Guideline

JOURNAL OF PANCREATOLOGY®

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# Guidelines for the diagnosis and treatment of acute pancreatitis in China (2021)

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**Abstract**

Acute pancreatitis (AP) is a common acute abdominal condition of the digestive system. In recent years, treatment concepts, methods, and strategies for the diagnosis of AP have advanced, and this has played an important role in promoting the standardization of AP diagnosis and treatment and improving the treatment quality of AP patients. On the basis of previous guidelines and expert consensus, this guideline adopts an evidence-based, problem-based expression; synthesizes important clinical research data at home and abroad in the most recent 5 years; and forms 29 recommendations through multidisciplinary expert discussion, including diagnosis, treatment, and follow-up. It is expected to provide evidence support for the treatment of AP in the clinical setting in China.

**Keywords:** Acute pancreatitis, Diagnosis, Follow-up, Guideline, Treatment

## Introduction

Acute pancreatitis (AP) is an acute abdominal condition caused by the abnormal activation of pancreatic enzymes, which can digest the pancreas and its surrounding organs. AP is characterized by local inflammation of the pancreas, and it may even lead to organ dysfunction. In 2014, after repeated discussion and

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*Journal of Pancreatology (2021) 4:2*

*Published online 15 June 2021*

*http://dx.doi.org/10.1097/JP9.0000000000000071*

revision by the Pancreatic Surgery Group of the Surgical Association of the Chinese Medical Association, the Guidelines for Diagnosis and Treatment of Acute Pancreatitis (2014)[1] were issued. The release of the guidelines has played an important role in promoting the standardization of diagnosis and treatment of AP and improving patient treatment quality. In the past 7 years, significant changes have taken place in terms of the concepts, methods, and strategies of diagnosis and treatment of AP. To reflect the progress of the discipline, the group revised the Guidelines for the Diagnosis and Treatment of Acute Pancreatitis (2014), so as to provide evidence for the clinical diagnosis and treatment of AP in China and promote it to align with international standards.

Based on previous guidelines and expert consensus, through an evidence-based and problem-oriented expression, this guideline consists of 29 recommendations, including diagnosis, treatment, and follow-up. The quality of evidence is classified as high, moderate, or low using the Grading of Recommendations, Assessment, Development, and Evaluation system. The strength of recommendation (strong or weak) indicates the degree of recognition of the recommendation by experts.

## Diagnosis of acute pancreatitis

### *Epidemiology and etiology*

At present, there is a lack of complete epidemiological data on AP in China. From a worldwide point of view, AP is a common digestive system emergency requiring hospitalization, but its incidence varies greatly among different parts of the world, ranging from 4.9 to 73.4/100000. In recent years, the incidence of AP has been on the rise and warrants clinical attention.[1]

There are many causes of AP, and the age, sex distribution, and disease severity of AP patients with different causes are different. In China, cholelithiasis remains the primary cause of AP, followed by hypertriglyceridemia and excessive drinking. Hypertriglyceridemia and alcoholic AP are more common in young male patients, while biliary AP is more common in elderly patients.[3] Other rare causes include drugs, endoscopic retrograde cholangiopancreatography (ERCP), hypercalcemia, infection, heredity, autoimmune diseases, and trauma. Early control of the etiology is helpful to alleviate the disease, improve the prognosis, and prevent the recurrence of AP.

### *Clinical manifestation*

The typical symptoms of AP are acute persistent severe epigastric pain, often radiating to the back, accompanied by abdominal distension, nausea, and vomiting, and the pain is not relieved after vomiting. Some patients may have shock manifestations such as tachycardia, hypotension, and oliguria, and mental state changes may occur in patients with severe dehydration and elderly adults. Patients with mild clinical signs only show mild abdominal tenderness, while those with severe clinical signs may have signs of peritoneal irritation, occasionally lumbar costal subcutaneous ecchymosis (Grey-Turner sign), and umbilical periumbilical subcutaneous ecchymosis (Cullen sign). AP can be complicated with 1 or more organ dysfunction, especially respiratory and renal dysfunction. Laboratory examination results show elevated serum amylase and lipase levels in patients with AP, and lipase has a higher specificity for the diagnosis of AP than amylase. Elevation of serum amylase and lipase does not affect the severity of AP. Computed tomography (CT) is an important imaging method for the diagnosis of AP. The typical imaging findings of AP in the early stage include pancreatic edema, peripancreatic exudation, and necrosis of the pancreas or peripancreatic tissue.

### *Diagnostic criteria of AP*

The diagnostic criteria of AP include (1) persistent upper abdominal pain, (2) concentration of serum amylase and/or lipase at least 3 times higher than the normal upper limit, and (3) abdominal imaging findings suggestive of AP. AP can be diagnosed if 2 of the above 3 criteria are met.[2]

**Recommendation 1:** The diagnosis of AP requires 2 of the 3 characteristics of clinical symptoms, laboratory examination, and imaging examination (quality of evidence: high; strength of recommendation: strong).

### *Imaging of AP*

The typical imaging findings of CT provide an important basis for the diagnosis of AP, but the initial imaging features cannot reflect the severity of the disease. Unless a diagnosis is needed, CT examination should be performed 72 hours after the onset of the disease. A contrast-enhanced CT scan can accurately reflect the presence and extent of pancreatic necrosis. The modified CT severity index is a useful tool for evaluating the severity of AP (Table 1).

Magnetic resonance imaging (MRI) can be used in patients with iodine contrast agent allergy or renal insufficiency and in young or pregnant patients. MRI can detect pancreatic edema with a higher sensitivity than CT, and it can also be used to determine the presence of local complications. However, MRI is less sensitive in terms of diagnosis of bubbles in the accumulated fluid.[4]

For patients with suspected biliary AP, ultrasonography should be performed at admission or within 48 hours after onset to determine whether there are biliary stones. Magnetic resonance cholangiopancreatography or endoscopic ultrasound can assist in detecting occult biliary stones.[5]

**Recommendation 2:** Contrast-enhanced CT is not recommended at the initial stage of AP unless it is needed for diagnosis (quality of evidence: moderate; strength of recommendation: strong).

**Recommendation 3:** Patients with suspected biliary AP should be routinely examined by ultrasonography on admission or at the initial stage of the disease to determine whether there are biliary stones (quality of evidence: moderate; strength of recommendation: strong).

**Table 1**

**MCTSI scoring**

| Prognostic indicator | Score |
|---|---|
| Pancreatic inflammation | |
| Normal pancreas | 0 |
| Inflammatory changes of pancreas and/or peripancreas | 2 |
| Single or multiple hydrops or peripancreatic fat necrosis | 4 |
| Pancreatic necrosis | |
| No pancreatic necrosis | 0 |
| Necrosis area $\leq$30% | 2 |
| Necrosis area $>$30% | 4 |
| Extra-pancreatic complications, including pleural effusion, ascites, and vascular or gastrointestinal involvement | 2 |

The MCTSI score is the sum of the scores for inflammation, necrosis, and extra-pancreatic complications. MCTSI = modified computed tomography severity index.

**Table 2**

**AP classification system**

| Classification system | Indicator | Mild AP | Moderately severe AP | Severe AP | Critical AP |
|---|---|---|---|---|---|
| RAC | Organ dysfunction | None | Transient (≤ 48 h) | Persistent (>48 h) | — |
| | Local complications | None | And/or local complications | — | |
| DBC | Organ dysfunction | None | Transient (≤48 h) | Persistent (>48 h) | Persistent (>48 h) |
| | Pancreatic (peripancreatic) necrosis | None | And/or aseptic necrosis | Or infectious necrosis | And infectious necrosis |

The RAC and DBC are used to diagnose organ dysfunction according to the modified Marshall score and Sequential Organ Failure Assessment score, respectively.
AP = acute pancreatitis, DBC = determinant-based classification, RAC = revised Atlanta classification.

### *Classification of AP severity*

The commonly used classification of AP severity includes the revised Atlanta classification (RAC) and the determinant-based classification (DBC). At present, the former is more commonly used (Table 2).

The RAC classifies AP severity into 3 grades: (1) mild AP, accounting for 80–85% of AP, without organ dysfunction and local or systemic complications, usually recovering within 1–2 weeks, and with a very low mortality rate; (2) moderately severe AP, with transient (≤48 hours) organ dysfunction and/or local complications, and a low early mortality rate. If necrotic tissue is complicated with infection, the mortality rate will increase; and (3) severe AP (SAP), accounting for 5–10% of AP, accompanied by persistent organ dysfunction (>48 hours), and a high mortality rate. The diagnostic criteria of organ dysfunction were based on the modified Marshall score system, and any organ score ≥2 was defined as organ dysfunction (Table 3).

The DBC classifies AP severity using two prognostic determinants: organ dysfunction and infection. AP severity is classified as follows: (1) mild AP: no pancreatic (peripancreatic) necrosis and organ dysfunction; (2) moderate AP: aseptic pancreatic (peripancreatic) necrosis and/or transient (≤48 hours) organ dysfunction; (3) SAP: infectious pancreatic (peripancreatic) necrosis or persistent (>48 hours) organ dysfunction; and (4) critical AP (CAP): persistent organ dysfunction with infectious pancreatic (peripancreatic) necrosis. The DBC diagnostic criteria of organ dysfunction are based on the Sequential Organ Failure Assessment score.

The current research results show that there is no significant difference between RAC and DBC classification in terms of predicting mortality, hospitalization rate in the intensive care unit (ICU), and length of ICU stay.[6] The DBC classification needs to determine whether there is pancreatic and/or peripancreatic infection, which is not suitable for early application in the course of AP. CAP complicated by persistent organ dysfunction and pancreatic or peripancreatic necrotic infection is uncommon and is associated with a high mortality rate. Therefore, CAP should be carefully monitored in the clinical setting.[6,7] In the present guideline, SAP refers to severe AP in the RAC classification.

**Recommendation 4:** Both RAC and DBC classifications can be applied to classify AP severity, and there is no significant difference between them in terms of predicting mortality, ICU occupancy rate, and ICU hospitalization time (quality of evidence: moderate; strength of recommendation: strong).

**Recommendation 5:** CAP patients with persistent organ dysfunction and pancreatic (peripancreatic) necrotic infection, and high mortality, should be carefully monitored (quality of evidence: moderate; strength of recommendation: strong).

### *Prediction of severe AP*

For the early identification of patients who may develop SAP, more active monitoring and treatment measures are beneficial for improving the prognosis of these patients. The levels of hematocrit, serum urea nitrogen, and C-reactive protein in laboratory examination are correlated with the severity of AP, but with low accuracy. A variety of scoring systems (such as APACHE II, Ranson score, and BISAP score) have been proposed to predict SAP[2] in clinical settings; however, they all have shortcomings and cannot fully meet clinical requirements. Therefore, it is critical to closely monitor the vital signs of patients and detect organ dysfunction. Patients with organ dysfunction should be admitted to the ICU for treatment.

**Table 3**

**Modified Marshall scoring system**

| | Score | | | | |
|---|---|---|---|---|---|
| Organ system | 0 | 1 | 2 | 3 | 4 |
| Respiratory ($PaO_2/FiO_2$) | >400 | 301–400 | 201–300 | 101–200 | ≤101 |
| Renal (serum creatinine, μM)* | ≤134 | 134–169 | 170–310 | 311–439 | >439 |
| Cardiovascular (systolic blood pressure, mmHg)† | >90 | <90, responsive to fluid resuscitation | <90, not responsive to fluid resuscitation | <90, pH <7.3 | <90, pH <7.2 |

For non-ventilated patients, the $FiO_2$ can be estimated using the following criteria:

| Oxygen inhalation (L/min) | $FiO_2$ (%) |
|---|---|
| Indoor air | 21 |
| 2 | 25 |
| 4 | 30 |
| 6–8 | 40 |
| 9–10 | 50 |

* Scoring of patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. There is no formal revised scheme for patients with baseline serum creatinine ≥134 μM. †Positive inotropic drugs are not used. 1 mmHg = 0.133 kPa.

**Recommendation 6:** There is no accurate SAP prediction system at present. Patients' organ function should be closely monitored to avoid the occurrence of SAP (quality of evidence: moderate; strength of recommendation: strong).

### *Phases of AP*

The course of AP can be divided into 2 overlapping phases (early and late), each of which corresponds to 1 of the 2 death peaks in the course of AP. The early phase refers to the period from onset to 2 weeks and is characterized by systemic inflammatory response syndrome (SIRS) and organ dysfunction. Although local complications may occur in the early phase, they are not the main determinant of disease severity. The late phase refers to the period of 2 weeks after onset and is characterized by persistent SIRS, organ dysfunction, and local complications. Persistent SIRS and organ dysfunction are important determinants of late-phase AP severity. Besides, local complications, especially infectious complications, can also affect the prognosis of patients.

**Recommendation 7:** The course of AP can be divided into 2 overlapping phases—early (≤2 weeks after onset) and late (>2 weeks after onset)—which correspond to two death peaks in the course of AP (quality of evidence: moderate; strength of recommendation: weak).

### *Complications of AP*

AP can cause both systemic and local complications. The systemic complications include SIRS, sepsis, multiple organ dysfunction syndrome, and abdominal compartment syndrome (ACS). Local complications are mainly associated with the pancreatic or peripancreatic fluid collection and tissue necrosis, including early (<4 weeks) acute peripancreatic fluid collection, acute necrotic collection (ANC), and late (>4 weeks) pancreatic pseudocysts (PPs) and walled-off necrosis (WON)[8] (Table 4). Local complications can be divided into two categories: aseptic and infectious complications. Other complications include gastrointestinal bleeding, abdominal bleeding, biliary obstruction, intestinal obstruction, and intestinal fistula.

### *Treatment of AP*

The treatment of AP, especially SAP with multiple complications, is complex, involving surgery, gastroenterology, emergency department, critical care medicine department, infection department, intervention department, nutritional department, and rehabilitation department. Multi-disciplinary diagnosis and treatment should be adopted.

### *Treatment of early-phase AP*

The early treatment of AP mainly includes fluid resuscitation, analgesia, and nutritional support, as well as the treatment of etiology and early complications.

***Fluid resuscitation:*** Early fluid resuscitation can improve tissue perfusion and should be carried out immediately after the diagnosis of AP. For patients with SAP, a goal-directed therapy mode should be adopted,[9] and the hemodynamic status should be evaluated repeatedly to guide fluid infusion. Crystalloid solutions such as Ringer lactate solution and normal saline should be used as the first choice for fluid resuscitation.[10] In the beginning, fluid resuscitation at a rate of 5–10 mL/kg per hour is recommended.[11] During fluid resuscitation, careful monitoring is required to avoid tissue edema and organ dysfunction caused by liquid overload. At present, there is no consensus on the indicators suggestive of successful fluid resuscitation. However, the following criteria of early goal-directed therapy are suggested as recovery goals: 1) urine volume >0.5–1 mL/kg per hour; 2) mean arterial pressure >65 mmHg (1 mmHg = 0.133 kPa), 3) central venous pressure 8–12 mmHg; and 4) central venous oxygen saturation ≥70%. In addition, a decrease in arterial blood lactic acid, serum urea nitrogen, and hematocrit also suggests that resuscitation is effective.[10] For AP patients with persistent hypotension, norepinephrine can be administered during or after fluid resuscitation to increase blood pressure.

**Recommendation 8:** Patients diagnosed with AP should be immediately treated with a crystalloid solution at a rate of 5–10 mL/kg per hour (quality of evidence: moderate; strength of recommendation: strong).

***Indications and timing for emergency ERCP:*** Biliary stones are the main cause of AP. For many years, there has been controversy around whether emergency ERCP treatment can help alleviate the condition of biliary AP. Hence, emergency ERCP treatment is currently not recommended for patients with mild AP.[12] The results of the APEC study confirmed that emergency ERCP did not help alleviate the condition of patients with SAP.[13] At present, it is considered that emergency ERCP is only suitable for patients with biliary pancreatitis complicated with cholangitis and should be performed within 24 hours of admission. ERCP

**Table 4**

**Clinical features of local complications of AP**

| Complication | Clinical features |
|---|---|
| Acute peripancreatic fluid collection | – Occurs in the early phase of AP<br>– Peripancreatic or interstitial fluid collection<br>– Lack of complete capsule<br>– Single or spontaneous regression |
| Acute necrotic collection | – Occurs in the early phase of AP<br>– Mixture of fluid and necrotic parenchyma or peripancreatic tissue<br>– Including necrosis of pancreatic parenchyma or peripancreatic tissue |
| Pancreatic pseudocyst | – Occurs 4weeks after onset<br>– Fluid collection is encapsulated by a complete non-epithelial capsule<br>– The capsule of pseudocyst is gradually formed |
| Walled-off necrosis | – Occurs 4weeks after onset<br>– Cystic solid structure with a clear boundary inflammatory capsule containing intra- or extra-pancreatic necrotic tissue |

AP = acute pancreatitis.

treatment can also be considered for patients with persistent biliary obstruction, in whom the operation time can be extended to 72 hours after admission.[14]

**Recommendation 9:** Emergency ERCP does not help alleviate biliary AP and is only suitable for AP patients complicated with cholangitis and persistent biliary obstruction (quality of evidence: high; strength of recommendation: strong).

***Analgesia:*** Pain is the main symptom of AP, and pain relief is an important clinical treatment goal. AP patients with obvious pain should be treated with analgesics within 24 hours of admission. Opioids and non-steroidal anti-inflammatory drugs have been used for analgesia in patients with AP. However, there is limited evidence regarding the efficacy and safety of various analgesic drugs in the treatment of AP, and there is no consensus on the analgesic effect of certain drugs on AP. A previous study showed that the analgesic effect of dihydromorphone hydrochloride was superior to that of morphine and fentanyl in patients without tracheal intubation.[15] Epidural analgesia should be considered for patients with SAP and CAP who need long-term high-dose opioid therapy. Another study found that AP patients who received epidural analgesia in ICU had a lower mortality rate within 30 days after onset compared with those who do not receive epidural analgesia.[16] At present, it is recommended to treat AP patients according to perioperative acute pain (combination of systemic and local administration, patient-controlled analgesia, and multimodal analgesia).

**Recommendation 10:** Analgesia is an important adjuvant therapy for AP, which can improve the prognosis of patients. Analgesic drugs and methods should be selected according to the condition of the disease (quality of evidence: moderate; strength of recommendation: weak).

***Nutritional support:*** Some studies have shown that enteral nutrition is safer and more tolerable than parenteral nutrition for patients with AP of varying severities and can reduce the incidence of infectious complications and multiple organ dysfunction and mortality rate.[17] There is no significant difference in tolerance, complication rates, and mortality rates associated with the use of nasogastric tubes and nasojejunal tubes. One meta-analysis showed the safety and feasibility of nasogastric tubes. Nasogastric tube placement is more convenient than a nasojejunal tube, but nasojejunal tubes should be used in patients with a gastric emptying disorder or pyloric obstruction.[18]

Multiple meta-analyses support the initiation of enteral nutrition within 24 or 48 hours after the onset of AP.[9] Enteral nutrition initiated within 48 hours was found to be more effective than that initiated late, as evidenced by lower incidences of infection and organ dysfunction and mortality rate. A multicenter randomized controlled trial involving 205 patients with AP investigated the effectiveness and safety of enteral nutrition initiation within 24 and 72 hours after the onset of AP. It was found that there was no significant difference in the incidence of infection and mortality rate during hospitalization, indicating that the early initiation of enteral nutrition is safe.[19] Studies on dietary components in patients with AP are limited. It has been confirmed that a low-fat diet and soft food are safe in patients with AP, and amino acids have no significant clinical benefits in terms of in-hospital mortality, sepsis development, mean hospital-free days, and mean total healthcare costs, compared with short peptide or whole protein nutritional preparations.[20]

**Recommendation 11:** In the case of gastrointestinal functional tolerance, oral or enteral nutrition should be performed as soon as possible (24–72 hours after admission) (quality of evidence: high; strength of recommendation: strong).

**Recommendation 12:** Enteral nutrition is more efficient than parenteral nutrition for AP patients who cannot consume food orally (quality of evidence: high; strength of recommendation: strong).

***Early treatment of hyperlipidemic AP:*** Clinical manifestations of acute hypertriglyceridemic pancreatitis are more serious than those of other causes of AP. Acute hyperlipidemic pancreatitis can be diagnosed when AP exists in conjunction with venous chylous blood or blood triglyceride levels >11.3 mM. In addition to the conventional treatment of AP, the early treatment of hyperlipidemic AP should include diet regulation after water fasting for at least 24–48 hours and the use of lipid-lowering drugs and other auxiliary lipid-lowering methods (low-dose and low-molecular-weight heparin, insulin, blood lipid adsorption, and/or plasma exchange) to control blood lipids.[21] It is disputed whether early control of triglyceride levels can affect the incidence of complications and mortality in AP patients.[17] The current recommendation is to decrease triglyceride levels to <5.65 mM as soon as possible after the diagnosis of hyperlipidemic AP.[22]

**Recommendation 13:** Hyperlipidemic AP is diagnosed when AP exists in conjunction with venous chylous blood or blood triglyceride levels >11.3 mM. Comprehensive treatment should be used to achieve a rapid decrease in triglyceride levels (quality of evidence: moderate; strength of recommendation: strong).

***Early treatment of ACS:*** SAP can be complicated with ACS. Intra-abdominal pressures >20 mmHg often induce new organ dysfunction, which is an important cause of death in AP patients. The main goal of treatment of ACS is to reduce intra-abdominal pressure in a timely and effective manner, which can be relieved by 1) increasing abdominal wall compliance using analgesics, sedatives, and muscle relaxants; 2) clearing gastrointestinal contents via gastrointestinal decompression, enema, and gastrointestinal motility-promoting drugs; 3) avoiding excessive fluid infusion; and 4) draining peritoneal or retroperitoneal effusion using percutaneous drainage.[23] It is not recommended to use ACS as an indication of laparotomy in early phase AP.[24]

**Recommendation 14:** ACS is an important cause of early death in patients with AP. Comprehensive measures should be taken to reduce intra-abdominal pressure by increasing abdominal wall compliance, clearing gastrointestinal contents, draining the abdominal cavity, and draining retroperitoneal effusion. Early laparotomy is not recommended (quality of evidence: moderate; strength of recommendation: strong).

***Prophylactic use of antibiotics in patients with AP:*** Prophylactic use of antibiotics in the treatment of AP remains controversial,[25] and reports suggest that it is incapable of reducing the incidence of peripancreatic or pancreatic infection, but may increase the chances of multiple drug-resistant bacteria and fungal infections.[26] Therefore, it is not recommended for AP patients without evidence of infection. For patients with suspected or confirmed pancreatic, peripancreatic, or extrapancreatic infections (such as biliary system, lung, urinary system, and catheter-related infection), antibiotics can be used empirically. Body fluid culture should be carried out as soon as

possible, so as to adjust antibiotics according to the results of bacterial culture and drug sensitivity test.

**Recommendation 15:** Routine use of antibiotics is not recommended to prevent pancreatic or peripancreatic infections (quality of evidence: high; strength of recommendation: strong).

***Drug treatment of AP:*** At present, specific drugs for the treatment of AP are still lacking. No high-quality clinical evidence regarding the therapeutic value of protease and trypsin inhibitors, such as somatostatin and its analogs in AP patients, has been reported.[27] Traditional Chinese medicine (rhubarb, mirabilite, and compound preparations such as Qingyi decoction and Dachengqi decoction) can be used as an alternative to drug therapy, as this promotes the recovery of gastrointestinal function and relieves abdominal pain and distension.

### *Treatment of late-phase AP*

The treatment of late-phase AP is mainly aimed at alleviating various local complications. In this phase, the patient may still have organ dysfunction. Persistent organ dysfunction is an independent risk factor for poor prognosis, which significantly increases the risk of surgical treatment. The complications of late-phase AP mainly include PPs, WON, hemorrhage, and gastrointestinal fistula. Asymptomatic PPs and WON do not need to be treated; however, WON co-infection is the main reason for surgical treatment.

***Diagnosis of infected pancreatic necrosis:*** Infected pancreatic necrosis (IPN) includes early ANC and late WON. Timely and accurate diagnosis is an important basis for follow-up treatment. Fever and abdominal pain are important for diagnosing IPN. Some patients with severe infection may experience systemic deterioration, such as renal insufficiency, respiratory insufficiency, coagulation dysfunction, and even circulatory instability. Dynamic monitoring of laboratory indexes such as white blood cell count, C-reactive protein, IL-6, and procalcitonin is helpful for the diagnosis and treatment of IPN. Some researchers believe that procalcitonin can be reliably used to evaluate the overall prognosis of patients with IPN.[28] Imaging examination contributes to judging the scope of infection, evaluating infection severity, and selecting the follow-up treatment measures, in which a "bubble sign" on CT examination is the direct evidence for IPN diagnosis. Routine fine needle aspiration is not recommended to determine the presence of infection.

**Recommendation 16:** IPN should be considered when patients with AP have infection symptoms such as fever, abdominal pain, and deterioration of general condition (quality of evidence: moderate; strength of recommendation: strong).

**Recommendation 17:** It is suggested that inflammatory markers including procalcitonin and CT should be detected in patients with suspected IPN to assist in the diagnosis. Routine fine needle aspiration examination is not recommended for patients suspected of having IPN (quality of evidence: high; strength of recommendation: strong).

***Treatment of IPN:*** IPN is a serious complication of late-phase AP. Approximately 30% of patients with necrotizing pancreatitis will have a secondary infection, with a mortality rate of 30%. The main treatments for IPN include the use of antibiotics, percutaneous puncture drainage (PCD) or endoscopic drainage, video-assisted debridement or endoscopic debridement, and laparotomy. The use of antibiotics is important for the treatment of IPN. For patients with suspected IPN, antibiotics should be used empirically, and bacterial culture of body fluid should be performed as soon as possible. Antibiotics should then be adjusted according to the results of drug-sensitivity testing to reduce the potential for drug-resistant bacteria. PCD or endoscopic drainage is effective in some patients, allowing further surgical treatment to be avoided. At present, video-assisted debridement and endoscopic debridement and other minimally invasive surgery have gradually become the main treatments for IPN. Laparotomy can be used as a supplementary therapy after the failure of minimally invasive treatment.

**Recommendation 18:** IPN is a serious complication of AP that often needs surgical treatment. Antibiotics, PCD, or endoscopic drainage can prevent some patients from requiring surgery. Minimally invasive debridement has gradually become the main treatment for IPN. Laparotomy can be used as a supplementary therapy to treat IPN after the failure of minimally invasive treatment (quality of evidence: moderate; strength of recommendation: strong).

***Surgical strategy of IPN:*** At present, the "Step-up" approach is considered the preferred intervention strategy for IPN[29]; that is, puncture and drainage are performed first, and video-assisted debridement and laparotomy are performed successively for patients with poor drainage.[30] With the progress of endoscopic technology, the use of endoscopic "Step-up" surgery is gradually increasing.[31] The advantage of puncture and drainage is to quickly improve the general condition of patients with less trauma and create conditions for follow-up treatment. However, after active supportive treatment, some IPN patients have normal organ function and good general condition, and there is no need to improve their general condition through PCD. In addition, a safe puncture approach is not feasible for some patients or PCD is estimated to be less beneficial for these patients, and they cannot adhere to the "Step-up" strategy and undergo surgical treatment directly.[32]

**Recommendation 19:** Patients with IPN are mainly treated with the "Step-up" strategy (quality of evidence: high; strength of recommendation: strong).

**Recommendation 20:** Some patients who meet the strict criteria described above can undergo surgery directly (quality of evidence: low; strength of recommendation: strong).

***"Step-up" strategy in surgery and endoscopy:*** In recent years, many studies have compared surgical "Step-up" and endoscopic "Step-up" strategies. However, in general, there is no significant difference in the mortality rate or the incidence of severe complications between the two groups.[33] The advantage of endoscopy is to reduce the incidence of pancreatic fistula and incisional hernia, but frequent endoscopic debridement is not suitable for all patients with IPN. Surgical "Step-up" is more advantageous for the treatment of infection in the bilateral retrocolonic space and pelvic retroperitoneal area. In addition, endoscopic treatment requires specialized instruments and experienced operators. At present, surgical "Step-up" is still the first choice for IPN treatment in most medical institutes.

**Recommendation 21:** Both surgical and endoscopic "Step-up" surgeries have advantages, as described above. However, the surgical "Step-up" strategy currently remains the first choice for

IPN in most medical institutes (quality of evidence: high; strength of recommendation: strong).

*Indication and timing of percutaneous/endoscopic drainage:* Puncture and insertion of a drainage tube under the guidance of ultrasound or CT or an endoscope is an important measure to control pancreatic or peripancreatic infection. PCD can be performed under the guidance of ultrasound or CT, and retroperitoneal puncture is preferred. Endoscopic drainage is usually performed through the stomach wall or duodenal wall. At present, whether drainage is feasible in early phase AP remains controversial. The consensus is that if medication is not sufficiently effective, PCD is still a safe and effective measure to control highly suspected or confirmed necrotic pancreatic infection, even if complete encapsulation has not occurred. Some researchers believe that early endoscopic drainage is also safe.[34] For AP patients with ACS, puncture and drainage should be considered to reduce intra-abdominal pressure in cases with a large amount of abdominal or retroperitoneal effusion. In late-phase AP, drainage treatment is also feasible for local complications caused by compression of the digestive tract or biliary tract.

**Recommendation 22:** Pancreatic and peripancreatic infections are important indications for PCD and endoscopic drainage, which can be performed in the early phase of AP (quality of evidence: moderate; strength of recommendation: strong).

**Recommendation 23:** For AP patients with extensive peritoneal or retroperitoneal effusion and ACS, puncture and drainage can be performed. The drainage tube should be removed early (<72 hours) to reduce the likelihood of secondary infection (quality of evidence: low; strength of recommendation: weak).

*Timing of IPN surgery:* Timing of surgery is an important factor to determine the prognosis of patients with IPN. A previous study showed that the mortality of patients subjected to surgery during the early phase of IPN can be >50% and that delayed surgery can reduce the incidence of complications and mortality.[35] Therefore, domestic and foreign guidelines clearly point out that IPN surgery should be delayed to 4 weeks after the onset of IPN.[1,24] However, all evidence regarding delayed IPN surgery is based on the practice of laparotomy. With the increasing popularity of the minimally invasive treatment, the potential need for adjusting the timing of surgery must be confirmed by future multicenter, prospective studies.

**Recommendation 24:** At present, the optimal intervention time for IPN surgery is 4 weeks after the onset of AP (quality of evidence: moderate; strength of recommendation: strong).

*Management of pancreatic fistula and pancreatic duct rupture syndrome:* Pancreatic fistula is mostly the result of pancreatic duct rupture due to various causes, and its treatment goal is unobstructed drainage and inhibition of pancreatic secretion. Endoscopic and surgical treatment is feasible if necessary. In a previous study, the percentage of patients in whom necrotizing pancreatitis was accompanied by partial or complete disconnection of the pancreatic duct ranged from 20% to 40%, and the proportion of WON patients with disconnected pancreatic duct syndrome was the highest.[36] The integrity of the pancreatic duct can be evaluated by magnetic resonance cholangiopancreatography. At present, there is no consensus on the optimal treatment for disconnected pancreatic duct syndrome. According to the European Society of Gastrointestinal Endoscopy in 2018, the long-term indwelling of double pigtail plastic stents after intracavitary drainage of WON is recommended to reduce the recurrence risk of fluid collection.[37] In cases of partial rupture of the main pancreatic duct, a stent should be used to bridge the break. In cases of complete rupture of the main pancreatic duct, endoscopic ultrasonography-guided drainage of the duct should be considered. If endoscopic surgery fails or fluid collection recurs, surgical treatment such as distal pancreatectomy or Roux-en-Y drainage can be performed.[37]

**Recommendation 25:** Endoscopic treatment is the first choice for patients with disconnected pancreatic duct syndrome (quality of evidence: moderate; strength of recommendation: strong).

*Treatment of portal vein thrombosis, splenic vein thrombosis, and pancreatic portal hypertension in AP:* The incidence of the portal and splenic vein thrombosis in patients with AP is approximately 13%.[38] Severe thrombosis of the portal and splenic veins can lead to liver failure, portal hypertension, and splenic and intestinal necrosis. Thrombosis is related to the location and degree of pancreatic necrosis. A previous study showed that after portal vein and splenic vein thromboses, anticoagulation therapy did not increase the recanalization rate but increased the incidence of bleeding.[38] Therefore, anticoagulation therapy is not recommended for AP patients with the portal vein and splenic vein thromboses.

Pancreatic portal hypertension, also known as left portal hypertension, is mostly caused by acute and chronic pancreatitis. The majority of patients with pancreatic portal hypertension have no obvious clinical manifestations and can be followed up. Few patients show massive hemorrhage of the upper digestive tract. In addition to symptomatic hemostasis, active treatment of the primary pancreatic disease is crucial for the overall treatment. Splenectomy can be considered for patients with recurrent bleeding. For patients with severe hypersplenism, splenic artery embolization or splenectomy is feasible.

**Recommendation 26:** Thrombosis of the portal and splenic veins is common in AP, which can manifest as left portal hypertension without anticoagulant therapy (quality of evidence: low; strength of recommendation: weak).

*Treatment of intestinal fistula and abdominal hemorrhage after AP:* A common cause of intestinal fistula after AP is colonic fistula, which is mostly caused by pancreatic juice corrosion or surgery. Treatment includes unobstructed drainage and colostomy. Patients with celiac hemorrhage should first be examined by angiography to determine the site of bleeding. If the results of angiography indicate arterial hemorrhage, vascular embolization should be performed. If the bleeding site is not clear or embolization fails and bleeding continues, surgical treatment is feasible.[2]

## Prevention of recurrence of AP and follow-up

Previous studies have found that 21% of patients with first-episode AP will develop recurrent AP, which is characterized by two or more episodes of AP, with an interval of at least 3 months between episodes.[39,40] Etiological treatment is the main method of preventing recurrent AP. Cholecystectomy is beneficial in preventing the recurrence of biliary pancreatitis. Moreover, oral lipid-lowering drugs are needed for patients with hyperlipidemia that has not been well-controlled through a low-fat diet and weight reduction.[41] Abstinence from alcohol is an important

treatment for alcoholic AP, with even short-term abstinence after admission being effective in the prevention of the recurrence of alcoholic AP.

**Recommendation 27:** Approximately one-fifth of patients with AP will develop recurrent AP. Etiology-based treatment is the most beneficial method for preventing recurrent AP (quality of evidence: moderate; strength of recommendation: strong).

### *Timing of cholecystectomy for biliary pancreatitis*

Laparoscopic cholecystectomy is the main method to prevent the recurrence of biliary pancreatitis and should be performed as soon as possible in principle. It is recommended that mild AP patients with cholecystolithiasis undergo cholecystectomy before discharge from the hospital.[42] For patients with MSAP and SAP, surgery can be performed 1–3 months after the onset of AP.[24]

**Recommendation 28:** Cholecystectomy is recommended as early as possible in patients with gallstones and biliary pancreatitis (quality of evidence: high; strength of recommendation: strong).

### *Follow-up of patients with AP*

A previous study indicated that 61–85% of patients with AP will suffer from pancreatic exocrine insufficiency within 1 year after onset, and exocrine insufficiency in some patients will last for 6–18 months.[43] Approximately one-third of patients with AP will develop pancreatic endocrine insufficiency,[44] and approximately 40% will develop diabetes or prediabetes after AP.[45] Therefore, patients with AP should be regularly followed up after rehabilitation. Mild AP patients should be followed up for 6 months after discharge, and moderately severe AP and SAP patients should be followed up for at least 18 months after discharge. Pancreatic function should be evaluated once every 6 months. Long-term complications and etiologies (such as gallstones and hyperlipidemia) should be carefully monitored.

**Recommendation 29:** Patients with AP require regular follow-up after rehabilitation for the timely diagnosis and treatment of long-term complications (quality of evidence: weak; strength of recommendation: weak).

These guidelines evaluate the evidence obtained so far and put forward guiding principles for the diagnosis and treatment of AP based on national conditions, hoping to provide a basis for clinical practice. It should be pointed out that the clinical process of AP, especially SAP, is complex with significant individual differences. Clinicians need to adopt individualized diagnosis and treatment measures to obtain the optimal curative effect.

## Acknowledgments

None.

## Author contributions

All authors contributed to searching the literature and writing the corresponding recommendations and statements. FL and FC are responsible for writing the manuscript. The Chinese Pancreatic Surgery Association, Chinese Society of Surgery, Chinese Medical Association critically revised the final manuscript. All authors approved the final version of the manuscript.

## Financial support

None.

## Conflicts of interest

None.

Editor note: CH, GJ, TL, WL, YM, HW, WW, YY, XY, CY, TZ, and YZ are Editorial Board members of *Journal of Pancreatology*. The article was subject to the journal's standard procedures, with peer review handled independently of these Editorial Board members and their research groups.

## Ethics approval

Not applicable.

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**How to cite this article:** Li F, Cai S, Cao F, Chen R, Fu D, Ge C, Hao C, Hao J, Huang H, Jian Z, Jin G, Li A, Li H, Li S, Li W, Li Y, Liang T, Liu X, Lou W, Miao Y, Mou Y, Peng C, Qin R, Shao C, Sun B, Tan G, Tian X, Wang H, Wang L, Wang W, Wang W, Wei J, Wu H, Wu W, Wu Z, Yan C, Yang Y, Yin X, Yu X, Yuan C, Zhang T, Zhao Y, on behalf of the Chinese Pancreatic Surgery Association. Guidelines for the diagnosis and treatment of acute pancreatitis in China (2021). J Pancreatol 2021;4:67–75. doi: 10.1097/JP9.0000000000000071