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JPN Guidelines for the management of acute pancreatitis: medical management of acute pancreatitis

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Abstract
The basic principles of the initial management of acute pancreatitis are adequate monitoring of vital signs, fluid replacement, correction of any electrolyte imbalance, nutritional support, and the prevention of local and systemic complications. Patients with severe acute pancreatitis should be transferred to a medical facility where adequate monitoring and intensive medical care are available. Strict cardiovascular and respiratory monitoring is mandatory for maintaining the cardiopulmonary system in patients with severe acute pancreatitis. Maximum fluid replacement is needed to stabilize the cardiovascular system. Prophylactic antibiotic administration is recommended to prevent infectious complications in patients with necrotizing pancreatitis. Although the efficacy of the intravenous administration of protease inhibitors is still a matter of controversy, there is a consensus in Japan that a large dose of a synthetic protease inhibitor should be given to patients with severe acute pancreatitis in order to prevent organ failure and other complications. Enteral feeding is superior to parenteral nutrition when it comes to the nutritional support of patients with severe acute pancreatitis. The JPN Guidelines recommend, as optional measures, blood purification therapy and continuous regional arterial infusion of a protease inhibitor and antibiotics, depending on the patient's condition.

Key words Acute pancreatitis · Conservative management · Antibiotics · Nutritional support · Protease inhibitor

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Clinical questions

CQ1. Is adequate fluid replacement crucial in the management of acute pancreatitis?
CQ2. Is pain control by analgesia crucial in acute pancreatitis?
CQ3. Are nasogastric suction and H2 blockers necessary?
CQ4. Is the continuous intravenous application of a large dose of a protease inhibitor useful for severe acute pancreatitis?
CQ5. Is enteral nutrition superior to total parenteral nutrition as nutritional support in severe acute pancreatitis?
CQ6. Is prophylactic antibiotic administration necessary for the prevention of infections in severe acute pancreatitis?
CQ7. Is blood purification therapy useful in severe acute pancreatitis?
CQ8. Does continuous regional arterial infusion of protease inhibitors and antibiotics reduce the mortality rate and incidence of infectious complications in acute necrotizing pancreatitis?

Introduction

In 70% to 80% of patients with acute pancreatitis, the disease is mild and promptly responds to supportive measures alone. The remaining 20%–30% of patients have a severe form of pancreatitis and develop shock, respiratory failure, and infectious complications. Patients with severe acute pancreatitis should be transferred to a medical facility where adequate monitoring and intensive medical care is available.[1]

The basic principles of the initial management of acute pancreatitis are adequate monitoring of vital signs, fluid replacement, correction of any electrolyte imbalance, nutritional support, and the prevention of local and systemic complications. In mild acute pancreatitis, adequate fluid replacement, pain relief, and monitoring of vital signs is enough to ensure recovery from the disease. In severe acute pancreatitis, strict cardiovascular and respiratory monitoring is mandatory for maintaining the cardiopulmonary system. Maximum fluid replacement is needed to stabilize the cardiovascular system, and adjustment of any electrolyte and acid-base imbalance is also required. Oxygen is administered, as needed, to maintain at least 95% oxygen saturation. Prophylactic antibiotic administration is recommended to prevent infectious complications in patients with necrotizing pancreatitis. Although the efficacy of intravenous protease inhibitor administration is still a matter of controversy, there is a consensus in Japan that a large dose of a synthetic protease inhibitor should be given to patients with severe acute pancreatitis in order to prevent organ failure and other complications. Nutritional support is crucial in patients with severe acute pancreatitis. Enteral feeding is superior to parenteral nutrition for the nutritional management of patients with severe acute pancreatitis.

Principles of medical management for acute pancreatitis

Clinical question (CQ) 1. Is adequate fluid replacement crucial in the management of acute pancreatitis?

An adequate volume of intravenous fluid should be promptly administered to correct the volume deficit and maintain basal fluid requirements **(Recommendation A)**

Increased vascular permeability in acute pancreatitis causes the loss of intravenous fluid and reduces plasma volume. In severe cases, in patients with massive ascites, pleural effusion, and retroperitoneal and mesenteric edema, circulating plasma volume decreases markedly. Hypovolemia may lead to shock and acute renal failure, and, because hypovolemic shock may impair the pancreatic microcirculation and promote pancreatic ischemia and necrosis, restoration and maintenance of plasma volume is crucial in severe acute pancreatitis.

An adequate volume of intravenous fluid should be promptly administered to correct the volume deficit and maintain basal fluid requirements. Balanced electrolyte solutions, such as Ringer's lactate, are recommended to stabilize the cardiovascular system. The infusion volume should be decided while monitoring blood pressure, heart rate, hematocrit, and urine output. Calcium and potassium chloride should be replaced if deficiencies arise. Hyperglycemia is managed with insulin as needed. In patients with severe acute pancreatitis, continuous monitoring of central venous pressure or pulmonary wedge pressure, blood gas analysis, and electrolyte measurement is crucial to determining the adequate volume that must be replaced. Oxygen is administered as needed to maintain at least 95% oxygen saturation. Fluid infusion may be complicated by pulmonary edema due to an increase in lung water and is an indication for artificial ventilation.

CQ2. Is pain control by analgesia crucial in acute pancreatitis?

Acute pancreatitis is accompanied by persistent severe abdominal pain. Analgesia is crucial **(Recommendation A)**

The pain associated with acute pancreatitis may cause anxiety in patients and adversely affect their clinical course; this may include respiratory distress, which should be relieved shortly after it develops. The nonnarcotic analgesic buprenorphine has an effect superior to procaine, and, unlike procaine, it does not exacerbate the pathology of acute pancreatitis by including contracting the sphincter of Oddi (Level 1b).[2] Buprenorphine has an analgesic effect similar to that of pethidine (Level 1b).[3]

CQ3. Are nasogastric suction and H2 blockers necessary?

Nasogastric suction through a nasogastric tube is unnecessary in patients with acute pancreatitis unless the disease is associated with paralytic ileus and/or frequent vomiting. H2 blockers are also unnecessary unless a stress ulcer develops **(Recommendation D)**

There are no definitive studies in humans to support the opinion that nasogastric suction is useful to the pancreas at rest in patients with acute pancreatitis. Randomized controlled trials (RCTs) in patients with mild to moderate acute pancreatitis have shown no ameliorating effect of gastric suction on the clinical course by, for example, alleviating pain or shortening the hospital stay.[4–11] Rather, there are some reports claiming that

nasogastric suction may prolong the period of abdominal pain and nausea.[7–10] The placement of a nasogastric tube in patients with acute pancreatitis is unnecessary unless the disease is associated with paralytic ileus and/or frequent vomiting. There are no reports suggesting that cimetidine, an H2 blocker, might ameliorate the clinical course of acute pancreatitis;[10,12–15] however, treatment with an H2 blocker should be considered when a patient with acute pancreatitis develops a stress ulcer or acute gastric mucosal lesion.

CQ4. Is the continuous intravenous application of a large dose of a protease inhibitor useful for severe acute pancreatitis?

Continuous intravenous infusion of a large dose of a protease inhibitor reduces the incidence of complications in the early phase of severe acute pancreatitis **(Recommendation B)**

In the 1960s, the protease inhibitor aprotinin was widely used to treat severe acute pancreatitis, but the drug failed to demonstrate clinical efficacy in three RCTs (Level 1b).[16–18] The efficacy of the synthetic protease inhibitor gabexate mesilate was investigated in five RCTs (Level 1b),[19–23] but a metaanalysis[24] of four of them[19–22] showed no reduction in the frequency of surgical intervention or in the mortality rate, although the incidence of complications was reduced (Level 1a). However, the remaining RCT (Level 1b),[23] the results of which were published in 2000, showed that continuous intravenous administration of gabexate mesilate (2400 mg/day) for 7 days significantly reduced the frequency of complications and the mortality rate. Although the efficacy of protease inhibitors in severe acute pancreatitis is still a matter of controversy, the consensus in Japan, as outlined in the JPN Guidelines, recommends the continuous infusion of an intravenous protease inhibitor in the early phase of severe acute pancreatitis. Nafamostat mesilate (NM), a synthetic serine protease inhibitor, and gabexate mesilate (GM) are widely used in Japan. NM has a longer half-life than GM (55 s for GM vs 23 min for NM) and is used in patients with disseminated intravasucular coagulation (DIC) and during hemodialysis, because of its potent anti-coagulant effect.

CQ5. Is enteral nutrition superior to total parenteral nutrition as nutritional support in severe acute pancreatitis?

Enteral nutrition starting in the early phase of severe acute pancreatitis is superior to total parenteral nutrition unless ileus is present **(Recommendation A)**

There is no evidence from human studies to show that parenteral nutrition is clinically more efficacious in acute pancreatitis than enteral nutrition. Recent clinical trials of nutritional management in acute pancreatitis have shown that enteral nutrition is more useful than total parenteral nutrition in terms of ability to alleviate the inflammatory response and reduce the incidence of infection, frequency of surgery, and medical costs. A metaanalysis (Level 1a)[31] of six RCTs (263 cases; Level 1b)[25–30] — which compared two methods of nutritional management of acute pancreatitis (total parenteral nutrition and enteral nutrition) — showed that enteral nutrition reduced the frequency of infection, surgery, and the length of hospital stay. However, there was no difference in the mortality rate or incidence of complications other than infection.

Enteral nutrition has been provided through feeding tubes inserted from the ligament of Treitz to the distal jejunum, and the infusion of nutrients into the stomach and duodenum has been avoided because of the possibility of stimulating pancreatic exocrine secretion. However, a report from Glasgow (Level 1b),[32] comparing nasogastric to nasojejunal feeding, found no difference in changes in the Acute Physiology and Chronic Health Evaluation (APACHE) II score, C-reactive protein (CRP) level, visual analogue scale (VAS) pain score, doses of analgesic administered, or mortality rates between the two methods. Nasogastric feeding is easier to perform and it is easier to locate the tube than it is to locate a nasojejunal tube. Nasogastric nutrition should be investigated further.

CQ6. Is prophylactic antibiotic administration necessary for the prevention of infection in severe acute pancreatitis?

Prophylactic administration of broad-spectrum antibiotics with good tissue penetration is necessary to prevent infection in severe acute pancreatitis **(Recommendation A)**

Pancreatic and extrapancreatic infections are a determining factor leading to death in severe acute pancreatitis. The mortality rate of patients with infected pancreatic necrosis or sepsis is extremely high, and antibiotic prophylaxis has been recommended to prevent infectious complications in severe acute pancreatitis. Three RCTs of the antibiotic ampicillin conducted in the 1970s showed that it did not reduce the frequency of infectious complications (Level 1b).[33–35] A human study investigating pancreatic tissue penetration by antibiotics demonstrated that broad-spectrum antibiotics such as ciprofloxacin, ofloxacin, imipenem, and pefloxacin provided sufficient tissue concentration in the pancreas.[36] Four RCTs (Level 1b)[37–40] of the prophylactic effect of antibiotics demonstrated that broadspectrum antibiotics with good pancreatic tissue penetration decreased the incidence of infectious complications and

the mortality rate. A metaanalysis of those RCTs showed that prophylactic antibiotic administration significantly improved the mortality rate in patients with severe acute pancreatitis (Level 1a).[41] An RCT comparing pefloxacin with imipenem reported that imipenem significantly lowered the incidence of pancreatic infection (Level 1b).[42] An RCT investigating the usefulness of prophylactic imipenem administration within 48 h after onset showed that the early administration of imipenem decreased the frequency of surgical intervention and the number of organs that failed (Level 1b).[43] A comparison between meropenem and imipenem showed no difference in the occurrence of pancreatic infection, complications, or mortality rates (Level 1b).[44] On the other hand, a placebo-controlled, double-blind trial of ciprofloxacin + metronidazole in patients with predicted severe acute pancreatitis showed that prophylactic administration of these antibiotics did not prevent pancreatic infection (Level 1b).[45]

Selective digestive decontamination (SDD) has also been reported as a means of antibiotic prophylaxis in severe acute pancreatitis (Level 1b).[46] Although SDD was reported in the 1980s as a method of preventing respiratory tract infection in patients with multiple trauma,[47] only one RCT assessed SDD in severe acute pancreatitis.[46] In that trial, antibiotics were given orally, enterally, and intravenously, as well as being applied topically to the gums and tracheotomy site. SDD significantly reduced the frequency of infectious pancreatic complications compared with that in the control groups, and multivariate analysis with severity assessment demonstrated a reduced mortality rate for SDD. In principle, SDD offers comprehensive infection management, not only by the enteral administration of nonabsorptive agents but also by the prevention of systemic infection through sterilization of the oral cavity, as well as by intravenous antibiotic administration and continuous surveillance cultures of the oral cavity and rectum.

Although the prophylactic application of broad-spectrum antibiotics reduces the incidence of infectious complications in severe acute pancreatitis, fungal infection in pancreatic necrosis is increasing.[48–53] The mortality rate of infected pancreatic necrosis complicated by fungal infection is higher than the mortality rate in the absence of fungal infection (Level 2b).[48–53] A human study reported that the antifungal agent fluconazole had good penetration into pancreatic tissue (Level 2b),[54] and clinical studies have demonstrated that the prophylactic administration of fluconazole reduced the incidence of fungal infection in patients with severe acute pancreatitis (Level 2b).[52–55] However, there have been no reliable RCTs of the prophylactic administration of antifungal agents in patients with pancreatic necrosis, and the efficacy of antifungal agents has yet to be investigated in an RCT.

CQ7. Is blood purification therapy useful in severe acute pancreatitis?

***Blood purification therapy may prevent the development of multiple organ failure in severe acute pancreatitis* (Recommendation C)**

The activation of proinflammatory cytokines in severe acute pancreatitis is a predominant factor leading to multiple organ failure. Blood purification therapy, particularly continuous hemodiafiltration (CHDF), should inhibit the systemic inflammatory response by removing humoral mediators. CHDF with a polymethylmethacrylate (PMMA) membrane removes various cytokines from the bloodstream and is widely used in Japan for blood purification therapy in patients with severe acute pancreatitis complicated by multiple organ failure. A national survey of the usefulness of CHDF in severe acute pancreatitis suggested that it may prevent the progress of multiple organ failure,[56] but its ability to reduce the mortality rate is still unknown.

CQ8. Does continuous regional arterial infusion of protease inhibitors and antibiotics reduce the mortality rate and incidence of infectious complications in acute necrotizing pancreatitis?

***Continuous regional arterial infusion of protease inhibitors and antibiotics may possibly reduce the mortality rate and incidence of infectious complications in necrotizing pancreatitis* (Recommendation C)**

The protease inhibitors used to treat acute necrotizing pancreatitis cannot easily reach the pancreas when administered intravenously, and, because of ischemia[57,58] or impaired microcirculation, they hardly penetrate into pancreatic tissue. Administration through a catheter placed in one of the arteries that supply the inflamed area of the pancreas, however, dramatically increases the tissue concentration of the protease inhibitor. A clinical study of continuous regional arterial infusion (CRAI) of a protease inhibitor and/or an antibiotic demonstrated that CRAI of nafamostat mesilate and imipenem/cilastatin was effective in reducing the mortality rate and preventing the development of pancreatic infection in acute necrotizing pancreatitis.[59] A nationwide survey of CRAI therapy in acute necrotizing pancreatitis reported that severe pain disappeared in a short period of time after the initiation of CRAI of a protease inhibitor; that the frequency of infected pancreatic necrosis in the group treated with both a protease inhibitor and antibiotic via CRAI was significantly lower than that in the group treated with the protease inhibitor alone; and that the mortality rate was significantly lower in the group in which CRAI of the protease inhibitor was started within 2 days after onset than that

in the group in which it was started 3 or more days after onset.[60] A historical study, comparing intravenous administration and CRAI of a protease inhibitor and antibiotic, revealed a significantly higher cumulative survival rate in the CRAI group.[61] In a clinical study in which arterial infusion was performed after confirming, by computed tomography (CT) arteriography, that the drug had reached the site of inflammation in the pancreas, the APACHE II score and the CT severity index were improved in all subjects.[62] CRAI of the protease inhibitor nafamostat also prevented pancreatic necrosis in patients with severe acute pancreatitis associated with nonocclusive mesenteric ischemia (NOMI).[63] Although the efficacy of CRAI of a protease inhibitor and the optimal timing is still being debated, CRAI therapy is given Recommendation C in the JPN Guidelines. The usefulness of CRAI of a protease inhibitor should be investigated further.

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