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**Study on acute pancreatitis in the recent stage**

Feng YC *et al*. Study on acute pancreatitis

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**Abstract**

Acute pancreatitis (AP) is an inflammatory disease of the pancreas which involves the pancreas and surrounding tissue, and systemic inflammation with characteristic systemic increase of vascular permeability and increased risk of multiple organ dysfunction. To this days, the pathogenesis of AP is fuzzy, the diagnosis and treatment is the need for further standardization. Nevertheless, increased knowledge of the AP may achieve more thorough understanding of the pathogenesis, meanwhile encourage the use of further advanced diagnostic tools and point to superior treatment, which potentially will help clinicians to manage AP at an appropriate stage. However, in view of the multi factorial disease and the complex clinical manifestation, the management of patients with AP is also remaining areas for improvement.

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**Key words:** Acute pancreatitis; Organ failure; Necrosis; Inflammation; Management

**Core tip:** Acute pancreatitis (AP) is a severe disease with high mortality. Increased knowledge of the AP may achieve more thorough understanding of the pathogenesis, meanwhile encourage the use of further advanced diagnostic tools and point to superior treatment, which potentially will help clinicians to manage AP at an appropriate stage.

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**INTRODUCTION**

Acute pancreatitis (AP) annual incidences are reported to range from 5 to 80 cases per 100000 population, which carry out a startling mortality rate and large amounts of annual cost. Quantity of studies have been occurrence every year to elucidate the pathogenesis of AP, to standardize the diagnosis and the treatment of AP. The pathophysiology of AP is complex and involves several inflammatory pathways. Clinical course is usually benign, and clinical signs and symptoms, as well as amylasemia/amylasuria levels, decrease within a few days; however, around 20% of cases develop complications both at the local and systemic levels, with pancreatic necrosis being most common and relevant[1]. At an early stage of the disease an acute inflammatory process of sudden onset occurs in the peripheral and internal areas of the pancreas, which induces multiple organ system dysfunction syndromes in the lung, kidney, liver, and other organs[2]. AP-related mortality still affects around 10% of patients; half of deaths occur during the first two weeks, usually related to distributive shock and multiple organ failure syndrome; the rest occur later in the course of the disease and result from complications related to the development of pancreatic necrosis and its complications. On account of a better understanding of physiopathology, the improvement of therapeutic armamentarium, advances in nutritional support[3], dynamic approaches of continuous extra renal replacement techniques, acknowledgement of the central role of pancreatic infection[4], and advances in surgical techniques in improve imflamtory response in AP[5], AP management achieved a major breakthrough. However, in view of the multi factorial disease and the complex clinical manifestation, the management of patients with AP is also remaining areas for improvement.

**PATHOGENESIS**

The pathophysiology of AP is complex and involves several inflammatory pathways. The initial trigger is the activation within the pancreatic parenchyma of various proteolytic enzymes, usually promoted by the presence of bile and duodenal contents inside pancreatic ducts[1]. In most western countries 30% to 55% of cases are caused by sludge or gallstones, which are known as biliary pancreatitis[5]. The others as a complication from excess nutritionand alcohol intake. The overproduction of inflammatory mediators (cytokines and non-cytokine) may result in the systemic manifestations of AP[6-8]. Acinar cell damage initiates AP, account for local inflammation and local activation of the immune system of the pancreas[6]. Some recent studies have shown that mild AP associated with extensive apoptotic acinar cell death, whereas acinar cell necrosis with minimal apoptosis involved in severe AP[9,10].

Pancreatic acinar cells can produce cytokines and chemokines that are involved in the inflammatory response, including the inflammasome-associated factors interleukin-6 (IL-6), IL-18 and caspase-1, which are found in the basolateral region of acinar cells[11,12]. IL-6 which is known to be involved in the signal transducer and activator of transcription 3/suppressor of cytokine signaling-3 (STAT3/SOCS3) cascade, transmits signals by binding to its membrane-bound receptor, IL-6 receptor, and the ubiquitously expressed. The inflammation-associated nuclear factor kappa B (NF-қB) induced myeloid cell secreting IL-6, and the effects of IL-6 were mediated by complexation with soluble IL-6 receptor, which is known as trans-signaling. The trans-signaling of IL-6 stimulated phosphorylation of STAT3 and the production of the neutrophil attractant chemokine ligand 1 (CXCL1) in pancreatic acinar cells. The expression of cytokines and chemokines, as well as the inflammasome-associated IL-18 and caspase-1, indicate that the inflammatory mediators released during the early response to lipopolysaccharide are produced exclusively by pancreatic acinar cells. In addition, a recent study suggested that the alcohol-exacerbated lipopolysaccharides (LPS) response that initiates sub-clinical AP is mediated by acinar cells. Thus, acinar cells are the major source of inflammatory mediators after early pancreatic injury and during the early onset of sub-clinical AP.

Acinar damage by such inflammatory mediators induces the expression of endothelial adhesion molecules and results in a vicious circle that determines a extensive involvement of the vascular endothelium, which in turn generates vasodilation, increased capillary permeability and interstitial edema. In most these cases the inflammatory process is similar to that of serious sepsis, which leads to multiple organ failure and death. Furthermore, as is the case with sepsis, where genetic polymorphisms for some cytokines are associated with prognosis. Meanwhile, free oxygen radicals regulate necrosis extent in acinar cells, the development of pancreatic edema, inflammatory cell sequestration within the pancreas, and the release of inflammation mediators from both acinar and non-acinar cells in the pancreas. The decreased in plasma antioxidant levels (total ascorbic acid) and the increased release of lipid peroxidation byproducts significantly reflect in patients with AP. The body has a number of free oxygen radical-clearing systems, both enzymatic (superoxide dismutase, catalase, myeloperoxidase, and glutathione peroxidase) and non-enzymatic (carotenes, ascorbic acid, tocopherol)[13]. Uric acid, albumin and ascorbic acid represent most of the antioxidant capability of human plasma. The other elements present include bilirubin, a-tocopherol, a-carotene, tryptophan, tyrosine and selenium. The antioxidant is dependent upon the conditions extant in a specific microenvironment at a given time, and the type of oxidative situation[1]. The antioxidant defense system represents a complex network with interactions, synergisms, and specific actions on a given oxidant[14]. A number of studies in animal models have analyzed the association between oxidative metabolism and pancreatic inflammation. Studies in laboratory animals suggest that pancreatic oxidative stress occurs in early stages following induction. Treatment with antioxidant agents has been seen to reduce acinar cell damage and edema in several animal models. This suggests that ongoing free oxygen radical formation reduces antioxidant defensive systems in cells. Regarding the role of bradykinin and nitric oxide, there is controversy in that on the one hand they seem to relieve pancreatic dysfunction by strengthening vascularization and its secretory capacity while on the other there is the notion that nitric oxide may enhance oxidative stress[15]. This mechanism of human beingsremainedpending further study.

**DIAGNOSIS**

The diagnosis of AP requires at least 2 of the 3 features: (1) abdominal pain (epigastric pain often radiating to the left flank and the back); (2) serum amylase and lipase levels at least three times greater than the upper limit of normal; and (3) characteristic findings on contrast-enhanced computed tomography (CT), magnetic resonance (MR) imaging or transabdominal ultrasonography (US)[16]. Sometimes the CT examination is essential to confirm the diagnosis of AP: abdominal pain suggestive for the disease but without serum amylase and lipase levels at least three times greater than normal paramanet, as it happens in late presentation of the patient[17]. If AP is on the basis of the first two criteria, contrast enhanced CT may not be necessary in emergency. The onset of AP is defined as the time of onset of abdominal pain and it is not the same with the time of admission to the hospital. The interval between onset of abdominal pain and admission to the hospital should be noted precisely, especially if patients with SAP are transferred to a intensive care unit (second admission) when this type of data are often neglected[16,18,19].

In the previous reports, classification of AP are still three subtypes. Involving multiple international pancreatic societies, a web-based institution recently consultative process revised and updated the Atlanta classification of AP[16,19,20]. According to the severity of AP, the disease is classified as mild, moderate, severe and critical by the absence or presence of organ failure and local or systemic complications.

The latest classification of AP: (1) Mild AP (MAP)is characterized by the absence of both pancreatic (peri) necrosis and organ failure; (2) Moderate APis characterized by the presence of sterile (peri)pancreatic necrosis and/ortransient organ failure; (3) Severe AP (SAP) is characterized by the presence of either infected (peri)pancreatic necrosis orpersistent organ failure; and (4) Critical APis characterized by the presence of infected (peri)pancreatic necrosis andpersistent organ failure (Table 1).

The organ failureis defined for 3 organ systems (respiratory, cardiovascular and renal) based on the worst measurement over a 24-h period. In patients without preexisting organ dysfunction, organ failure is defined as either a score of 2 or more in the assessed organ system using the Sepsis-related Organ Failure Assessment (SOFA) score[21] or when the relevant threshold is breached, as shown: (1) Respiratory:partial pressure of oxygen (PaO2) < basal 60 mmHg (with supplementary O2); or PaO2/fraction of inspiration O2 (FiO2) ≤ 300 mmHg (≤ 40 kPa); (2) Cardiovascular:systolic arterial pressure (SAP) less than 90 mmHg or a reduction of 40 mmHg in basal SAP, with tisular hypoperfusion signs (lactate > 3 mmol/L); Saturation of central venous oxygen SvcO2 < 70%; and (3)Renal: an increase of basal creatinine by 2 (AKI-2, RIFLE-I) and/or reduction of urinary flow (oliguria) < 0.5 mL/kg/h × 12 h[22,23].

The most accurate marker in defining the severity of disease is dysfunction/persistent organ failure (lasting over 48 h)[19,24]. Scoring systems on Table 2, was chosen for its simplicity, universal applicability in clinical practice and in research and its ability to stratify disease[19]. Some others like the SOFA scoring system and APACHE II for patients managed in a critical care unit, which includes inotropic and respiratory support, can be determined to assess the severity of dysfunction/organ failures. However, for an easier hierarchy, these scores are not included in current classification[16,19]. A score equal to or greater than 2 of each system defines the presence of organ failure.

The presence or absence of local complications is very important. Local complications of AP are: acute peri-pancreatic fluid collections, acute necrotic collections, pancreatic pseudocyst and walled off necrosis[16,18,19,25]. Other local complications of AP include perturbance of gastric emptying, splenic or portal vein thrombosis, necrosis of the colon[18,26]. Local complications may be suspected in the presence of recurrent or persistent abdominal pain, increased serum enzymes, worsening of the organ dysfunction and/or clinical signs of sepsis (fever or leukocytosis) that require imaging evaluation[27-29].

We think that the accurate description of local complications and of the natural evolution of the disease's specific stages, along with the standardization of terminology will improve the therapeutic management and scientific research data reporting quality.

**TREATMENT AND MANAGEMENT OF AP**

We recommend the early detection and treatment of AP patients who are organ failure in progress so as to initiate invasive measures to revive the patients as soon as possible. “Potentially severe AP”(PSAP) , which is a new concept in Consensus Statement for intensive care management of AP comference in 2012 was introduced which was defined as a modality of AP which presents one or more organ failures (respiratory problems , renal, arterial hypotension) or alarm signs and it is useful for initial management of AP. Some of the previously published criterias show that the severity indicated that patients may fail to recover satisfactorily and called these “alarm signs”. The “alarm signs” are those forms of symptoms/signs or data in an AP patient that indicate a probable failure to recover well and alarn signs can be of a radiological, clinical or prognostic scales or analytical nature that were particularized in the Atlanta classification[23].

The AP alarm signs are the following: (1) Clinical: age, obesity, pleural effusion, abdominal defenses, alteration of consciousness; (2) Radiological:free peritoneal fluid, pleural effusion; (3) Analytical: Hematocrit > 44%, Procalcitonin greater than 0.5 ng/mL during the first 24 h; C-reactive protein (CRP) > 150 mg/L, or a progressive increase in 48 h; and (4) Prognosis scales: APACHE-0 > 6; APACHE II > 8; Ranson-Glasgow > 3 points.

Early administration of fluids is recommended in patients with PSAP, mainly during the first 72 h, during which the first 24 h is the most important[30,31]. Regarding the genre of fluid to be administered, colloid versus crystalloid, there is no general recommendation for AP treatment, although balanced crystalloid solutions have been observed to control systemic inflammatory response syndrome (SIRS) in PSAP, as well as CRP levels when compared to physiological saline serum[32-34].

In the amount of balanced crystalloids are preferable not exceeding 4.3 L during the first 24 h treatment. It must be taken with special care in reviving patients with more severe pancreatitis and more comorbidities. Nevertheless, in the first 24 h the administration of more than 3-4 L of fluids seems to be associated with a poor prognosis on account of an increased rate of acute respiratory failure and a greater need for admission to intensive care units, either because of the deleterious direct effects of fluid infusion, or it involved a patient with complicated AP[35-37]. Stroke volume variation (SVV), systolic pulse variation (SVP), pulse pressure variation (PPV) and the overall volume at the end of diastole can be considered useful parameters for assessing IAH patient response to fluids treatment, when taking into account that the response thresholds that distinguish responders from nonresponders can be increased[38,39].

Chronic alcoholic pancreatitis (CAP) and SAP produce a SIRS which result in a highly catabolic, hyper-dynamic and hyper-metabolic stress situation[40,41]. The determining factor in patient recovery is previous nutritional status. Consisting of implementing total parenteral nutrition and bowel rest have became the classic concept of treating AP. Specialized nutritional support in PSAP, in its CAP and SAP forms, should be unilized early, in the first 48 h after initial resuscitation. If enteral nutrition cannot be administered, the intolerance to this nutrition or if it results in an exacerbation of SAP, parenteral nutrition is indicated. SEMICYUC-SENPE (2011) Consensus: a total caloric intake of 25-30 Kcal/kg/d, without exceeding an glucose intake of > 4 g/kg/d, protein intake of 1-1.8 g/kg/d and an intake 0.7-1.5 g/kg/d of lipid. Emerging data suggest that the time, quantity, route and composition of artificial nutrition aim to reduce pancreatic secretion, modulate inflammatory response, prevent and treat malnutrition associated with a severe metabolic-catabolic situation, prevent the development of systemic and local infections in pancreatitis patients[42-45]. In conclusion, nutritional support has become one of the most important factors in the treatment and management of PSAP patients.

Owing to the systemic release of cytokines and pancreatic enzymes, SAP can affect most remote organs by systemic vascular. By inhibiting pancreatic secretion, somatostatin and its analogues, which have been reported to indirectly reduce the activity of myeloperoxidase (MPO) [46], the inflammatory mediators release[47], the prevention of ischemia-reperfusion injury[48] and bacterial translocation[49], have been used in severe AP patients[50]. Octreotide and its analogues have been recommended in conventional treatment of SAP for a long time, though the actual effects have been discussed[51]. Octreotide in the SAP treatment is dose-dependent and its effect might be limited by the blood-pancreatic tissue interface, *e.g.,* by ischemia and impaired microcirculation [52-54]. In a recent study, continuous regional artery infusion (CRAI) with Octreotide in SAP reduced the pancreatic amylase release into peripheral blood, improved the effects of both local and systemic inflammatory response[55], confirmed the achievement of octretide beneficial effects locally in the pancreas.

5-fluorouracil (5-Fu) is considered as an another specific, which has been tried in AP treatment since the 1970s[56,57]. Essentially, 5-Fu can reduce the synthesis of pancreatic enzymes, or serve as a proteinase inhibitor[58]. Continuous regional arterial infusion with 5-Fu can reduce the serum amylase levels in patients. A recent study demonstrated that the combined use of Octreotide an 5-Fu, administered *via* CRAI, would achieve a synergetic effect in treatment.

The acute necrotizing pancreatitis-induced changes in inflammatory factors and intra-abdominal pressure (IAP), meanwhile intestinal barrier were especially obvious at 6 h post-induction, which is suggested an early therapeutic window for the AP treatment. IAP is the abdominal cavity pressure. The normal value of IAP in noncritical patients is < 0 mmHg and critical patients is < 12 mmHg. The increase in IAP or in intra-abdominal hypertension (the pressure ≥ 12 mmHg) was detected more than a century, which has been known to lead to some alterations in the functioning of the organism[59-62]. The reduction of intra-abdominal pressure is the pivotal of preventing AP progress and organ failure, which can be achieved by non-surgical clinical therapies and/or surgical techniques. Among the non-surgical therapies used to reduce IAP of intestinal contents by means of the administration of prokinetics (erythromycin, neostigmine, metoclopramide), the gastric or rectal probe, relaxation and sedation and the reduction of the third space with diuretics exerted and/or Kidney dialasis techniques should be considered. If it is fail to attempt to reduce and optimize IAP and abdominal perfusion pressure, surgical management should be considered. Among the surgical techniques, percutaneous drainage[63,64] or decompressive laparotomy[65,66] should be considered first in those cases where there is quantity of free intraabdominal fluid. If surgical techniques are performed and there is no suspicion of infected necrosis, it is important that no necrosectomy should be performed to prevent it from occurring.

In the 1970s, a group of investigators first proposed a change of strategy in the therapeutic approach of “reducing or mitigating the inflammatory process in the pancreas”, by initially using peritoneal lavage[67,68]. With the development of the medical technology, hemofiltration play a critical role in removing inflammatory mediator [IL-1, IL-6, tumor necrosis factor (TNF)- α , platelet-activating factor (PAF) and complementary fractions] in acute pancreas. They obtained consistent data which support the beneficial effect of hemofiltration on the clinical situation and recovery of patients with SIRS or MOF, which conduces especially to the stabilization of the hemodynamic and respiratory systems[69-72]. It is based on some fasciting arguments using hemofiltration as a specific immunomodulating treatment in SAP, such as the positive effect these techniques have on maintaining cellular defense capacity, preventing the development of infections and maintaining the function of certain organs and, finally, improving the possibility of having a positive impact on the prognosis of SAP patients. Early application of continuous veno-venous haemofiltration promotes negative fluid balance and reduction of intra-abdominal hypertension in patients with SAP, meanwhile without associated with increased infection or mortality rate and may reduce hospital stay[73].

 Nevertheless, there is a consensus on the conservative management of AP patients with sterile necrosis, which is based on the triditional medical treatment. Some published studies advocate conservative treatment, even in patients with infected pancreatic necrosis[74-77]. On account of the high mortality rates for patients who are infected pancreatic necrosis performed conservative treatment, this treatment is not advisable unless the patients refuse to adopt pancreatic necrosectomy or are considered inoperable due to some high comorbidities[78]. Radiologically guided percutaneous catheters is applied which is considered as a “bridge” technique until a more specific treatment can be applied and can obtain beneficial effect for stabilizing patients who is too serious to tolerate any type of necrosectomy[79]. In a systematic review of the literature suggested the usefulness of percutaneous drainage as the sole technique in the treatment for patients with pancreatic necrosis, the use of it was detected to be adequate for some of patients who may not require surgery. A recent national study on patients undergoing surgery, shows that necrosectomy for patients with sterile necrosis is associated with increased mortality, meanwhile supporting conservative treatment unless a pancreatic or peri-pancreatic infection is detected[80].

A fraction of situations of patients with non-infected necrosis can benefit from surgical treatment after the acute stage in pancreatitis: (1) After several weeks of conservative treatment, patients who are still suffering from, fever, nausea and/or vomiting, lethargy and hyperamylasemia after attempts to return to an oral diet, typically have large amounts of necrotic tissue with concealed retroperitoneal infections that are objectified after debridement[81]; (2) Patients who are suffering from postnecrotic rupture of the main pancreatic duct, which is defined as “disconnected duct syndrome”, are tributaries of surgical treatment[82]; and (3) Organization of necrosis lead to biliary stenosis and/or intestinal obstruction.

Pancreatic necrosis has two distinct phases, the early and late phases, that indicates its dynamic process. The conclusive evidence which advised against necrosectomy of sterile necrosis[83,84] is that the best time to perform surgery is during the late phase, often after three or four weeks from the disease onset, in which the necrosis infection is common[79].

Minimally invasive pancreatic necrosectomy (MIN)[85], relatived to open necrosectomy, has been developed in surgical treatment remaining controversial. One group of surgeons who support the management, which relegates open necrosectomy to a secondary option after the failure of a minimally invasive technique. On the other hand, there is another group of surgeons who suggest it as a complementary method of open necrosectomy, which is only helpful for the management of waste collection after conventional surgical treatment. Currently endoscopic techniques, with some exceptions, have failed to demonstrate its superiority over conventional techniques; however, the future of minimally invasive techniques in the treatment of patients with infected pancreatic necrosis is promising, as long as the experience in handling it increases and the new technology needed for obtaining the best results appears[82,86].

Due to the physiological stress to the patient of SAP with infected necrosis, a laparotomy and open necrosectomy produces a further exacerbated called the “second hit”, which brings an increasing mortality rate. Carter’s group in Glasgow[87] described retroperitoneal approach which is a classic lumbotomy adaptation for debridement of infected necrosis basically localized on (peri)pancreas. Some surgeons suggest that compared with open necrosectomy, the operation using retroperitoneal access to pancreatic area is a minimal access approach for drainage and debridement of infected pancreatic necrosis. Some studies report that this technique does not increase mortality rate of patients after surgery, which can be applied as many times as necessary, and has advantages over other access approaches.

In summary, patients with sterile necrosis may perform conservational treatment and necrosectomy can be applied in the best time, and who with infected necrosis should be treated surgically based on the clinical situation. Retroperitoneal approach pancreatitis necrosectomy can be performed to reduce ”second hit” compared with open surgeries and mortality rate.

**CONCLUSION**

AP is a disease of high mortality, and thousands of studies about it have been reported in the world. Increased knowledge of the AP may achieve more thorough understanding of the pathogenesis, meanwhile encourage the use of further advanced diagnostic tools and point to superior treatment, which potentially will help clinicians to manage AP at an appropriate stage. However, in view of the multi factorial disease and the complex clinical manifestation, the management of patients with AP is also remaining areas for improvement.

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**Table 1 Determinant-based classification of acute pancreatitis severity**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Classification** | **Mild AP** | **Moderate AP** | **Severe AP** | **Critical AP** |
| (peri) Pancreatic necrosis | No | Sterile | Infected | Infected |
| Organ failure | No | (And/or) transeint | (Or) persistent | (And) persistent |

AP: Acute pancreatitis.

**Table 2 Modified Marshall Scoring System for organ failure**

|  |  |
| --- | --- |
| **System** | **Score** |
|  | 0 | 1 | 2 | 3 | 4 |
| Respiratory (PaO2/FiO2) | > 400 | 301-400 | 201-300 | 101-200 | ≤ 101 |
| Renal (Serum creatinene, mg/dL) | ≤ 1.4 | 1.4-1.8 | 1.9-3.6 | 3.6-4.9 | > 4.9 |
| Cardiovascular (systolic blood pressure mmHg, without inotropic support) | > 90 | < 90Fluid responsive | < 90Not fluid responsive | < 90PH < 7.3 | < 90PH < 7.2 |

PaO2: Partial pressure of oxygen; FiO2: Fraction of inspiration O2.