



Revised Clinical Practice Guidelines of the Korean Pancreatobiliary Association for Acute Pancreatitis

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Acute pancreatitis can range from a mild, self-limiting disease requiring no more than supportive care, to severe disease with life-threatening complications. With the goal of providing a recommendation framework for clinicians to manage acute pancreatitis, and to contribute to improvements in national health care, the Korean Pancreatobiliary Association (KPBA) established the Korean guidelines for acute pancreatitis management in 2013. However, many challenging issues exist which often lead to differences in clinical practices. In addition, with newly obtained evidence regarding acute pancreatitis, there have been great changes in recent knowledge and information regarding this disorder. Therefore, the KPBA committee underwent an extensive revision of the guidelines. The revised guidelines were developed using the Delphi method, and the main topics of the guidelines include the following: diagnosis, severity assessment, initial treatment, nutritional support, convalescent treatment, and the treatment of local complications and necrotizing pancreatitis. Specific recommendations are presented, along with the evidence levels and recommendation grades. (*Gut Liver*, Published online August 17, 2022)

Key Words: Acute pancreatitis; Management; Guideline; Evidence-based medicine

INTRODUCTION

The clinical manifestations of acute pancreatitis vary from mild to severe. Most cases are mild and improve within 3 to 5 days. However, despite easy access to treatment and technological advances in imaging and interventions, severe acute pancreatitis still shows serious morbidity and mortality. Recently, various therapies for

clinical features and complications have been attempted, and treatment strategies based on clinical reports have been proposed. However, the majority of acute pancreatitis treatments are still based on the experience and judgment of individual doctors, resulting in different treatment methods. To reduce such deviations and suggest appropriate treatment based on evidence, the Korean Pancreatobiliary Association (KPBA) developed the Clinical Practice

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Guidelines for Acute Pancreatitis in 2013. The guidelines were based on sufficient medical experience in Korea, and also foreign guidelines such as those in North America, Europe, and Japan were referenced.¹⁻⁵ A number of new studies has been reported since the 2013 guidelines, and with accumulated knowledge and information, various evidence-based diagnosis and treatment methods have been proposed. Therefore, it was necessary to update the guidelines with the latest knowledge and revise them to accommodate the current medical situation in Korea. Accordingly, in September 2020, KPBA decided to produce a revised version of the guidelines for acute pancreatitis under the leadership of the Pancreas Study Group of KPBA (PSG). This paper introduces the purpose of revision, the target group and users, the revision process and content, and the evidence levels and recommendation grades of the guidelines.

METHODS

1. Purpose of revision

In 2013, the KPBA published treatment guidelines for acute pancreatitis including severity assessment, initial treatment, and management of necrotizing pancreatitis and local complications.¹ The PSG initiated guideline revisions to derive new recommendations by reflecting the results of domestic and international studies published since 2013. The final purpose of the revised clinical practice guidelines for acute pancreatitis was to establish comprehensive and practical guidelines suitable for medical situations in Korea. It should be understood that these guidelines do not constrain the discretion of the clinician, but rather provide general information for the diagnosis and treatment of acute pancreatitis. The treatment of patients with acute pancreatitis should be decided after the clinician comprehensively considers each patient's situation and hospital facilities, and following sufficient consultation with the patient or guardian. Therefore, it is inappropriate for the guidelines to be used as a standard for evaluating the adequacy of medical expenses, as a legal judgment, or as an absolute standard in medical disputes. In the future, additional studies regarding the pathophysiology, diagnosis, severity assessment, and treatment of acute pancreatitis should be conducted along with changes in clinical evidence. In addition, the revised guidelines were developed without external financial support, and all of the members who participated in forming the guidelines did not have any conflicts of interest.

2. Subjects and users of the clinical treatment guidelines

Patients diagnosed with acute pancreatitis are the main target population of the guidelines. Disorders range from mild acute pancreatitis to severe acute pancreatitis with a systemic inflammatory response, as well as local complications, i.e., peripancreatic fluid collection, pancreatic necrosis, pancreatic pseudocyst, and pancreatic abscess. The guidelines are intended to present helpful recommendations for all medical staff practicing in various medical fields at primary, secondary, and tertiary medical institutions. The guidelines can also be used as educational materials for training. Ultimately, the guidelines are intended to improve the life quality of patients and public health through enhanced medical diagnosis and treatment of acute pancreatitis in Korea.

3. Revision process and content

In May 2020, in response to the demands of KPBA members regarding the need to modify the guidelines for acute pancreatitis in Korea, a strategy to revise the guidelines was established, under the leadership of the KPBA president and executives. The latest important literature related to acute pancreatitis was collected, analyzed, and reviewed. Through several meetings, a revision to the guidelines for the diagnosis of acute pancreatitis, its severity assessment, initial treatment, and treatment for necrotizing pancreatitis and local complications was planned. The PSG completed the first questionnaire by selecting key questions and phrases for clinical practice guidelines and categorizing the evidence levels and recommendation grades. For the first questionnaire, e-mail voting was conducted for a group of experts based on the Delphi method. The expert group included former and current executives and members of the KPBA, and a group of 30 experts was constituted with a consideration of regional distribution. Each recommendation in the questionnaire was evaluated on a five-point Likert scale (completely agree, mostly agree, partially agree, mostly disagree, and completely disagree). If the number of experts who answered "completely agree" and/or "mostly agree" in the questionnaire item exceeded 75% of the total respondents, it was selected as an appropriate clinical practice guideline phrase. As a result of the first survey, the opinions of 28 from a total of 30 experts were reflected in the revision of the clinical practice guidelines. Two experts were excluded as one did not respond and another responded incompletely. Sufficient consensus was not reached for two recommendations, and thus the PSG appropriately revised the phrase and prepared a second survey. In the second survey, one recommendation was agreed upon and selected as an appropriate guideline

phrase. However, the remaining recommendation was not agreed upon until the third survey, and thus it was excluded from the revised clinical practice guidelines.

The revised guidelines provide a total of 24 recommendations and their rationales. The 24 guidelines consist of four guidelines for the diagnosis of acute pancreatitis; five guidelines for severity assessment; nine guidelines for the initial treatment of pancreatitis, nutritional support, and convalescent treatment; and six guidelines for the treatment of local complications and necrotizing pancreatitis. Regarding surgery, advice was requested from external advisors from the Korean Surgical Society. In addition, the National Evidence-based Healthcare Collaborating Agency provided counsel on the method to developing consensus guidelines and expert consensus.

4. Levels of evidence and recommendation grades

The levels of evidence and recommendation grades were determined according to the definitions in the GRADE system, but were modified to suit the consensus recommendations of the guidelines.⁶ Evidence levels were classified as A, B, or C according to the possibility of changes in results or conclusions based on relevant evidence in follow-up studies. In level A, the predicted outcome was unlikely to change with future research. Level B indicated future research may have an important influence on the outcome prediction and also the prediction may change. Level C signified future research to have a significant impact on the confidence of the prediction, with results that were likely to change. Recommendation grades were classified into strong recommendation (1) and weak recommendation (2) grades, considering not only the level of evidence for the study itself, but also the quality of the study results, clinical ripple effect, and socioeconomic aspects such as cost and convenience.

RECOMMENDATIONS

1. Diagnosis of acute pancreatitis

Recommendation 1

(1) Acute abdominal pain in the upper abdomen or the epigastrium. (2) Elevated levels of pancreatic enzymes (serum amylase and/or lipase) ≥ 3 times the upper limit of normal. (3) Abnormal findings of acute pancreatitis detected by abdominal images such as ultrasonography (USG), computed tomography (CT) or magnetic resonance imaging (MRI). Patients who present with at least two of the above three manifestations, and with other pancreatic diseases and acute abdomen

ruled out are diagnosed with acute pancreatitis.

· Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (67.9%), mostly agree (32.1%), partially agree (0%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Acute pancreatitis is typically suspected based on compatible clinical conditions including abdominal pain, nausea, and vomiting. Radiating back pain is experienced in 40% to 70% of patients. Pain usually reaches its peak within 30 to 60 minutes and persists for days or weeks.⁷⁻⁹

Acute pancreatitis should be suspected when serum amylase and/or lipase levels are elevated. The pancreas is responsible for about 40% of total serum amylase, with the rest originating primarily in the salivary glands. The diagnosis can be made when levels are elevated up to at least three times the upper limit of normal as the most accurate cutoff.⁸ In one prospective analysis of 500 patients presenting to an emergency department with acute abdominal pain, the sensitivity of serum amylase estimation was 85%, with a specificity of 91%.¹⁰

The diagnosis of acute pancreatitis is best corroborated by imaging tests, particularly CT.¹¹ USG is not accurate at identifying gland necrosis or assessing the severity of peripancreatic inflammation and fluid.¹² MRI with gadolinium enhancement is as accurate as CT in imaging the pancreas and staging the severity of acute pancreatitis, including documenting the degree of pancreatic necrosis.¹³⁻¹⁵

Recommendation 2

Abdominal CT is quite useful for excluding conditions that masquerade as acute pancreatitis, identifying local complications of pancreatitis, defining the severity of acute pancreatitis, and predicting the final outcome of pancreatitis.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (55.6%), mostly agree (44.4%), partially agree (0%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Although a number of conditions may be similar to the clinical features of acute pancreatitis and even be associated with elevations in amylase and/or lipase levels, the combination of clinical features, laboratory tests, and imaging studies should allow the diagnosis to be reliably made within 48 hours of admission. The early use of CT can exclude acute appendicitis, ischemia, perforation, pseudo-obstruction, ureter stone, intestinal obstruction and etc.

CT findings of acute pancreatitis can range from isolated diffuse or focal enlargement of the gland to peripancreatic stranding and peripancreatic fluid collections and,

at its most severe form, pancreatic gland necrosis.^{11,16}

Pancreatic necrosis has long been recognized as a poor prognostic factor in acute pancreatitis and is included in the Atlanta criteria of severity. Balthazar^{11,17} produced a scoring system for acute pancreatitis based on the presence or absence of necrosis. The extent of necrosis is an important factor in the CT severity index. Patients with a CT severity index >5 were eight times more likely to die, 17 times more likely to have a prolonged hospital course, and 10 times more likely to undergo necrosectomy than their counterparts with CT scores <5.¹⁸

Recommendation 3

Abdominal MRI should be considered when the etiology of acute pancreatitis is not clear in discerning anatomical variant, tumor or stone.

· Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (21.4%), mostly agree (71.4%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Malignancy should be considered as a potential etiology of unexplained acute pancreatitis, especially when patients are older than 40 years and/or have worrisome associated features such as weight loss, new-onset diabetes mellitus.¹⁵ In such a patient, a CT with pancreas protocol or MRI with magnetic resonance cholangiopancreatography should be considered. Alternatively, endoscopic ultrasonography (EUS) could be used in this situation to screen not only for malignancy but also for ampullary masses, pancreatic ductal dilatation, signs of underlying chronic pancreatitis, and microlithiasis.^{13,15,19,20} EUS is particularly well-suited for such a situation. If EUS is not available, MRI and magnetic resonance cholangiopancreatography are preferred to endoscopic retrograde cholangiopancreatography (ERCP).

Recommendation 4

After the diagnosis of acute pancreatitis, its etiology should be discerned as soon as possible. It should be assessed by clinical history, laboratory tests such as serum liver function tests, measurement of serum calcium and serum triglycerides and abdominal images.

· Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (55.6%), mostly agree (37.0%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Accurate determination of an etiology allows the clinician to choose the most appropriate therapy for an individual patient. A detailed clinical history, simple laboratory tests, and imaging studies such as abdominal USG will

contribute in finding the likely cause of acute pancreatitis. At first, the majority of patients will be identified with the two most common causes of acute pancreatitis: gallstones and alcohol. Clinical history may also reveal a history of hyperlipidemia, drug exposure, iatrogenic events (e.g., emboli after cardiac catheterization, post-ERCP pancreatitis), or associated autoimmune disorders (e.g., sicca syndrome) that may provide important clues to etiology.⁸ Laboratory testing should include liver chemistries and serum calcium and triglyceride levels. In patients with a suspicion of autoimmune pancreatitis, levels of antinuclear antibody and serum IgG4 should also be obtained.

The abdominal USG could identify gallstones or dilation of the common bile duct due to choledocholithiasis. The sensitivity of USG to detect gallstones in patients with acute biliary pancreatitis is about 70%.¹²

2. Severity assessment of acute pancreatitis

Recommendation 5

The severity of acute pancreatitis is classified into mild, moderately severe, and severe. If a patient develops persistent organ failure (>48 hours), he or she should be classified as a patient with severe acute pancreatitis.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (53.6%), mostly agree (42.9%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), not sure (0%)

The 2012 revised Atlanta classification is widely accepted for the severity classification of acute pancreatitis.²¹ The severity of acute pancreatitis is classified into mild, moderately severe, and severe.^{22,23} Mild acute pancreatitis shows no organ failure, local or systemic complications. Organ failure is usually defined as a score of two or more for one of three organ systems (respiratory, cardiovascular, and renal systems) using the modified Marshall scoring system.²⁴ Moderately severe acute pancreatitis is defined by the presence of transient (\leq 48 hours) organ failure, local complications or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent (>48 hours) organ failure.^{25,26} In 15% to 20% of patients with acute pancreatitis may progress to severe pancreatitis or develop complications.^{7,27-29} The mortality rates of mild and severe acute pancreatitis are less than 5%³⁰ and 36% to 50%,^{25,26,31} respectively. Therefore, evaluating the severity of patients with acute pancreatitis in the initial stage is important in predicting such prognosis and determining treatment policies such as admission to the intensive care unit or transfer to a tertiary hospital.^{21,29,32}

Table 1. Evidence Levels and Recommendation Grades

Evidence levels	A	Further research is unlikely to change our confidence in the estimate of the effect.
	B	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
	C	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
Recommendation grades	Strong	The recommendation can apply to most patients in most circumstances. The desired effect is greater than the harmful effect.
	Weak	The best action may differ depending on circumstances or patient or society values. Other alternatives may be equally reasonable. The desired effect may be slightly larger than the harmful effect.

Recommendation 6

The evaluation of the severity of acute pancreatitis using imaging modalities is necessary to predict the prognosis and determine the initial treatment policy. After the diagnosis of acute pancreatitis, repeated evaluations using imaging modalities should be considered.

- Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (35.7%), mostly agree (46.4%), partially agree (17.9%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Contrast-enhanced CT (CECT) is required to diagnose acute pancreatitis as well as evaluate pancreatic ischemia, necrosis, extent of lesions, and local complications.³³ Pancreatic ischemia and parenchymal necrosis progress over several days, and CECT at diagnosis may not reflect the actual extent of pancreatic necrosis.³⁴⁻³⁷ Therefore, the actual extent of pancreatic necrosis and occurrence of local complications can be more accurately evaluated by additional CECT performed 5 to 7 days after diagnosis.^{21,33,38,39} CT severity index has been used to evaluate the severity of acute pancreatitis using CECT images (Table 1).³⁷ MRI is known to be advantageous in evaluating pancreatic necrosis and inflammatory changes to a degree similar to CECT, and has an advantage in evaluating the pancreatic duct and presence of gallstones.^{13,40}

Recommendation 7

In the initial evaluation of patients with acute pancreatitis, hemodynamic status and accompanying organ failure must be confirmed, and objective laboratory tests such as C-reactive protein, hematocrit, procalcitonin, blood urea nitrogen, and creatinine should be considered.

- Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (53.6%), mostly agree (42.9%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), not sure (0%)

The initial evaluation of acute pancreatitis is necessary to evaluate the need for admission to the intensive care

unit, transfer to a tertiary center, and interventions to treat necrotizing pancreatitis. A patient's vital signs, organ failure, hematological tests, and various indicators are used as tools for initial evaluation. The mortality rate is high when accompanied by unstable hemodynamic signs and organ failure.^{26,41,42}

Various studies suggest laboratory tests that can predict the severity of acute pancreatitis even with a single test. C-reactive protein elevation is known to peak at about 48 to 72 hours after the onset of acute pancreatitis and is considered a reliable factor suggesting exacerbation of acute pancreatitis.^{43,44} According to a systematic literature review study including 17 prospective studies, procalcitonin predicted progression to severe acute pancreatitis with a sensitivity of 72% and a specificity of 86%, and predicted infectious pancreatic necrosis with a sensitivity of 80% and specificity of 91%.⁴⁵ Hematocrit, blood urea nitrogen, and creatinine have been reported to be associated with the prognosis of acute pancreatitis in several studies.⁴⁶⁻⁵⁰ In addition, various other blood markers have been suggested as an initial evaluation index for acute pancreatitis, although further research is required.

Recommendation 8

For the severity assessment of patients with acute pancreatitis, consider evaluations using various severity criteria such as bedside index for severity in acute pancreatitis (BISAP), systemic inflammatory response syndrome (SIRS), and Acute Physiology and Chronic Health Evaluation II (APACHE II) index.

- Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (28.6%), mostly agree (50.0%), partially agree (21.4%), mostly disagree (0%), completely disagree (0%), not sure (0%)

In order to evaluate the severity of acute pancreatitis, starting with the Ranson index published in 1974, various indexes such as the APACHE II, the Glasgow, and the BISAP index have been used. The usefulness of each indicator has been proven through research, however, the superiority and inferiority of each indicator has yet to be

determined.^{51,52} Each indicator needs to be judged and applied by the clinician according to the ease and accuracy of the indicator in each clinical situation.

APACHE II is not an indicator for a specific disease, but has been used to assess patients in the intensive care unit. High APACHE II scores of patients with acute pancreatitis at admission and 72 hours after admission are known to be associated with higher mortality (<4%, APACHE II <8; 11% to 18%, APACHE II >8).^{51,53}

BISAP scores one point each for five items: blood urea nitrogen >25 mg/dL, impaired mental status, SIRS, age >60 years, and pleural effusion during 24 hours of hospitalization.⁵⁴ According to previous reports, the mortality rate of acute pancreatitis patients increases in proportion to BISAP scores. It is also considered as a simple and useful test with similar accuracy to the APACHE II index and CT severity index.^{52,55}

SIRS indicates a serious condition with inflammation throughout the whole body. SIRS criteria were defined as tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38°C or <36°C), and leukocytosis, leukopenia, or bandemia (white blood cells >12,000/mm³, <4,000/mm³ or bandemia ≥10%).⁵⁶ SIRS lasting more than 48 hours is associated with multi-organ failure and is known to be a predictor of mortality in acute pancreatitis.⁵⁷ The SIRS index does not lack predictive rates for severe pancreatitis and death compared to other indexes, and the evaluation items are relatively simple and easy.³³

Recommendation 9

Patients evaluated for severe acute pancreatitis should be transferred to a hospital that has an intensive care unit and is capable of endoscopic intervention, radiologic intervention, and surgical treatment.

- Recommendation grade: strong, Evidence level: C, Expert opinion: completely agree (50.0%), mostly agree (35.7%), partially agree (14.3%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Several studies have reported that the prognosis of patients with acute pancreatitis becomes better as the size of the hospital increases.⁵⁸⁻⁶¹ It has been reported that even small institutions can improve the treatment outcome of severe acute pancreatitis through a multidisciplinary approach, and some studies have shown that there is no relationship between hospital size and patient survival benefit.⁶²⁻⁶⁴ However, even a study that reported no survival benefit confirmed that the hospital stay was shortened in a large hospital, and a study on severe acute pancreatitis reported better treatment outcomes in large hospitals.^{59,64} In

the case of gallstone pancreatitis, the need for endoscopic/radiologic intervention, and surgical treatment is high, and thus, such a patient should be considered for transfer to a tertiary hospital.⁶⁵

3. Initial treatment, nutritional support, and convalescent treatment

Recommendation 10

Goal-directed therapy is recommended for initial fluid resuscitation in acute pancreatitis.

- Recommendation grade: weak, Evidence level: C, Expert opinion: completely agree (21.4%), mostly agree (67.9%), partially agree (10.7%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Among a number of studies on the initial infusion volume of fluids, a randomized controlled trial (RCT) comparing the prognosis by the amount of fluids administered for 24 hours reported that excessive fluid supply exceeding 4.1 L increased persistent organ failure.⁶⁶ In addition, there was another report that rapid and excessive fluid supply, which diminishes hematocrit levels to less than 35% within 48 hours, increases sepsis and mortality in patients with severe acute pancreatitis.⁶⁷ Therefore, for the treatment of acute pancreatitis, determining the proper initial infusion rate and volume of fluids is very important, and goal-directed therapy through appropriate monitoring may be preferred. Goal-directed therapy is generally defined as the titration of intravenous fluids to specific clinical and biochemical targets of perfusion including mean arterial pressure, central venous pressure, heart rate, urine output, blood urea nitrogen concentration, and hematocrit. According to an RCT conducted on patients with severe acute pancreatitis, the goal-directed therapy group, which is set to reduce the infusion rate when the initial goal is reached, exhibited better results such as reduced multiple organ failure and mortality in terms of clinical outcome.⁶⁸ However, a technical review of seven RCTs regarding goal-directed therapy in acute pancreatitis showed that there was no significant difference in clinical outcomes including infected pancreatic necrosis, multiple organ failure, and mortality.⁶⁹ Therefore, additional large-scale RCTs should be performed in the future owing to the low quality of evidence about the clear effectiveness of the therapy.

Recommendation 11

Pain control associated with acute pancreatitis should be actively considered during initial treatment.

- Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (64.3%), mostly

agree (32.1%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Acute pancreatitis-associated pain is extremely severe and persistent, and as a result, it can cause anxiety and exert a negative influence on the clinical progress. Accordingly, it is crucial to use appropriate analgesics to lessen abdominal pain in the initial treatment for acute pancreatitis. Up to date, it is believed that the use of analgesics, including narcotics, does not interfere with the diagnosis and treatment of acute pancreatitis.⁷⁰ However, exact evidence as to which analgesic is most useful for pain relief in acute pancreatitis is yet to be discovered.⁷¹⁻⁷³ Therefore, additional large-scale RCTs should be carried out in the future. The frequency or amount of analgesic administration should be monitored by experienced physicians and, if necessary, the level of oxygen saturation should be monitored in bed. In addition, if the patient has severe abdominal pain, patient-controlled analgesia may be conducted.

Recommendation 12

The routine use of prophylactic antibiotics is not recommended in acute pancreatitis.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (21.4%), mostly agree (64.3%), partially agree (14.3%), mostly disagree (0%), completely disagree (0%), not sure (0%)

The Japanese guideline recommends the use of prophylactic antibiotics within 72 hours of onset of severe acute pancreatitis and necrotizing pancreatitis based on the result that mortality and infectious pancreatic complication rates were significantly reduced in a meta-analysis of 6 RCTs on patients with severe acute pancreatitis or necrotizing pancreatitis within 48 and 72 hours of onset.⁷⁴ However, three RCTs reported that the use of prophylactic antibiotics to prevent pancreatic infection in patients with severe acute pancreatitis or acute necrotizing pancreatitis without clinical evidence of infection did not reduce mortality or morbidity.⁷⁵⁻⁷⁷ Also, other studies reported that the use of prophylactic broad-spectrum antibiotics may increase the risk of multidrug-resistant or fungal infections.^{78,79} In addition, a technical review of 10 RCTs conducted on patients with severe acute pancreatitis or acute necrotizing pancreatitis showed that the use of prophylactic antibiotics does not significantly reduce mortality and infected pancreatic necrosis in a subgroup analysis that includes only recent RCTs reported after 2002 or higher-quality trials.⁸⁰ Consequently, these studies indicate that the evidence is still insufficient concerning the use of prophylactic antibiotics for the purpose of reducing infection-related complica-

tions and mortality in acute pancreatitis, including severe or necrotizing pancreatitis. Therefore, additional large-scale RCTs regarding this issue should be conducted in the future.

Recommendation 13

Early ERCP should be performed in acute gallstone pancreatitis with cholangitis or persistent biliary obstruction.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (60.8%), mostly agree (32.1%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

An RCT reported that biliary obstructions lasting more than 48 hours significantly increased complications in patients with acute gallstone pancreatitis. Based on this finding, early ERCP should be performed in acute gallstone pancreatitis accompanied with persistent biliary obstruction.⁸¹ Similarly, a meta-analysis of seven RCTs comparing the early ERCP group and the conservative treatment group in patients with acute gallstone pancreatitis reported that the complications and mortality of the early ERCP group were significantly lower than those of the conservative treatment group in a subgroup analysis of the patients accompanied with cholangitis or biliary obstruction.⁸² In addition, a recent multicenter RCT reported that no difference in major complications and mortality was found when comparing the early ERCP with sphincterotomy group and the conservative treatment group in patients with severe acute gallstone pancreatitis without concomitant cholangitis.⁸³ Therefore, such results suggest that early ERCP is useful when cholangitis is accompanied or persistent biliary obstruction is suspected in patients with acute gallstone pancreatitis.

Recommendation 14

In patients with acute pancreatitis, early oral feeding should be considered, if possible.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (35.7%), mostly agree (53.6%), partially agree (10.7%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Traditionally, “nil per os (NPO) and bowel rest” was believed to be the gold standard to reduce pancreatic stimulation in patients with acute pancreatitis. However, recent evidence including randomized controlled studies suggests the complete opposite of this traditionally accepted belief. Early refeeding reduced the incidence of acute pancreatitis related complications such as infection, comorbidity and

mortality.⁸⁴⁻⁸⁷ Gut-mucosal barrier is considered the possible mechanism for such results.⁸⁸ A systematic review of 11 RCTs addressing the role of early enteral refeeding demonstrated early enteral refeeding within 48 hours of admission reduced the incidence of organ failure, infection, and mortality.⁸⁹ However, an RCT which compared refeeding within 24 hours of admission versus refeeding after 72 hours of admission demonstrated no difference in terms of infection and mortality.⁹⁰ High levels of evidence support early refeeding may help reduce the risk of infection and mortality by protecting the gut-mucosal barrier and reducing bacterial translocation. However, there is still a lack of evidence regarding when clinically significant damage to the gut-mucosal barrier occurs during NPO period. Therefore, recommendations for the specific time of refeeding in acute pancreatitis patients, such as within 24 hours or 48 hours were discouraged in this guideline.

Recommendation 15

Enteral tube feeding should be considered in patients with acute pancreatitis who cannot tolerate oral feeding.

· Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (25.0%), mostly agree (53.6%), partially agree (14.3%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Although early refeeding should be considered as possible to protect the gut-mucosal barrier, for patients who cannot tolerate oral feeding, enteral tube feeding can be considered if there are no contraindications such as ileus, abdominal compartment syndrome, etc.⁸⁴⁻⁸⁷ Traditionally, nasojejunal (NJ) tube beyond the ligament of Treitz was the preferred route for enteral feeding to reduce pancreatic stimulation. However, several recent RCTs showed that both nasogastric (NG) tube feeding and NJ tube feeding were comparable in terms of safety and mortality.⁹¹⁻⁹⁴ Placing an NG tube is safe and technically easier than an NJ tube with comparable safety, and thus, both routes for enteral feeding can be chosen based on the clinical status of a patient.^{28,74,80,95} Parenteral nutrition can be considered in patients who cannot tolerate enteral nutrition or in cases where sufficient daily caloric intake is not possible by enteral or oral feeding.

Recommendation 16

Any form of low-fat diet is recommended as long as it is tolerated by the patient.

· Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (28.6%), mostly agree (53.6%), partially agree (17.8%), mostly disagree (0%), completely disagree (0%), not sure (0%)

In a number of RCTs comparing different types of initial oral diets such as liquid diet, soft diet, and solid diet with low-fat composition in patients with acute pancreatitis, there was no difference in terms of safety. Rather, soft or solid diet was equally tolerated and could provide a higher daily caloric intake compared with liquid diets.⁹⁶⁻⁹⁹ In an RCT of 101 patients with mild acute pancreatitis comparing soft diet and liquid diet, even shorter hospital stay was observed in the soft diet group.⁹⁹ However, there is not enough concrete evidence that suggests a specific type of initial oral diet affects the safety and/or prognosis of acute pancreatitis. Thus, any form of diet can be chosen as an initial meal as tolerated. Although there is limited data for the ideal composition of a restarting diet, low-fat (<30% of total energy), high protein and carbohydrate diet can be recommended as an initial meal.^{96,97,99,100}

Recommendation 17

It is recommended to perform cholecystectomy within the same hospitalization period for mild acute biliary pancreatitis, and delayed cholecystectomy for severe acute pancreatitis after the inflammatory reaction has been sufficiently resolved.

· Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (28.6%), mostly agree (53.6%), partially agree (10.7%), mostly disagree (7.1%), completely disagree (0%), not sure (0%)

Acute biliary pancreatitis is one of the indications of cholecystectomy to reduce the risk of recurrent gallstone related complications such as recurrent acute pancreatitis, acute cholecystitis and cholangitis. However, surgical complication risks should be considered for the appropriate timing of cholecystectomy. In an RCT of 120 patients with acute biliary pancreatitis comparing cholecystectomy versus wait-and-see approach, 47% of patients in the wait-and-see approach group developed at least one recurrent biliary event during the follow-up period.¹⁰¹ In another RCT which compared same-admission versus delayed cholecystectomy for mild biliary pancreatitis, same-admission cholecystectomy reduced gallstone related events with a very low risk of surgical complications.^{102,103} However, there are limited data that support early cholecystectomy for severe acute biliary pancreatitis.¹⁰⁴ In an RCT which included 187 patients with moderately severe or severe acute biliary pancreatitis, infectious complications were common when cholecystectomy was performed within 3 weeks after development of severe acute pancreatitis.¹⁰⁵ Although cholecystectomy is indicated for acute biliary pancreatitis, optimal timing of cholecystectomy should be tailored to the patient according to the severity of acute pancreatitis.

Recommendation 18

Alcohol abuse treatment should be considered for patients with recurrent acute alcoholic pancreatitis.

- Recommendation grade: weak, Evidence level: C, Expert opinion: completely agree (67.9%), mostly agree (25.0%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Alcohol abstinence is essential for alcoholic pancreatitis. In a prospective cohort study of 68 patients with acute alcoholic pancreatitis, during the follow-up period of median 38 months, alcohol abstinence was a significant protective factor against recurrent episodes of acute pancreatitis after the first attack.¹⁰⁶ In another study which followed 118 patients with first attack of acute alcoholic pancreatitis for 5 years, alcohol abstinence after the first episode was a significant protective factor against recurrent attacks. This study also demonstrated that pancreatic dysfunction was rare in abstinent patients.¹⁰⁷ Currently, non-pharmacological and pharmacological treatment such as naltrexone or acamprosate are being used for alcohol use disorder.¹⁰⁸ In an RCT of 120 patients with first episodes of acute alcoholic pancreatitis, repeated visits with 6-month intervals including an intervention against alcohol consumption showed better results than single interventions during initial hospitalization, in terms of recurrence rate of acute pancreatitis for a period of 2 years.¹⁰⁹ Although there are only limited data that support treatments of alcohol abuse for patients with acute alcoholic pancreatitis, non-pharmacological/pharmacological treatment for alcohol use disorder can be considered in patients with recurrent episodes of acute alcoholic pancreatitis.

4. Treatment of local complication and necrotizing pancreatitis

Recommendation 19

Pancreatic fluid collection is classified as acute peripancreatic fluid collection (APFC), pancreatic pseudocyst, acute necrotic collection and walled-off necrosis depending on the nature of the content, the time of formation and the presence or absence of a wall encapsulating the fluid collection.

- Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (71.4%), mostly agree (28.6%), partially agree (0%), mostly disagree (0%), completely disagree (0%), not sure (0%)

The Atlanta classification was published in 1992, and the revised Atlanta classification in 2012.²¹ In the revised version, local complication was defined in four categories

according to the nature of the content, the time of formation and the presence or absence of well-defined wall encapsulation. APFC is associated with interstitial edematous pancreatitis without necrosis. Peripancreatic fluid retention lacks a defined wall encapsulation within 4 weeks of onset of pancreatitis. Pancreatic pseudocyst is defined as the retention of fluids well encapsulated by an inflammatory wall without solid content and necrosis. It has a round or oval shape and usually occurs after 4 weeks or more of acute interstitial edematous pancreatitis. Acute necrotic collection is related to the necrosis of pancreatic parenchymal and/or tissue surrounding the pancreas for the first 4 weeks. It contains variable amounts of fluid and necrotic material. Walled-off necrosis has a well-defined wall that encapsulates fluid and necrotic materials. Typically, this maturation could occur over 4 weeks.

Recommendation 20

Conservative (medical) treatment is considered for APFC.

- Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (60.7%), mostly agree (39.3%), partially agree (0%), mostly disagree (0%), completely disagree (0%), not sure (0%)

On CECT, APFC demonstrates homogeneous internal density, could be multiple lesion, and may exist within the normal fascial plan of the retroperitoneum.²¹ Most APFCs are sterile and, in most cases, resolve spontaneously, so no additional procedures are needed.¹¹⁰ Some APFCs persist for more than 4 weeks, and may rarely develop into pancreatic pseudocyst. If intestinal perforation or abdominal compartment syndrome or infection occurs, surgery or intervention may be required.^{111,112}

Recommendation 21

Indications for treatment of pseudocysts in patients with clinical symptoms and complications. For treatment, endoscopic drainage could be preferentially performed, and percutaneous drainage and surgical drainage could also be considered.

- Recommendation grade: strong, Evidence level: B, Expert opinion: completely agree (42.9%), mostly agree (50.0%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

The probability of spontaneous resolution of pseudocysts is variously reported to be 60%–70%.¹¹³ Some studies report no difference in prognosis even when the size of cysts is large.¹¹⁴ Therefore, pseudocysts drainage is performed only when there are symptoms and complications.

According to a systematic review of comparing pseudocyst drainage methods, surgical treatment showed better results than percutaneous drainage regarding mortality rate (odds ratio, 1.37; 95% confidence interval, 1.12 to 1.68). Endoscopic drainage showed similar results to surgery, however, it displayed a low rate of adverse events and short length of stay.¹¹⁵ Endoscopic drainage can be divided into transpapillary and transmural drainage. Transpapillary drainage is effective when there is a connection between the pancreatic duct and the pseudocyst. It is also adequately used when it is difficult to perform transmural drainage due to the distance between the intestinal wall and the pseudocyst. The clinical success rate is known as 85% to 90% from retrospective studies.^{116,117} EUS-guided transmural drainage has a technical success rate of over 90% and a clinical success rate of over 80%, which is a treatment success rate similar to surgical treatment.¹¹⁸⁻¹²⁰

Recommendation 22

Conservative treatment is preferred for the initial treatment of necrotizing pancreatitis. Intervention is considered when an infection is suspected or confirmed necrotizing pancreatitis is accompanied by clinical deterioration.

- Recommendation grade: strong, Evidence level: C, Expert opinion: completely agree (35.7%), mostly agree (57.1%), partially agree (7.1%), mostly disagree (0%), completely disagree (0%), not sure (0%)

Considering that early necrosectomy within 72 hours showed high mortality and necrosectomy within 2 weeks displayed high complications, conservative treatment should be prioritized for the initial treatment of necrotizing pancreatitis.¹²¹⁻¹²³ The best indication of intervention for necrotizing pancreatitis is when infectious pancreatic necrosis is confirmed or suspected and accompanied by clinical deterioration.¹²⁴ Even when infectious pancreatic necrosis is diagnosed, if the general condition is stable, conservative treatment including antibiotic treatment can be considered first.⁷⁹ Most patients with sterile necrotizing pancreatitis can be treated without intervention. However, intervention may be required if symptoms such as abdominal pain, nausea, and vomiting persist or if complications such as gastrointestinal obstruction, bile duct obstruction, or fistula are present.^{95,124}

Recommendation 23

In patients with necrotizing pancreatitis, therapeutic intervention should be performed 4 weeks after the onset of pancreatitis if possible, and early drainage may be considered if the intervention cannot be delayed until 4

weeks depending on the patient's condition.

- Recommendation grade: weak, Evidence level: C, Expert opinion: completely agree (32.1%), mostly agree (50.0%), partially agree (14.3%), mostly disagree (3.6%), completely disagree (0%), not sure (0%)

Early open necrosectomy is associated with high mortality and complications, whereas interventions performed 4 weeks after the onset of pancreatitis are associated with lower mortality.^{122,123,125,126} Thus, it is recommended to perform therapeutic intervention 4 weeks after the onset of pancreatitis when acute necrotic collection is walled-off. Even if early drainage was performed according to the patient's condition, necrosectomy should be considered to postpone until walled-off necrosis is formed.⁹⁵

Recommendation 24

Intervention decisions in patients with necrotizing pancreatitis should follow a step-up approach.

- Recommendation grade: strong, Evidence level: A, Expert opinion: completely agree (42.9%), mostly agree (53.6%), partially agree (3.6%), mostly disagree (0%), completely disagree (0%), not sure (0%)

For interventions in patients with necrotizing pancreatitis, a step-up approach is recommended, starting with percutaneous or endoscopic drainage, followed by endoscopic or surgical necrosectomy if there is no clinical improvement. In the initially proposed step-up approach, video-assisted retroperitoneal debridement was suggested as a minimally invasive surgical necrosectomy method.¹²⁷ This surgical step-up approach consisting of percutaneous drainage and video-assisted retroperitoneal debridement reduced new onset multi-organ failure in the short term and had fewer complications such as incisional hernias and endocrine insufficiency in the long term compared to open necrosectomy.^{127,128} In recent years, with the development of endoscopic intervention, the endoscopic step-up approach, which performs endoscopic necrosectomy after endoscopic drainage, is also preferred. In particular, the endoscopic step-up approach causes fewer complications such as fistulas compared to the surgical step-up approach.^{129,130}

CONCLUSION

Since the KPBA established Korean guidelines for acute pancreatitis in 2013, new clinical evidence for acute pancreatitis was emerged through several studies. Accordingly, this revised guideline was prepared including the latest

clinical evidence and fitting the medical situation in our country. It is hoped that this revised clinical practice guideline will help provide appropriate diagnosis, evaluation, and optimized treatment for patients with acute pancreatitis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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