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Fundamental and intensive care of acute pancreatitis

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Abstract Patients who have been diagnosed as having acute pancreatitis should be, on principle, hospitalized. Crucial fundamental management is required soon after a diagnosis of acute pancreatitis has been made and includes monitoring of the conscious state, the respiratory and cardiovascular system, the urinary output, adequate fluid replacement and pain control. Along with such management, etiologic diagnosis and severity assessment should be conducted. Patients with a diagnosis of severe acute pancreatitis should be transferred to a medical facility where intensive respiratory and cardiovascular management as well as interventional treatment, blood purification

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therapy and nutritional support are available. The disease condition in acute pancreatitis changes every moment and even symptoms that are mild at the time of diagnosis may become severe later. Therefore, severity assessment should be conducted repeatedly at least within 48 h following diagnosis. An adequate dose of fluid replacement is essential to stabilize cardiovascular dynamics and the dose should be adjusted while assessing circulatory dynamics constantly. A large dose of fluid replacement is usually required in patients with severe acute pancreatitis. Prophylactic antibiotic administration is recommended to prevent infectious complications in patients with severe acute pancreatitis. Although the efficacy of 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 continuous regional arterial infusion and blood purification therapy.

Keywords Acute pancreatitis · Guidelines · Prophylactic antibiotics · Nutritional support · Protease inhibitor

Introduction

Acute pancreatitis is potentially a fatal disease and its mortality rate is 2.1–7.8%. In 10–20% of patients with acute pancreatitis, the disease becomes severe and the mortality rate associated with acute pancreatitis increases up to 14–25% if the disease is aggravated [1]. The prognosis of acute pancreatitis is determined by two factors including organ failure and pancreatic necrosis.

Patients with a diagnosis of acute pancreatitis should be hospitalized. Initial treatment should be started as soon as possible. Adequate respiratory and cardiovascular monitoring is crucial involving the conscious state, temperature, pulse rate, blood pressure, urinary output, respiratory frequency, and oxygen saturation. Initial treatment and adequate monitoring should be continued while patients are being transferred from the emergency room to a sick ward and from a clinic to a general hospital. Initial treatment includes fasting, adequate dose of fluid replacement and sufficient pain relief. Along with the etiologic diagnosis of acute pancreatitis, severity assessment of acute pancreatitis should be conducted based on the severity scoring system of acute pancreatitis of the Japanese Ministry of Health, Labour, and Welfare (2008). Acute pancreatitis can become severe even if it is mild at the initial visit of a patient, so repeated severity assessment is crucial. Strict respiratory and cardiovascular management is required in patients with a diagnosis of severe acute pancreatitis, so transference to a medical facility should be considered where intensive care, interventional treatment, blood purification therapy and nutritional support are available. Prophylactic antibiotic administration is recommended for severe acute pancreatitis. There is no consensus on the usefulness of protease inhibitors. Enteral nutrition initiated in the early phase of the disease is superior to intravenous hyperalimentation.

Principles of medical management for acute pancreatitis

Clinical Question (CQ) 1. What are the parameters for adequate dose of fluid replacement as the initial treatment of acute pancreatitis?

Initial fluid replacement should be performed to secure, as its target, stable cardiovascular dynamics with an average blood pressure of more than 65 mmHg as their parameters and the urinary output of 0.5–1 ml/kg/h. (Recommendation A)

In acute pancreatitis, increased vascular permeability and decreased colloid osmotic pressure give rise to a leakage of extracellular fluid into the peripancreas, the retroperitoneum as well as into the abdominal and thoracic cavities, which results in a loss of a large volume of the circulating plasma. Acute cardiovascular disorders brought about in this manner are one of the causes of aggravated initial condition of acute pancreatitis. Therefore, it is mandatory to stabilize the cardiovascular dynamics mainly through replacing a sufficient dose of extracellular fluid initiated in the early phase of the disease.

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.

A recent report shows that excessive fluid replacement that has been conducted rapidly and continuously for a long time despite the presence of acute pancreatitis has adverse effects on the prognosis (Level 2b) [2]. When the initial treatment is delivered, repeated assessment of the cardiovascular dynamics should be conducted. Immediately after the start of treatment in particular, the assessment should be conducted every 4–6 h and the transfusion speed should

be adjusted so that an adequate dose of fluid can be achieved.

CQ 2. Is pain control by analgesia necessary?

The pain associated with acute pancreatitis is severe and persistent, so pain control is crucial in the management of acute pancreatitis. (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 of the sphincter of Oddi (Level 1b) [3]. Pentazocine has an analgesic effect superior to that of procaine (Level 1b) [4]. According to an randomized controlled trial (RCT) comparing metamizole and morphine, the analgesic effect was similar for both agents (Level 2b) [5].

CQ 3. Are nasogastric suction and use of H_2 blockers necessary?

Nasogastric suction is not necessary in mild acute pancreatitis except for cases that are accompanied by paralytic ileus and frequent vomiting. H_2 blockers are not required in an acute pancreatitis except for cases accompanying acute gastric mucosal lesion and hemorrhagic ulcer. On the contrary, H_2 blockers may increase the incidence of complications and prolong the duration of pain. (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. 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 (Level 1b) [6–13]. Rather, there are some reports claiming that nasogastric suction may prolong the period of abdominal pain and nausea (Level 1b) [9–12]. 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 H_2 blocker, might ameliorate the clinical course of acute pancreatitis (Level 1b) [12–16]. According to a systematic review (Level 1a) [17], use of cimetidine resulted in a tendency to increase the incidence of complications associated with acute pancreatitis and to prolong the duration of pain. There are no reports of RCTs to date that examined the efficacy of proton pump inhibitors (PPI) in acute pancreatitis.

However, treatment with an H_2 blocker or a PPI should be considered when a patient with acute pancreatitis develops a stress ulcer or acute gastric mucosal lesion.

CQ 4. Is the prophylactic administration of antibiotics in severe acute pancreatitis effective in preventing bacterial infections?

Prophylactic administration of broad-spectrum antibiotics with good tissue penetration in severe acute pancreatitis is effective in reducing the frequency of complications related to infections. (Recommendation B)

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) [18–20]. A human study investigating pancreatic tissue penetration by antibiotics such as ciprofloxacin, ofloxacin, imipenem, and pefloxacine (pefloxacin) provided sufficient tissue concentration in the pancreas [21]. Four RCTs (Level 1b) [22–25] of the prophylactic effect of antibiotics demonstrated that broad-spectrum antibiotics with good pancreatic tissue penetration decreased the incidence of infectious complications and the mortality rate. RCTs investigating the prophylactic effects of imipenem demonstrated that imipenem decreased the occurrence of infectious pancreatic complications (Level 1b) [26, 27]. Two RCTs (Level 1b) [28, 29] that investigated the prophylactic effects of meropenem also showed a decrease in the occurrence of infectious complications and the occurrence of pancreatic infections, complications, or mortality was similar as that of imipenem [28].

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) [30]. According to an RCT that examined the prophylactic effects of meropenem in patients with necrotizing pancreatitis, the incidence and mortality rates of pancreatic infections and the rate of cases that required surgical intervention were not different from those in a placebo-controlled group (Level 1a) [31].

Meta-analyses (Level 1a) [32–37] concerning these RCTs demonstrated a decrease in the mortality rate associated with the prophylactic use of wide-spectrum

antibiotics with good tissue penetration into the pancreatic tissue [32–35] and in the incidence of infectious complications [33, 34]. On the other hand, there are meta-analyses (Level 1a) [36, 37] showing that no decrease was observed both in the mortality rate and the incidence of infectious complications. The reason for such inconsistent results is the difference in diagnostic criteria from institution to institution. RCTs of higher quality should eventually be conducted for further examination.

Selective digestive decontamination (SDD) has also been reported as a means of antibiotic prophylaxis in severe acute pancreatitis (Level 1b) [38]. Although SDD was reported in the 1980s as a method of preventing respiratory tract infection in patients with multiple trauma [39], only one RCT assessed SDD in severe acute pancreatitis (Level 1b) [38]. 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 (Level 2b) [40–45]. 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) [40–45]. A human study reported that the antifungal agent fluconazole had good penetration into pancreatic tissue (Level 2b) [46], 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) [44–47]. 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.

CQ 5. Is the continuous infusion of a large dose of protease inhibitors effective in severe acute pancreatitis?

Continuous intravenous infusion of a large dose of protease inhibitors may reduce the mortality rate of severe acute pancreatitis and the frequency of complications in the early phase of severe acute pancreatitis. (Recommendation C1)

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) [48–50]. The efficacy of the synthetic protease inhibitor gabexate mesilate was investigated in five RCTs (Level 1b) [51–55], but a meta-analysis of four of them [51–54] showed no reduction in the frequency of surgical intervention or in the mortality rate, although the incidence of complications was reduced (Level 1a) [56]. However, the remaining RCT (Level 1b) [55], 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. According to a meta-analysis (Level 1a) [57] of ten RCTs (6 trials of gabexate mesilate [51–53, 55, 58, 59] and 4 trials of aprotinin [49, 50, 60, 61]) reported in 2004, use of protease inhibitors did not lead to a decreased mortality rate in patients with acute pancreatitis. On the other hand, a meta-analysis concerning the data sampled from patients with moderate ~ severe acute pancreatitis showed that the mortality rate decreased significantly owing to the infusion of protease inhibitors.

Since the efficacy of protease inhibitors in severe acute pancreatitis is still a matter of controversy, their use was classified into recommendation grade "B" in the JPN GL 2007 but it was changed to "C1" in the present edition.

CQ 6. Is enteral nutrition initiated in the early phase of severe acute pancreatitis more useful than intravenous hyperalimentation?

If there is no ileus, enteral nutrition initiated in the early phase of severe acute pancreatitis is superior to intravenous hyperalimentation. (Recommendation B)

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 meta-analysis (Level 1a) [62] of six RCTs (263 cases; Level 1b) [63–68]—which compared two methods of nutritional management of acute pancreatitis (total parental nutritional 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.

According to an RCT concerning severe pancreatitis (Level 1b) [65], medical costs per capita in patients who underwent enteral nutrition were one-third of those in

patients who underwent intravenous nutrition. A recent RCT has found that the mortality rate of infected pancreatic necrosis and the incidence and mortality rates of multiple organ failure decreased in patients who underwent enteral nutrition compared in those who underwent intravenous nutrition (Level 1b) [69].

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) [70], comparing nasogastric to nasojejunal feeding, found no difference in changes in the Acute Physiology and Chronic Health Evaluation (APACHE) II sore, C-reactive protein (CRP) level, visual analogue scale (VAS) pain score, doses of analgesic administered, or mortality rates between the two methods. A recent systematic review has shown that, in terms of safety, nasogastric feeding yielded results as good as did nasojejunal feeding in acute pancreatitis. Further accumulation of cases was considered necessary (Level 1a) [71]. 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.

An RCT [72] comparing a group of patients with acute pancreatitis in whom lactic acid bacteria was administered in addition to enteral nutrition and a group in which lactobacillus inactivated by heating was administered showed that the incidence of pancreatic infections was decreased by the addition of lactic acid bacteria (Level 2b). According to reports (Level 1b) [73–76] and a meta-analysis (Level 1a) [77] that examined the survival rate and incidence of the use of glutamine, arginine, omega-3 fatty acid and probiotics besides lactic acid bacteria in addition to enteral nutrition, no improvement was observed in the survival rate compared with a control group and no consistent results were obtained in the incidence of infectious diseases. Furthermore, an RCT (Level 1b) [78] examining the effects of administering probiotic agents enterally in patients with predicted severe acute pancreatitis reported that probiotic administration resulted, not in a decrease in the incidence of infections, but rather an increase in the mortality rate. As yet, there is no conclusion about the merits and demerits of using these agents. Further discussion is needed from now on.

CQ 7. Is regional intra-arterial infusion of protease inhibitors and antibiotics able to reduce the mortality rate and frequency of infectious pancreatic complications?

Intra-arterial local infusion of protease inhibitors and antibiotics in the early phase of the disease may lead to a decrease in the mortality rate of acute necrotizing pancreatitis and in the frequency of infectious pancreatic complications. (Recommendation C1)

The protease inhibitors used to treat acute necrotizing pancreatitis cannot easily reach the pancreas when administered intravenously and, because of ischemia [79, 80] 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 (Level 3b) [81]. 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 three or more days after onset (Level 2c) [82]. A multi-center trial conducted recently in Japan using gabexate mesilate and antibiotics compared a group in which CRAI was performed with a group in which CRAI was not performed. The trial found that the duration of abdominal pain and systemic inflammatory response syndrome (SIRS) and the length of hospital stay were shortened. Also, CRP, interleukin 6 (IL6)/interleukin 10 (IL 10) ratio was found to be improved in a shorter time (Level 3b) [83].

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 (Level 4) [84]. 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 (Level 4) [85]. CRAI of the protease inhibitor nafamostat also prevented pancreatic necrosis in patients with severe acute pancreatitis associated with nonocclusive mesenteric ischemia (NOMI) (Level 4) [86]. 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.

CQ 8. Is blood purification therapy useful in severe acute pancreatitis?

Continuous blood purification therapy performed in the early phase of severe acute pancreatitis is likely to prevent progression to multiple organ failure. (Recommendation C1)

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), may inhibit the systemic inflammatory response by removing the humoral mediators. CHDF with a polymethylmethacrylate (PMMA) membrane may remove 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 (Level 4) [87]. It is also reported that CHDF using PMMA is useful in treating intra-abdominal hypertension (IHA) and abdominal compartment syndrome (ACS) (Level 4) [88].

However, its ability to reduce the mortality rate is still unknown.

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