

## Treatment strategy for acute pancreatitis

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**Abstract** When a diagnosis of acute pancreatitis (AP) is made, fundamental medical treatment consisting of fasting, intravenous (IV) fluid replacement, and analgesics with a close monitoring of vital signs should be immediately

started. In parallel with fundamental medical treatment, assessment of severity based on clinical signs, blood test, urinalysis and imaging tests should be performed to determine the way of treatment for each patient. A repeat evaluation of severity is important since the condition is unstable especially in the early stage of AP. At the time of initial diagnosis, the etiology should be investigated by means of blood test, urinalysis and diagnostic imaging. If a biliary pancreatitis accompanied with acute cholangitis or

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biliary stasis is diagnosed or suspected, an early endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES) is recommended in addition to the fundamental medical treatment. In mild cases, the fundamental medical treatment should be continued until clinical symptom is subsided with normal laboratory data. In cases with severe acute pancreatitis (SAP) referral should be considered to medical centers experienced in the treatment of SAP, and intensive care is recommended for preventing both organ failures and infectious complications. Hemodynamic stabilization with vigorous fluid resuscitation, respiratory support and antibiotics are the major parts of intensive care in the early period of SAP. Continuous hemodiafiltration (CHDF) and continuous regional arterial infusion (CRAI) of protease inhibitor and/or antibiotics may be effective to improve pathophysiology of AP especially in the early stage of the disease. In the late stage of AP, infectious complications are critical. If an infectious complication is suspected based on clinical signs, blood test and imaging, a fine needle aspiration (FNA) is recommended to establish a diagnosis. The accuracy of FNA is reported to be 89 ~ 100%. For patients with sterile pancreatitis, non-surgical treatment should be indicated. For patients with infected pancreatic necrosis, therapeutic intervention either by percutaneous, endoscopic, laparoscopic or surgical approach are indicated. The most preferred surgical intervention is necrosectomy, however, non-surgical treatment with antibiotics is still the treatment of choice if the general condition is stable. Necrosectomy should be performed as late as possible. For patients with pancreatic abscess, drainage is recommended.

**Keywords** Acute pancreatitis · Guidelines · Gallstone pancreatitis · Intensive care · Interventional treatment

## Introduction

Acute pancreatitis (AP) is a disease showing wide range in severity from mild to severe, and severe acute pancreatitis (SAP) has a potential of leading to death. As a result of recent advances in diagnostic imaging and intensive care, the outcome of acute pancreatitis is being improved, nevertheless, high mortality is still reported in the most serious cases [1–6]. So far, clinical practice guidelines (CPG) for acute pancreatitis have been developed in many countries and regions [7–13]. The first Japanese CPG for acute pancreatitis (JPN guidelines) was published in Japanese in 2003, and in English in 2006 [14–20]. Subsequently, the mortality of SAP improved dramatically from 21.4 to 8.9% in Japan, however, the most severe cases of SAP still have a high mortality rate of 30%. In 2008, the Japanese

Ministry of Health, Labour and Welfare devised new diagnostic criteria and the severity scoring system of acute pancreatitis and Japanese CPG were revised and published (Tables 1, 2). In this article, the treatment strategy for acute pancreatitis in new Japanese Guidelines (JPN guidelines 2010) is described.

Flowchart for the management of acute pancreatitis (Fig. 1)

A patient who is diagnosed as acute pancreatitis should be hospitalized, and a fundamental medical treatment consisting of fasting, giving intravenous (IV) fluid replacement, oxygen and analgesics (if necessary) under an adequate vitals monitoring should be immediately started. At the same time, establishment of the etiology based on blood tests and imaging, and assessment of the severity based on the severity scoring system should be conducted (Table 2). It is advisable to conduct the assessment of the severity within 3 h after diagnosis. As the condition is unstable in the early stage of acute pancreatitis, repeated assessment of the severity is important even after admission. Particularly, repeated assessment of the severity within 48 h after admission is strongly recommended.

## Medical treatment

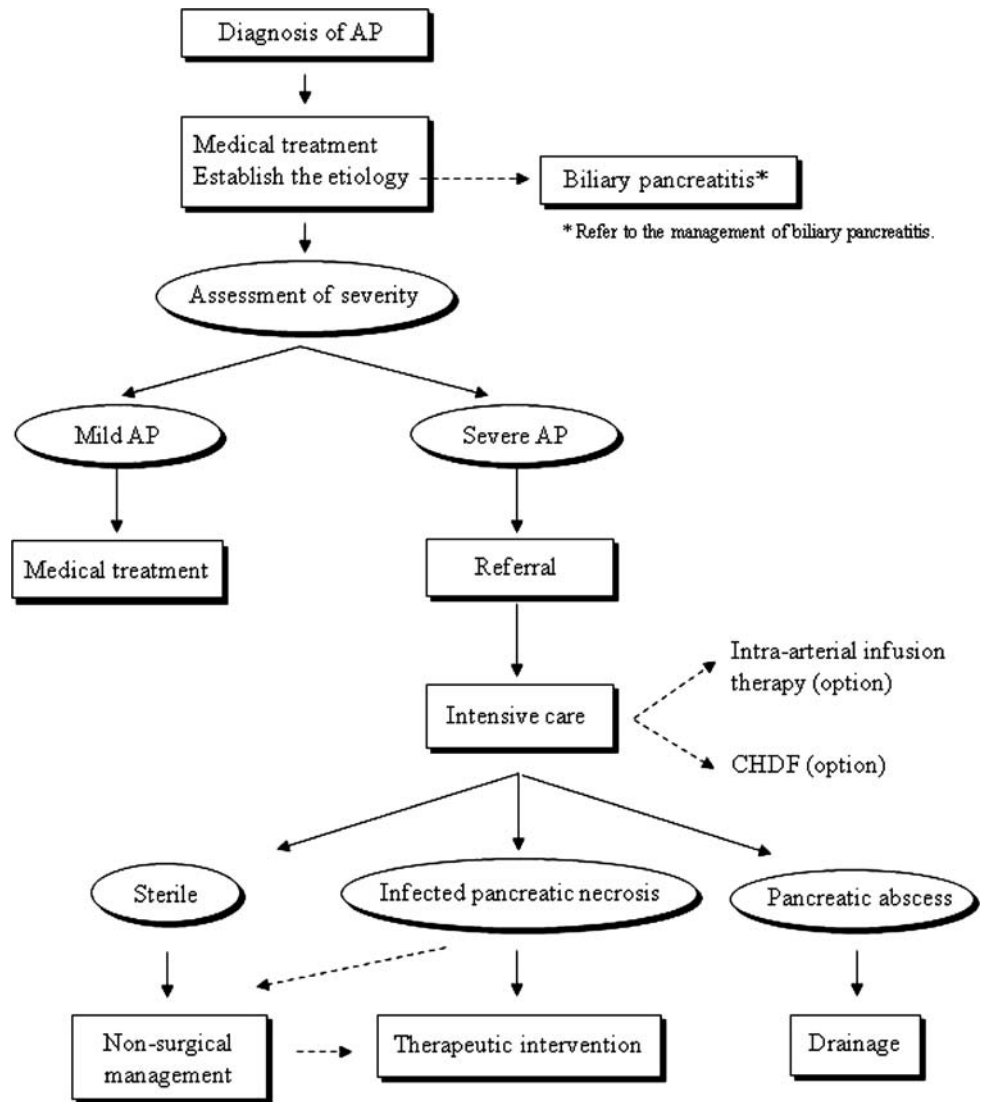
In the early stage of acute pancreatitis, it is important to stabilize the hemodynamics with sufficient IV fluid resuscitation. Prolongation of shock due to insufficient fluid replacement may cause organ failure, which has strong relation to early mortality due to acute pancreatitis [21, 22]. Vigorous IV fluid resuscitation should be applied to maintain a mean blood pressure of 65 mmHg and urine volume of 0.5 mL/kg/h while monitoring pulse, blood pressure, urine volume, oxygen saturation, and blood test data. For severe cases, if necessary, a central venous line is secured to monitor central venous pressure (CVP) (Recommendation A).

The pain caused by acute pancreatitis is severe and persistent, and therefore it is important that it should be fully controlled (Recommendation A) [23, 24].

Nasogastric suction is not always necessary because previous randomized controlled trials (RCTs) showed no clinical efficacy such as relief of pain or shortening of hospital stay (Recommendation D) [25–32]. Therefore, nasogastric suction should be selectively used for patients with bowel obstruction or severe nausea.

Administration of H<sub>2</sub>-blockers has no direct effectiveness on acute pancreatitis. Rather, it may exacerbate the incidence of the complications or duration of the pain (Recommendation D) [27, 29, 31, 33–36]. Moreover, there are no reports demonstrating the effectiveness of proton

**Fig. 1** Flowchart for the management of acute pancreatitis



pump inhibitors (PPI) on acute pancreatitis. Administering H<sub>2</sub>-blockers and PPIs should be considered for those with acute gastric mucosal lesions or with gastrointestinal bleeding.

The use of prophylactic antibiotics should not be routinely used for acute pancreatitis. Some systematic reviews showed that the prophylactic antibiotics for acute pancreatitis improve the incidence of infectious complications and mortality [37, 38], while others reported no improvement [39, 40], which makes it difficult to obtain a solid conclusion. In mild cases, incidences of infectious complications themselves are low, and thus routine use of prophylactic antibiotics is not recommendable; however, its efficacy on SAP is expected in terms of lowering of incidences of infectious complications and mortality (Recommendation B) [41–46]. Thus, concerning prophylactic antibiotics, it is advisable to select antibiotics having a broad spectrum and good penetration to the pancreatic

and peripancreatic tissues and not to use them beyond 2 weeks. Moreover, the effect of prophylactic antifungal agents remains to be established currently (Recommendation C2) [47–50].

The clinical usefulness of protease inhibitors for acute pancreatitis to decrease incidences of complications and mortality is unknown still now. Although studies so far have not demonstrated clinical usefulness in mild cases, part of the studies in serious cases and sub-analysis based on the severity in meta-analysis have reported decreases in mortality and incidences of complications (Recommendation C1) [51, 52].

#### Establishing the etiology

Acute pancreatitis develops due to various causes and clarification of its etiology is important for deciding the treatment plan and preventing recurrence. Particularly,

making the diagnosis of biliary acute pancreatitis is most important and of the highest priority because it is greatly related to the treatment plan, including urgent endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES). To make a diagnosis of biliary pancreatitis, medical history, blood test and external ultrasonography are useful (Recommendation A). When the blood ALT is higher than 150 IU/L [sensitivity 48 ~ 93%, specificity 34 ~ 96%, positive likelihood ratio (PLR) 1.4 ~ 12.0, negative likelihood ratio (NLR) 1.8 ~ 4.9] [53, 54] or when the blood test shows abnormalities in more than three of the five measures including bilirubin, ALP,  $\gamma$ -GTP, ALT and ALT/AST ratio (sensitivity 85%, specificity 69%, PLR 2.7, NLR 4.6) [55], biliary pancreatitis is greatly suspected.

#### Referral and intensive care

A frequent complication of SAP is organ failure, which is a significant prognostic factor. According to the reports since 2000, about half of the deaths due to acute pancreatitis occur early, i.e., within 2 weeks after onset, and a main cause of death is organ failure associated with circulatory failure [21, 22]. In contrast, the main causes of death in those who died in the late stage include infectious complications, especially, infected pancreatic necrosis [56–58]. Thus, in the diagnosis of acute pancreatitis, it is strongly recommended to immediately (within 3 h) judge the severity according to the severity scoring system (Table 2). Furthermore, referral should be made to the institutions having various experiences in the treatment of SAP when the diagnosis of SAP is established (Recommendation A).

Intensive care includes hemodynamic stabilization by vigorous fluid management, respiratory management, nutrition, prevention of infected complications, and, if necessary, CVP and pulmonary arterial monitoring are performed. For cases that show unstable hemodynamics

and have no diuresis in spite of sufficient IV fluid resuscitation, introduction of continuous hemodiafiltration (CHDF) should be considered (Recommendation B). CHDF with a polymethylmethacrylate (PMMA) membrane also may remove various cytokines, and potentially have an advantage in preventing systemic inflammation and organ failure (Recommendation C1) [59].

In SAP, the energy requirement increases. So, when oral nutrition is impossible for a long period, nutritional support should be indicated. In cases with SAP, application of early enteral alimentation with careful attention to ileus or enteric ischemia/necrosis decreases the incidence of infectious complications and helps to shorten hospital stay and reduce medical costs (Recommendation B) [60–63].

If possible, contrast enhanced computed tomography (CECT) should be applied to those with SAP. The findings such as pancreatic swelling, peripancreatic inflammatory changes, fluid collection, pseudocyst, fat necrosis, calcified gallstone, etc. are evaluable by a plain CT. However, diagnosis of pancreatic necrosis and related evaluations are difficult by plain CT, and CECT is necessary [64]. The CECT is useful to identify hypo-enhanced lesions in pancreatic parenchyma suggestive of necrotizing pancreatitis and is also useful to identify pancreatitis-related complications (bleeding in pseudocyst, and portal thrombosis) and the concomitance of pancreatic cancer.

Necrotizing pancreatitis develops in 10 ~ 20% of the patients with acute pancreatitis and the mortality is unfavorable, reaching 15 ~ 20%. The prognosis after complications of organ failure or infections with necrotizing pancreatitis is further worse. Because in the cases with necrotizing pancreatitis pancreatic ischemia and disturbance of the pancreatic microcirculation are observed from the early stage, it is difficult for an intravenously administered drug to reach the pancreatic tissue. Continuous regional arterial infusion (CRAI) of protease inhibitors and/or antibiotics in the early stage of onset potentially decreases the mortality of acute necrotizing pancreatitis and the incidence of infectious complications (Recommendation C1) [65–68].

#### Surgical management

Most of the late death in cases of acute pancreatitis is caused by infectious complications. Particularly, the mortality of infected pancreatic necrosis is high [56–58]. High fever, leukocytosis, marked elevation of CRP, positive blood culture, endotoxemia, intra-abdominal gas in the pancreas and peripancreatic soft tissue on CT scan, etc. are the findings suggestive of infected pancreatic necrosis. Fine needle aspiration (FNA) is useful for diagnosing infectious pancreatic necrosis

**Table 1** The diagnostic criteria of acute pancreatitis of the Japanese Ministry of Health, Labour and Welfare (2008)

1. Presence of acute abdominal pain and tenderness in the epigastric region
2. Elevation of the pancreatic enzymes in the blood or urine
3. Presence of abnormal findings associated with acute pancreatitis in the pancreas on ultrasonography, CT or MRI

The patients who show more than two among the above three conditions and who have no other pancreatic diseases or acute abdominal diseases are diagnosed as having acute pancreatitis. Exacerbating chronic pancreatitis is included in acute pancreatitis

Measurement of the pancreatic enzymes highly specific for the pancreas (pancreatic amylase, lipase, etc.) is advisable

**Table 2** The severity scoring system of acute pancreatitis of the Japanese Ministry of Health, Labour and Welfare (2008)

Prognostic factors (1 point for each factor)	
1. Base Excess $\leq -3$ mEq/L or shock (systolic blood pressure $<80$ mmHg)	
2. PaO <sub>2</sub> $\leq 60$ mmHg (room air) or respiratory failure (respirator management is needed)	
3. BUN $\geq 40$ mg/dL (or Cr $\geq 2$ mg/dL) or oliguria (daily urine output $<400$ mL even after IV fluid resuscitation)	
4. LDH $\geq 2\times$ of upper limit of normal	
5. Platelet count $\leq 100,000/\text{mm}^3$	
6. Serum Ca $\leq 7.5$ mg/dL	
7. CRP $\geq 15$ mg/dL	
8. Number of positive measures in SIRS criteria $\geq 3$	
9. Age $\geq 70$ years old	
CT Grade by CECT	
1. Extrapancreatic progression of inflammation	
Anterior pararenal space	0 point
Root of mesocolon	1 point
Beyond lower pole of kidney	2 points
2. Hypoenhanced lesion of the pancreas. The pancreas is conveniently divided into three segments (head, body and tail)	
Localized in each segment or only surrounding the pancreas	0 point
Covers 2 segments	1 point
Occupies entire 2 segments or more	2 points
1 + 2 = Total scores	
Total score = 0 or 1	Grade 1
Total score = 2	Grade 2
Total score = 3 or more	Grade 3
Assessment of severity	
1. If prognostic factors are scored as 3 points or more, or	
2. If CT Grade is judged as Grade 2 or more, the severity grading is evaluated to be “severe”	
Measures in SIRS diagnostic criteria: (1) Temperature $>38$ or $<36^\circ\text{C}$ , (2) Heart rate $>90$ beats/min, (3) Respiratory rate $>20$ breaths/min or PaCO <sub>2</sub> $<32$ torr, (4) WBC $> 12,000$ cells/mm <sup>3</sup> , $<4,000$ cells/mm <sup>3</sup> , or $>10\%$ immature (band) forms	

(Recommendation A) [2, 69]. For sterile pancreatic necrosis, non-surgical management is the rule (Recommendation B). For infectious pancreatic necrosis, therapeutic interventions including percutaneous, endoscopic, laparoscopic and surgical interventions should be applied (Recommendation B) [7, 13, 70]. In cases of a stable general condition, a follow-up of conservative therapies with antimicrobial agents is applicable (Recommendation C1) [71–73]. Early surgery is not recommended for necrotic pancreatitis due to high mortality (Recommendation D) [74]. The surgery should be performed as late as possible (Recommendation C1) [13, 75]. As for the operative method for infectious pancreatic necrosis, necrosectomy is recommended (Recommendation A) [76].

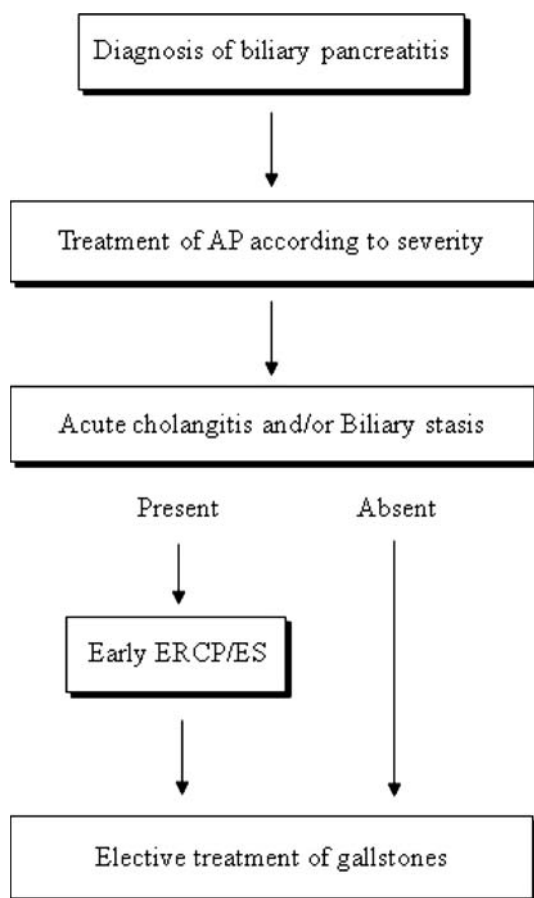
As the treatment of pancreatic abscess, drainage either by percutaneous, endoscopic or surgical means is recommended (Recommendation B) [77, 78]. If no improvements

in clinical findings are observed by percutaneous or endoscopic drainage, surgical drainage is advisable.

In cases with symptoms, complications or enlargement of pancreatic pseudocyst, therapeutic interventions should be performed (Recommendation A) [79, 80]. In cases with pancreatic pseudocyst, any treatment should be selected case by case depending on communication between the cyst and pancreatic duct and positional relationship with the gastrointestinal wall (Recommendation A).

Flowchart for the management of biliary pancreatitis (Fig. 2)

In cases with biliary pancreatitis accompanied by acute cholangitis and/or persistent biliary stasis, early endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES) should be conducted (Recommendation B) [81–83]. When a gallbladder



**Fig. 2** Flowchart for the management of biliary pancreatitis

stone complicates biliary pancreatitis, cholecystectomy should be performed immediately after remission of pancreatitis (Recommendation B) [84–86].

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