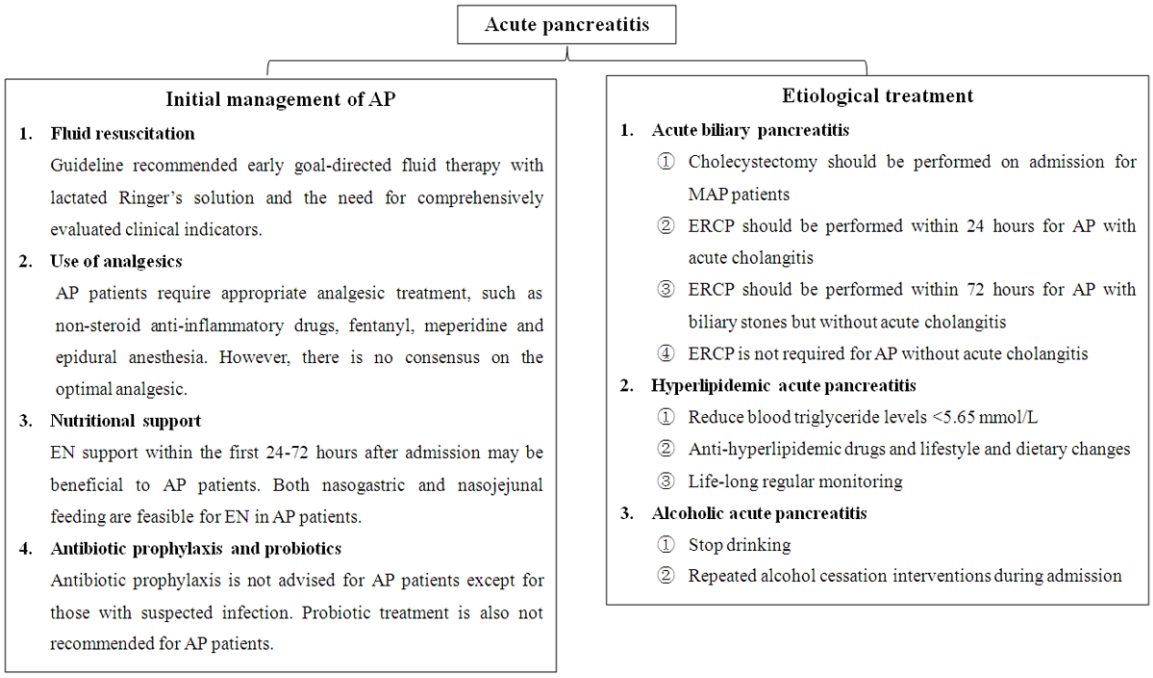

Figure 3. Initial management and etiological treatment of AP.

inal compartment syndrome [32]. On the contrary, insufficient or slow fluid replacement will also adversely affect organ function and inflammation control [33], prolonging the duration of hospitalization. Consequently, the American Gastroenterological Association (AGA) has recommended early goal-directed fluid therapy for the management of AP [8]; however, the evidence basis is relatively weak [31]. Although the early goal-directed fluid therapy has no effect on the long-term mortality of patients (28 days vs 90 days), it can reduce short-term mortality and still has significance in the treatment of patients with SAP [34, 35].

In addition, there is a need to monitor clinical indicators to determine if treatment goals have been reached. Non-invasive and invasive indicators can be used in most cases to monitor whether fluid resuscitation goals have been achieved, including mean arterial pressure >65 mmHg, urine volume >0.5-1 mL/kg/h, heart rate <120 beats/min, urea nitrogen <7.14 mmol/L, and a hematocrit level of between 35% and 44% [9, 36]. Patients' fluid requirement should be assessed every 4-6 hours after the first 24-48 hours of admission [37]. After reaching the goal of resuscitation, the speed and volume of fluid infusion should be controlled, and small doses of diuretics may be used to prevent tissue edema if necessary. In summary, the above-mentioned indicators need to be comprehensively and collectively evaluated to avoid clinical misdiagnosis, which can lead to serious adverse consequences.

A study in China showed that infusion with lactated Ringer's solution can decrease the C-reactive protein (CRP) levels and inhibit the systemic inflammatory response compared with normal saline solution [38]. Of note, previous studies have reported a higher rate of morbidity and mortality when using saline compared to other crystalloid fluids for the treatment of systemic inflammatory response syndrome (SIRS) [39, 40]. In addition, a meta-analysis of five studies also suggested that lactated Ringer's solution was associated with a lower incidence of SIRS in AP patients [41]. Therefore, the IPA/APA guideline suggests that lactated Ringer's solution be the preferred choice for AP treatment [8, 9, 42]. 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 [43], including large-sample, multicenter RCTs.

Use of analgesics

Pain requiring appropriate analgesic treatment is the main symptom of AP [44]. Several types

of analgesics including non-steroid anti-inflammatory drugs, fentanyl, and meperidine may be used. However, there is no consensus on the optimal analgesic [45]. One research using a rat model indicated that morphine might have an adverse effect, causing spasm of the Oddi sphincter, which aggravates the disease status of AP [46]. Of note, however, is a meta-analysis that reported contradictory results that there is insufficient evidence that using morphine to control pain in AP has a negative effect on disease status [47]. Due to the current evidence being unclear, morphine is best avoided in AP patients. Considering the addictive effect of opioids, non-steroidal anti-inflammatory drugs should be selected as the first line treatment for pain associated with AP without acute kidney injury or peptic ulcers [24]. Another study reported that epidural anesthesia can improve the perfusion of the pancreas and the clinical outcomes of AP patients [48]. A multicenter observational study also found that critically ill AP patients who received epidural analgesia showed a reduced rate of 30-day mortality compared with patients who did not [49]. Although epidural analgesia has a positive effect on AP recovery, there is a need for RCTs involving this form of analgesia to determine if its use should be routinely recommended in the treatment of AP, and form part of the treatment guidelines for this disease.

Nutritional support

The traditional view is that the treatment of pancreatitis requires fasting to rest the intestines so as not to further stimulate the pancreas. However, recent evidence has suggested just the opposite, that early enteral nutrition (EN) is beneficial for these patients. EN is thought to help protect the intestinal mucosal barrier and inhibit bacterial translocation, thereby reducing the risk of infectious peripancreatic necrosis and a systemic inflammatory response [45, 50].

A technical review of 12 RCTs and 11 different meta-analysis comparing total parenteral nutrition (TPN) and EN in AP patients; shows clear evidence that EN is superior to TPN, and the risk of infectious peripancreatic necrosis (OR = 0.28, 95% CI: 0.15-0.51), single organ failure (OR = 0.25, 95% CI: 0.10-0.62), and multi-organ failure (OR = 0.41, 95% CI: 0.27-0.63) are reduced [31, 51, 52]. A review of 18 RCTs comparing EN to PN provided evidence that EN has the benefit of 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 [53]. Other studies reported a superiority of EN over PN or delayed EN in reducing the rate of complications due to severe pancreatitis infection [54, 55]. Consequently, the AGA recommend that EN is preferable to PN for AP patients who cannot be fed orally [8].

However, the optimal timing of nutritional support for AP patients remains controversial [56]. A meta-analysis comparing delayed EN or PN (>24 hours) with early EN (<24 hours) found that early EN decreased the rate of multi-organ failure and pancreatic-related infections among patients with SAP [55, 57]. A review of three meta-analyses indicated that compared to delayed EN or PN, early EN (<48 hours) significantly reduced the rate of mortality, surgical intervention, multi-organ failure, and SIRS among patients with AP [58-60]. Another prospective trial reported that the optimal time for early EN was within 72 hours after admission (receiver operating characteristic = 0.744). Provided there is patient tolerance, early EN can effectively reduce secondary infection and improve the nutritional status of patients [61]. Therefore, several authoritative guidelines suggest that EN support within the first 24-72 hours after admission may be beneficial to AP patients compared with delayed EN or PN [8, 62, 63].

EN can be administered via a nasogastric or a nasojejunal tube. In 2005, the first RCT regarding EN approaches was conducted and reported that there was no difference between nasogastric and nasojejunal feeding with regard to mortality, tolerance to EN, and length of hospital stay [64]. Other studies also 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 [65-67]. In addition, there are two meta-analyses that reported that nasogastric nutrition is an effective approach to improving nutritional status in SAP patients [68, 69]. Therefore, both nasogastric and nasojejunal feeding are feasible for EN in AP patients. However, the above findings do not solve the problem of safety [31]. Generally, nasojejunal feeding would be useful

for patients at high risk of aspiration, gastric emptying, or pyloric obstruction, with nasogastric feeding proving more useful for patients with a low risk of aspiration [8].

Antibiotic prophylaxis and probiotics

The academic community has continued to debate the use of antibiotic prophylaxis and its effectiveness in the treatment of AP [70, 71]. Currently, several RCTs and meta-analyses have found that prophylactic antibiotics are ineffective in preventing infections and do not reduce the incidence of complications and mortality among SAP patients [72, 73]. Moreover, prophylactic antibiotics may be related to the occurrence of hospital-acquired infections, fungal infections, and multi-drug resistance, rather than being beneficial to AP patients [74, 75]. Consequently, AGA guidelines indicate that antibiotic prophylaxis is not advised as a means of infection prevention in AP patients [5, 8, 9, 76]. However, patients with AP clearly accompanied by an infection, infection-related shock, and systematic inflammatory response need to be treated with antibiotics [8].

Meanwhile, there remains no consensus on whether AP patients should be treated with probiotics. A multicenter clinical study has shown that probiotic prophylaxis does not decrease the risk of infectious complications and may even increase the rate of mortality [77]. Therefore, the AGA guidelines do not recommend probiotic treatment for AP patients [8].

Etiological treatment

Acute biliary pancreatitis: Cholelithiasis is currently the main etiology of AP in China. Any patient with biliary stone obstruction requires timely removal, and the treatment approach includes an endoscopic procedure or surgery. However, the optimal timing for the treatment of acute biliary pancreatitis with biliary stones remains under dispute. The PONCHO trial reported that delayed cholecystectomy may increase the risk of recurrence by 30% compared with early cholecystectomy [78]. A meta-analysis also showed that early cholecystectomy neither increased the risk of operation-related complications nor increased the readmission rate for gallstone recurrence in MAP patients [79]. Therefore, the AGA guidelines suggest that cholecystectomy should be performed on admission for MAP patients [8, 80]. Moreover, endoscopic retrograde cholangiopancreatography (ERCP) should be performed within 24 hours for SAP associated with acute cholangitis or performed within 72 hours for AP associated with biliary stones but without acute cholangitis, as a delay is associated with an increased risk of mortality [81, 82]. For those patients without acute cholangitis, urgent ERCP is not required, and for patients with an inflammatory response, delaying cholecystectomy of ≥6 weeks is recommended until regression of the inflammatory response is achieved [82] (**Figure 3**). For elderly patients with MASP and SAP who are not suitable for cholecystectomy, endoscopic sphincterotomy (EST) provides a temporary alternative to ERCP and can decrease the risk of biliary pancreatitis recurrence [82]. However, EST does not only carry the risk of introducing bacteria into sterile pancreatic necrosis but also increases the risk of infectious complications. As such, the pros and cons of EST need to be weighed on a patient-by-patient basis.

Hyperlipidemic and alcoholic AP: A key point in the treatment of hyperlipidemic AP (HLAP) is the rapid reduction in the blood triglyceride (TG) levels to <5.65 mmol/L to delay 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 [83]. Recent data also reported that a TG level <2.26 mmol/L can prevent HLPA recurrence [84]. Thus, the long-term use of anti-hyperlipidemic drugs in combination with lifestyle and dietary changes is a key component of HLAP management. If the above therapy cannot control the TG level, plasmapheresis can be used to reduce the serum TG level, remove inflammatory lipoproteins, and shorten the length of hospital stay [83, 85]. Furthermore, serum TG levels should be monitored regularly after discharge in HLAP patients to prevent recurrence [83, 86].

The incidence of alcoholic pancreatitis is second only to ABP and HLAP in China. There is a high rate of recurrence of alcoholic pancreatitis, with 24% of these patients experiencing a relapse several years after the initial episode, a rate that is significantly higher than the recurrence rate of ABP [87]. Another study found a higher rate of pancreatic exocrine dysfunction

among patients with alcoholic pancreatitis, compared to other types of AP [3]. In addition, another RCT reported that repeated interventions at 6-month intervals is better than a single initial intervention for alcoholic pancreatitis patients [88]. Therefore, routine treatment of alcoholic pancreatitis should be supplemented with lifestyle management and health education for cessation of alcohol consumption, thus lowering the risk of recurrence [8] (**Figure 3**).

Local complications

Symptomatic pseudocysts and walled-off necrosis: Regarding non-infected acute peripancreatic fluid collection (APFC) and acute necrotic collection (ANC); these can disappear spontaneously within a few weeks after onset. For an asymptomatic pancreatic pseudocyst (PPC) and a walled-off necrosis (WON), surgical intervention is not recommended regardless of size, location, and range. For pseudocysts >6 cm that persist for >6 weeks, surgical or endoscopic intervention is recommended when symptomatic (such as gastrointestinal or biliary obstruction, or abdominal pain), as the cyst wall is mature and, thus, the cyst cannot resolve spontaneously [89, 90]. Several approaches can be used to drain pseudocysts, including surgical, percutaneous, and endoscopic approaches. However, the diameters of the PPC and WON do not directly determine the need for surgical treatment, and it is generally believed that patients with pseudocysts >6 cm are prone to develop clinical symptoms [45, 76, 82]. Several studies have confirmed endoscopy as one of the most common and effective approaches for fluid drainage, as it is associated with a lower rate of mortality and complications compared to the surgical and percutaneous approaches [91, 92]. Based on this evidence, endoscopic techniques, such as transmural or trans-papillary drainage, and stenting, are the best choices for the treatment of symptomatic pseudocysts [93].

Infected pancreatic necrosis: Infected pancreatic necrosis (IPN) refers to the collection of acute necrotic by-products or walled-off necrosis secondary to infection [6]. Imaging has a high diagnostic value for IPN, with characteristic features including the "bubble sign" (a gas/liquid level) and morphological features of cellulitis observed on CT scans of the area of necrosis [6, 94]. Clinical symptoms, such as SIRS and organ dysfunction, can provide auxiliary indicators for diagnosis [10, 95, 96]. Bacterial culture from pancreatic tissue, obtained by percutaneous fine needle aspiration (FNA), may also assist in the diagnosis of IPN [97]. Although Japanese guidelines are 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 [98]. For patients with clinically confirmed or highly suspected IPN, surgical intervention is an important treatment method [99] and should follow the "3 D" principles, namely delay, drain, and debride [76]. Currently, the "step-up" approach has become the first-line treatment for IPN [100-102]. Several studies have reported that neither endoscopic nor surgical step-up, or open surgery make a difference to patient mortality [101]. However, a 10-year follow-up study has reported on the benefits of a step-up approach relative to open necrosectomy, without an increased risk of mortality, reintervention, and long-term complications [103]. Meanwhile, a multicenter study also found that endoscopic and surgical step-up can decrease the mortality rate compared with open surgery [104]. The step-up approach uses percutaneous catheter drainage or endoscopic necrosectomy (EN) as the initial treatment with the purpose of alleviating the systematic inflammatory response of IPN [105, 106]. With IPN progression, laparoscopic necrosectomy (LN) or retroperitoneal necrosectomy (RN) can be performed, with the use of the sinus tract created by percutaneous catheter drainage being a good approach for these two surgical procedures [107]. 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 [5, 108]. The PANTER study showed that the step-up approach can reduce the incidence of organ failure (12% vs 40%), incised hernia (7% vs 24%), and diabetes (16% vs 38%) compared with open surgery. An 8-year follow-up of patients who enrolled in the PANTER study found that compared with open surgery, exocrine dysfunction (29% *vs* 56%) and endocrine dysfunction (40% *vs* 64%) could be reduced in the step-up approach. However, there were no significant differences between the two groups in the rates of redrainage and debridement, the incidence of recurrent AP and

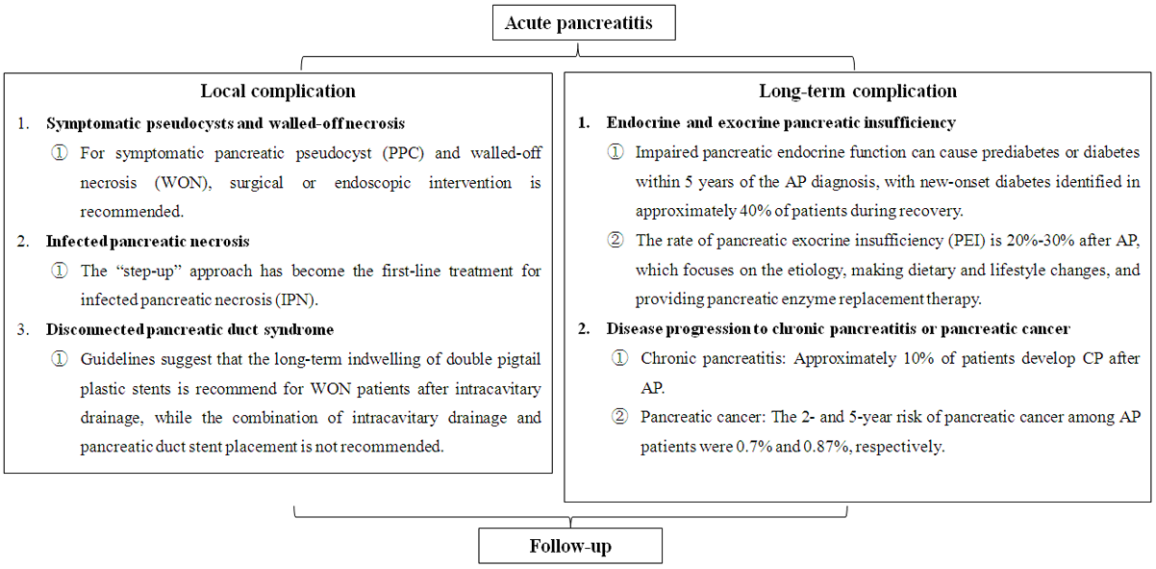

Figure 4. Local complication and long-term complication.

CP, pain score, hospital cost, and quality of life. Therefore, compared with open surgery, although the number of interventions increased, the step-up approach did not increase the risk [109]. However, how can we choose whether to use the endoscopic step-up or surgical step-up approach for treating IPN; there is still no consensus. The TENSION study reported that there were no differences in mortality and complication rates, but that the endoscopic step-up approach was superior to the surgical step-up approach regarding the length of hospital stay and incidence of pancreatic fistulae [102]. The MISER study also found that the endoscopic and surgical step-up approaches had no significant differences in mortality and new-onset organ failure, while endoscopic step-up was superior in terms of major complications, pancreatic fistulae, and patients' quality of life. However, endoscopic step-up is not applicable to all AP patients, and, surgical step-up may be better for the management of bilateral paracolic sulci and pelvic cavity [110]. Due to the complexity and variability of the presentation of SAP, multi-disciplinary collaboration is required, with the focus being on minimally invasive treatment.

Disconnected pancreatic duct syndrome: Regarding acute necrotizing pancreatitis, 20-40% may be accompanied by a partially or completely disconnected pancreatic duct. This interruption results in various clinical symptoms, including abdominal pain, pseudocysts, diabetes, and portal hypertension, which commonly occur in WON patients [111]. Among these, the integrity of the pancreatic duct can be evaluated by MRCP. At present, there is no standard treatment for disconnected pancreatic duct syndrome. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines suggest that the long-term indwelling of double pigtail plastic stents is recommend for WON patients after intracavitary drainage, while the combination of intracavitary drainage and pancreatic duct stent placement is not recommended. For patients with local pancreatic duct disruption, a stent can be placed via ERCP to promote duct healing. For patients with extensive pancreatic duct disruption, a multi-disciplinary approach may be necessary [112, 113] (**Figure 4**).

Long-term complications

Endocrine and exocrine pancreatic insufficiency

Impaired pancreatic endocrine function has been shown to cause prediabetic symptoms or diabetes within 5 years of the AP diagnosis, with new-onset diabetes identified in approximately 40% of patients during recovery [114]. The mechanism of endocrine injury in AP remains unclear, with further clinical and experimental research being required to clarify the pathophysiological process. Since pancreatic

endocrine insufficiency may occur after recovery from AP, monitoring the endocrine function of the islets of Langerhans is necessary over the follow-up period. For patients diagnosed with pancreatic endocrine insufficiency via fasting plasma glucose (FPG), C-peptide, glycosylated hemoglobin A1C (HBA1c), or oral glucose tolerance test (OGTT), appropriate drug therapy should be initiated as soon as possible. However, there are no specific treatment guidelines for post-AP diabetes, which generally refer to the type II diabetes guidelines [115].

Pancreatic exocrine insufficiency (PEI) is usually the main clinical manifestation and complication of SAP. The rate of PEI after AP has been increasing in recent years, estimated at 20-30% after AP, with the risk of PEI being specifically higher for alcoholic AP and necrotizing pancreatitis [3]. The degree of PEI depends on the severity of AP and the residual volume and function after AP recovery. Currently, the management of PEI focuses on the etiology, making dietary and lifestyle changes, and providing pancreatic enzyme replacement therapy, as needed, to improve digestion [45].

Disease progression to chronic pancreatitis or pancreatic cancer

Repeated episodes of AP can progress to CP or pancreatic cancer, which have a negative impact on prognosis and patient quality of life [116]. The rate of new-onset diabetes after recovery of ANP is 45%, with a rate of pancreatic enzyme replacement therapy of 25% and disability of 53%. Moreover, APN negatively impacts quality of life and survival, with a median survival of AP patients aged 53±16 years of 9.1 years compared to 26.1 years for an age- and sex-matched general population ($P<0.001$) [117]. The absolute 2- and 5-year risk of pancreatic cancer among patients with AP has been reported at 0.7% and 0.87%, respectively, with the risk of pancreatic cancer being higher among patients with AP than the general population matched for age and sex [118]. Approximately 10% of patients develop CP after an initial episode of AP, with 36% experiencing recurrent AP. The primary risk factors for AP progression to CP include smoking, alcohol abuse, and gender [119]. Therefore, treatment should focus on reducing the rate of disease progression and improving patients' quality of life (**Figure 4**).

Prevention and follow-up strategy

The current global annual incidence of AP is on the rise. The prevention of AP requires the joint efforts of medical personnel from primary and comprehensive tertiary medical institutions, and the Center for Disease Control. Among these, primary prevention is mainly for the general population who do not suffer from AP, through health education to reduce alcohol consumption and smoking, and to promote weight loss in overweight and obese individuals through a low-fat diet and physical exercise. Regular physical examinations should be conducted to actively control blood lipids and glucose once hyperlipidemia and diabetes are found, and prompt endoscopic or surgical intervention for biliary tract diseases should be conducted to reduce the incidence of AP. Secondary prevention mainly involves early diagnosis of AP and early effective treatment to prevent the aggravation of the disease and reduce the incidence of complication. Tertiary prevention mainly refers to the regular monitoring of diabetes and pancreatic exocrine insufficiency after diagnosis of AP, and the promotion of functional recovery through standardized treatment (**Table 2**). In addition, there is also a need to establish a detailed follow-up strategy. Studies have shown that the probability of exocrine insufficiency in AP patients is 60.5%-85% within 1 year, and that exocrine insufficiency in some patients will last 6-18 months [37, 120]. In addition, one-third of patients develop pancreatic endocrine insufficiency [3]. A meta-analysis reported that approximately 40% of patients will become prediabetic and develop diabetes [114]. Consequently, AP patients need to be followed-up regularly after recovery. Among them, MAP patients should be followed-up at 1, 3, and 6 months after discharge, and MSAP and SAP patients need to be followed-up for more than a year. SAP patients require evaluation of pancreatic endocrine and exocrine function every 6 months for at least 18 months. However, pancreatic function tends to improve in AP patients over time. Meanwhile, during the follow-up period, patients need to undergo routine blood tests for liver function, blood lipid, glucose and amylase levels, as well as routine stool analysis and abdominal ultrasound examination to evaluate whether there are systemic or local complications, and whether the etiology (such as gallstones and hyperlipidemia) has

Table 2. Prevention and intervention for AP patients

Category	Primary prevention	Secondary prevention	Tertiary prevention
Prevention strategy	Public health education	Early diagnosis and effective treatment of AP	Follow-up screening of high-risk patients
Intervention	1. Stop drinking and smoking 2. Follow a low-fat diet 3. Restrict use of AP-induced drug 4. Cautious of ERCP	1. Early diagnosis of AP and removal of etiology 2. Rational use of opioid analgesics 3. Active fluid resuscitation and early enteral nutrition prevented AP progression	1. Through regular follow-up, timely detection of sequelae (such as exocrine or, endocrine insufficiency) 2. Medical treatment
Medical Practitioners	1. Public health specialist 2. Primary care physicians 3. Gastroenterologist	1. Primary care physicians 2. Gastroenterologist 3. Surgeon 4. Radiologist	1. Primary care physicians 2. Gastroenterologist 3. Nutritionist 4. Endocrinologist

been removed. After 2-3 regular examinations, the follow-up can be terminated if there are no complications and there is complete removal of the etiology. Patients with hyperlipidemia should be followed-up for life, and blood lipids should be monitored 1-2 times per month [1].

Conclusion

AP is a common inflammatory pancreatic disease, which can progress to SAP with a high mortality rate, and without effective control. Exosomes may play an important regulatory role for AP and AP-related organ injury. With the recent updates of several authoritative guidelines, considerable progress has been made in fluid resuscitation, use of antibiotics and probiotics, timing and approach of nutritional support, and the treatment of complications, which play an important guiding role in the treatment of AP patients. However, there is still a lack of strong clinical evidence for the optimal timing of invasive interventional therapy for IPN, the optimal type of fluid resuscitation and infusion speed, and the prevention and follow-up strategy of AP. Therefore, there is an urgent need to establish a hospital collaboration network for large-scale clinical trials in the future, so as to better provide high-quality data for improving the disease status and long-term quality of life of AP patients.

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Disclosure of conflict of interest

None.

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