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ORIGINAL ARTICLE

Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015

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Abstract

Background Japanese (JPN) guidelines for the management of acute pancreatitis were published in 2006. The severity assessment criteria for acute pancreatitis were later revised by the Japanese Ministry of Health, Labour and Welfare (MHLW) in 2008, leading to their publication as the JPN Guidelines 2010. Following the 2012 revision of the Atlanta Classifications of Acute Pancreatitis, in which the classifications of regional complications of pancreatitis were revised, the development of a minimally invasive method for local complications of pancreatitis spread, and emerging evidence was gathered and revised into the JPN Guidelines.

Methods A comprehensive evaluation was carried out on the evidence for epidemiology, diagnosis, severity, treatment, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and clinical indicators, based on the concepts of the GRADE system (Grading of Recommendations Assessment, Development and Evaluation). With the graded recommendations, where the evidence was unclear, Meta-Analysis team for JPN Guidelines 2015 conducted an additional new meta-analysis, the results of which were included in the guidelines.

Results Thirty-nine questions were prepared in 17 subject areas, for which 43 recommendations were made. The 17 subject areas were: Diagnosis, Diagnostic imaging, Etiology, Severity assessment, Transfer indication, Fluid therapy, Nasogastric tube, Pain control, Antibiotics prophylaxis, Protease inhibitor, Nutritional support, Intensive care, management of Biliary Pancreatitis, management of Abdominal Compartment Syndrome, Interventions for the local complications, Post-ERCP pancreatitis and Clinical Indicator (Pancreatitis Bundles 2015). Meta-analysis was conducted in the following four subject areas based on randomized controlled trials: (1) prophylactic antibiotics use; (2) prophylactic pancreatic stent placement for the prevention of post-ERCP pancreatitis; (3) prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of post-ERCP pancreatitis; and (4) peritoneal lavage. Using the results of the meta-analysis, recommendations were graded to create useful information. In addition, a mobile application was developed, which made it possible to diagnose, assess severity and check pancreatitis bundles.

Conclusions The JPN Guidelines 2015 were prepared using the most up-to-date methods, and including the latest recommended medical treatments, and we are confident that this will make them easy for many clinicians to use, and will provide a useful tool in the decision-making process for the treatment of patients, and optimal medical support. The free mobile application and calculator for the JPN Guidelines 2015 is available via http://www.jshbps.jp/en/guideline/jpn-guideline2015.html

Keywords Acute pancreatitis · Antibiotics · Bundles · Diagnosis · Guidelines · Intensive care · Nutrition · Pancreas · Post-ERCP pancreatitis · Severity assessment · Surgery

Introduction

The Japanese (JPN) Guidelines for the management of acute pancreatitis were published in the *Journal of Hepato-Biliary-Pancreatic Surgery* in 2006, as evidence-based guidelines consisting of nine original papers [1–9]. They were then revised in 2010, including pancreatitis bundles as clinical indicators [10–20].

In 2012 the classification of localized complications of pancreatitis was revised in the Atlanta Classifications [21], and at the same time, minimally invasive surgeries such as interventional endoscopy (IVE), and interventional radiology (IVR) were advanced. Further, the definitions of treatment guidelines were revised in 2011 and the GRADE system (Grading of Recommendations Assessment, Development and Evaluation) [22–43] was adopted in this revision, leading to the development of guidelines, which are applied closer to the site of treatment and which better consider the benefits and risks to patients.

Methods

Scope/purpose

The purpose of these guidelines remains the same as that of the JPN Guidelines (2006) [1–9], and the JPN Guidelines 2010 [10–20], namely to provide practical medical guidelines for clinicians treating acute pancreatitis, to assist general clinicians to quickly determine the severity of acute pancreatitis and take effective and appropriate medical treatments for the patients with acute pancreatitis.

Stakeholder involvement

Members of the Revision Committee of JPN Guidelines 2015 included gastroenterologists, surgeons, emergency physicians, radiologists, and endoscopists etc., and the guidelines were then evaluated by a wide range of external parties, including the general public, attorneys, internal medicine physicians and surgeons.

These guidelines are designed to be used by all physicians who treat acute pancreatitis, ranging from general clinicians to physicians that specialize in severe acute pancreatitis.

Guideline preparation method

CQ preparation and literature search

Members of the Revision Committee of JPN Guidelines 2015 reviewed the Clinical Questions (CQ) used in the JPN Guidelines (2006) and JPN Guidelines 2010, based on the important clinical issues listed under the Scope, and then prepared new CQ where needed. Keywords were extracted from the CQ, and academic papers were collected. The MEDLINE, Cochrane Library databases and Japana Centra Revuo Medicina Web were used for this. In addition to a systematic search using the JPN Guidelines 2010, papers published from September 2008 to April 2014 were searched, and papers published outside of this period were treated as being outside of the scope of the search period.

Method of systematic literature review

Evidence assessment was performed following the procedures described below (Table 1).

(1) Extraction of risk/benefit outcomes from the CQ
(2) Evaluation of each paper: Preparation of structured abstracts
The information in each article was summarized, including the study design, and the risk of bias in the randomized controlled trials (RCTs) and observational studies was determined.
(3) Method of defining the quality of evidence supporting recommendations

Table 1 Quality of evidence

Comprehensive assessment of stored multiple papers by outcomes and design.
(1) Initial assessment: Assessment by each study design group
A: SR (systematic review), MA (meta-analysis), RCT (randomized controlled trial)
C: OS (observational study)
D: CS (case series, case report)
(2) Assessment of the presence/absence of factors which decrease evidence levels
• Risk of bias in study quality
• Inconsistent results (different conclusions by various papers)
• Indirect evidence (inconsistency between content within a paper and CQ, or content in a paper which is not directly applicable to clinical use)
• Inaccurate data (insufficient number of cases)
• High probability of publication bias (only favorable results reported)
(3) Assessment of the presence/absence of factors which increase evidence levels
• Profound effects with no confounders (profound effects expected for all cases)
• Dose-response gradient (more profound effects expected with increased dosage)
• Possible confounders which diminish actual effects
Comprehensive assessment: The final quality of evidence was assessed and graded as A, B, C, D

A comprehensive evaluation of the evidence was carried out using the GRADE system [22–43] and each of the papers evaluated in (2) were evaluated in relation to each of the outcomes presented in (1) above.

Grading the strength of recommendations

The strength of recommendations was graded with reference to (1) the quality of the evidence, (2) the preferences of the patient, (3) risks and benefits and (4) cost estimates, etc. In terms of consensus-building, a vote was taken using the Delphi method and nominal group technique (NGT) method, and issues with a support rate of more than 70% were approved.

The grading of recommendations was divided into two categories, "1: Strong Recommendations" and "2: Weak Recommendations" which are described, respectively, as "recommendations" and "suggestions."

Meta-analysis

The Meta-Analysis team for JPN Guidelines 2015 conducted a new meta-analysis of four subjects of study using the evidence obtained in the preparation of the guidelines, and used the results for the grading of recommendations.

(1) prophylactic antibiotics use [44]
(2) prophylactic pancreatic stent placement for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis
(3) prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of post-ERCP pancreatitis
(4) peritoneal lavage (PL)

Results

Thirty-nine questions were prepared in 17 subject areas, for which 43 recommendations were made (Table 2).

Diagnosis

CQ1 Which pancreatic enzyme measurements are important when diagnosing acute pancreatitis?

The measurement of serum lipase is recommended for the diagnosis of acute pancreatitis.

However, when the measurement of lipase is difficult, serum amylase (pancreatic amylase) should be measured.

(**1B**)

<Comment> The detection of elevated levels of blood pancreatic enzymes is crucial in the diagnosis of acute pancreatitis [4, 13, 21, 45–52]. When the diagnosis acute pancreatitis cannot be differentiated from other diseases, serum lipase is superior to any other pancreatic enzymes, including serum amylase [53] (Table 3).

CQ2 Is a urinary trypsinogen-2 dipstick useful in diagnosing acute pancreatitis?

Urinary trypsinogen-2 dipstick may be useful for minimally invasive method and rapid diagnosis of acute pancreatitis. However, this is not commercially available in Japan and therefore it cannot be recommended at this time.

(**ungraded B**)

<Comment> The diagnosis of acute pancreatitis using a urinary trypsinogen-2 dipstick is highly effective in medical institutions where a blood test cannot be examined, not requiring blood sample, given the short time (5 min) required for the test, its diagnostic ability, and the fact that it is roughly equivalent to serum pancreatic enzymes [54–56].

Diagnostic imaging

CQ3 Is ultrasonography recommended for the diagnosis of acute pancreatitis?

When acute pancreatitis is suspected, ultrasonography is recommended.

(**1C**)

<Comment> Ultrasonography, which enables the visualization of findings associated with acute pancreatitis such as pancreatic enlargement and inflammatory changes around the pancreas, is useful in diagnosing acute pancreatitis [57, 58]. It can also visualize causes and abnormal findings associated with the pathological conditions of acute pancreatitis such as ascites, bile duct stones and bile duct dilatation (Fig. 1). Color Doppler ultrasonography is useful in the diagnosis of pseudoaneurysm developing inside the pseudocyst [59].

CQ4 Is computed tomography (CT) recommended in the diagnosis of acute pancreatitis?

CT is recommended for the diagnosis of acute pancreatitis.

(**1C**)

<Comment> When a definitive diagnosis of acute pancreatitis is not possible based on clinical findings, blood/urine tests or ultrasonography, or where the etiology of pancreatitis is uncertain, contrast-enhanced dynamic CT should be actively used as long as no renal function problems are observed. Particularly in acute pancreatitis caused by pancreatic ductal stenosis due to pancreas tumors such as cancer, a simple CT alone is very likely to overlook the causative pancreatic cancer [60–62].

Table 2 Summary of recommendation

A. Diagnosis

1 The measurement of serum lipase is recommended for the diagnosis of acute pancreatitis. However, when the measurement of lipase is difficult, serum amylase (pancreatic amylase) should be measured. (1B)

2 Urinary trypsinogen-2 dipstick may be useful for minimally invasive method and rapid diagnosis of acute pancreatitis. However, this is not commercially available in Japan and therefore it cannot be recommended at this time. (ungraded B)

B. Diagnostic imaging

3 When acute pancreatitis is suspected, ultrasonography is recommended. (1C)

4 CT is recommended for the diagnosis of acute pancreatitis. (1C)

5 MRI is more useful than CT in diagnosing bile duct stones causing pancreatitis and hemorrhagic necrotizing pancreatitis. (2C)

6 Contrast-enhanced CT is useful for the diagnosis of active hemorrhage and thrombosis associated with pancreatitis. (1C)

C. Etiology

7 During etiological diagnosis, the diagnosis of gallstone-induced acute pancreatitis should be determined as the most important and urgent issue, as this greatly affects the treatment, such as whether endoscopic papillary treatment should be performed or not. (1A)

D. Severity assessment

8 In principle, it is recommended that a severity assessment be made immediately after diagnosis and repeated over time (especially within 48 h of the diagnosis). (1C)

9 It is recommended that a scoring system is used for severity assessments. (1B)

10 Contrast-enhanced CT is recommended for identifying poorly contrasted areas of acute pancreatitis and is also useful in the diagnosis of complications. However, the possibility of exacerbating pancreatitis and renal function and allergic reactions associated with the contrast must be considered. (2B)

E. Transfer indication

11 Severe cases should be treated immediately at a facility capable of providing treatment for severe acute pancreatitis. Where such treatment is difficult at the facility, it is strongly recommended that the consideration be given to the immediate transfer of the patient. Even where the case is mild in the early stages, severity assessments should be carried out repeatedly over time, and when the criteria are met, transfer should be considered. (1C)

F. Fluid therapy

12 An extracellular solution (Ringer's Lactate solution, etc.) is recommended as the initial infusion solution for acute pancreatitis. (1C)

13 For patients in shock or with dehydration in the early phases of acute pancreatitis, short-time rapid fluid resuscitation (150–600 mL/h: depending on the presence of shock and the dehydration level) is recommended. However, this should be carried out with great care in order to avoid excessive fluid infusion. For patients without dehydration, they should be monitored closely with an appropriate amount of fluid infusion (130–150 mL/h). Particularly for patients with comorbidities such as cardiac or renal failure, the circulating blood volume should be careful evaluated to determine the rate of fluid infusion. (1C)

14 If a mean arterial pressure of 65 mmHg or more and a urine output of 0.5 mL/kg per h or more has been secured in patients with acute pancreatitis, rapid fluid infusion should be discontinued and a reduction of the rate of fluid infusion is suggested. The volume of infusion should be adjusted to maintain these levels. (2C)

G. Nasogastric tube

15 No remedial effect of nasogastric tube insertion has been observed for mild acute pancreatitis. Therefore, the routine use of nasogastric suction tubes is not required. (1A)

H. Pain control

16 Pain associated with acute pancreatitis is severe and persistent, raising the need of sufficient pain control. (1A)

I. Antibiotics prophylaxis

17 The prophylactic administration of antibiotics is not necessary in mild acute pancreatitis, since the incidence and mortality rates of infectious complications from mild acute pancreatitis are low. (1A)

The prophylactic administration of antibiotics in severe acute pancreatitis and necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset). (2B)

18 No remedial effect of the prophylactic administration of antifungal agents for acute pancreatitis has been observed. Therefore, routine administration is not recommended. (1C)

J. Protease inhibitor

19 The effectiveness of intravenous administration of protease inhibitor (gabexate mesilate) for improving the life prognosis and the rate of complications of acute pancreatitis has not been clearly proven. Further consideration of the efficacy of continuous high-dose intravenous administration for severe cases is required. (ungraded B)

K. Nutritional support

20 Intravenous hyperalimentation is not recommended for mild cases. (1B)

Total parenteral nutrition (not performed with oral or enteral nutrition) should be avoided if possible. (1B)

(*Continues*)

Table 2 (Continued)

21 In severe cases, it is more significant as a measure to prevent infection rather than as a route of nutrition support. It can be applied and implemented for severe cases which do not have accompanying intestinal complications. (1A)

22 If initiated in the early phase, enteral nutrition can reduce the incidence of complications and can contribute to an increased rate of survival. Therefore, it is desirable that it be started within at least 48 h of admission. (2A)

23 In principle, it is recommended that enteral feeding tubes be inserted into the jejunum through the Treitz ligament. However, if a feeding tube cannot be inserted into the jejunum, nutrients can be infused into the duodenum or stomach instead. (2B)

24 The initiation of oral administration should be determined using indicators such as the subsidence of abdominal pain and the serum pancreatic enzyme (especially serum lipase) level, etc. (2B)

L. Intensive care

25 No life-saving effect has been observed from peritoneal lavage for acute pancreatitis, and therefore it is not recommended. (2B)

26 For severe cases where circulation dynamics are not stable with anuria even after sufficient initial fluid infusion or cases with abdominal compartment syndrome (ACS), CHF/CHDF should be introduced. (1C)

The efficacy of CHF/CHDF in cases of severe acute pancreatitis not mentioned above is uncertain. Therefore, routine use is not recommended. (2C)

27 Continuous Regional Arterial Infusion therapy is reported to be effective in reducing pancreatic infection and mortality rates for severe acute pancreatitis and acute necrotizing pancreatitis, but its efficacy has not been confirmed. (ungraded B)

M. Management of biliary pancreatitis

28 Early ERCP/ES should be performed in gallstone-induced acute pancreatitis when complications of cholangitis or prolonged passage disorder of the biliary tract are suspected. (1A)

29 To prevent the recurrence of gallstone-induced acute pancreatitis, cholecystectomy is recommended for cases where such surgery is possible. (1B)

30 A cholecystectomy should be performed as soon as gallstone-induced acute pancreatitis has been resolved. (1B)

N. Management of abdominal compartment syndrome

31 The sequential measurement of IAP is recommended for cases with excessive fluid infusion, high severity, renal and respiratory complications, and fluid accumulation in multiple areas as observed by CT, since the onset of ACS increases the mortality rate in such cases. (2C)

32 When there is persistent or recurrent IAP≧12 mmHg, conservative treatment (gastrointestinal decompression, intra-abdominal decompression, improvement of abdominal wall compliance, appropriate fluid infusion and circulation management) should be initiated. The goal should be to manage for IAP≦15 mmHg. Surgical decompression should be considered only when internal treatment is not effective for patients with IAP > 20 mmHg and where the additional complication of organ failure is of concern. (2D)

O. Interventions for the local complications

33 In principle, conservative treatment should first be performed for necrotizing pancreatitis. The best indication for intervention is applied to cases of infected pancreatic necrosis with suspected or confirmed infection accompanying an aggravated general condition. (1C)

34 Infected pancreatic necrosis should be suspected when clinical symptoms and blood test findings deteriorate. Routine use of FNA is not required for diagnosis, and clinical signs and CT should be used for a comprehensive determination. If an aggravated general condition is observed, percutaneous drainage or endoscopic drainage should be given for diagnosis and treatment. (1C)

35 If possible, therapeutic intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off, or in other words, during WON period. (2C)

36 During therapeutic intervention for infected pancreatic necrosis, percutaneous (retroperitoneal) drainage or endoscopic transluminal drainage should be first given, and if no improvement is achieved, necrosectomy should then be performed. Necrosectomy by endoscopic or retroperitoneal approach is recommended. (2B)

P. Post-ERCP pancreatitis

37 Prophylactic temporary pancreatic stent placement is useful as an effective endoscopic procedure for the prevention of post-ERCP pancreatitis. This should only be performed in the high-risk groups* for post-ERCP pancreatitis given the risks and cost. (2A)

The guidewire method is very likely to reduce the incidence of post-ERCP pancreatitis. (2A)

38 For the prevention of post-ERCP pancreatitis, the intrarectal administration of NSAIDs should be carried out for all cases undergoing ERCP with no contraindications. (2A)

(Other drugs should not be used as routine preventive measures, since their efficacy has been refuted or is uncertain.)

Q. Clinical indicators (Pancreatitis Bundles 2015)

39 A high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis. (1C)

4–1: Can acute interstitial edematous pancreatitis be differentiated from acute necrotizing pancreatitis using imaging diagnosis?

By referring to the non-contrast CT level and the imaging ability of contrast-enhanced CT for pancreas and peripancreatic tissues, acute peripancreatic fluid collection (APFC) associated with edematous pancreatitis can be differentiated from acute necrotic collection (ANC) associated with necrotizing pancreatitis. This can be useful in determining a treatment strategy (Fig. 2).

(**C**)

Table 3 JPN diagnostic criteria*

1. Acute abdominal pain and tenderness in the upper abdomen.
2. Elevated levels of pancreatic enzymes in the blood or urine.
3. Abnormal findings of acute pancreatitis detected by US, CT or MRI.
Patients who present with at least two of the above three manifestations and in whom other pancreatic diseases and acute abdomen have been ruled out are diagnosed as having acute pancreatitis. However, acute aggravation in chronic pancreatitis should be included as the category of acute pancreatitis.

Note: Measurement of pancreatic enzymes (such as pancreatic amylase and lipase) with high specificity for the pancreas is desirable.
* The diagnostic criteria of acute pancreatitis was established by the Japanese Ministry of Health, Labour, and Welfare 2008
Cited from Ref. [13]

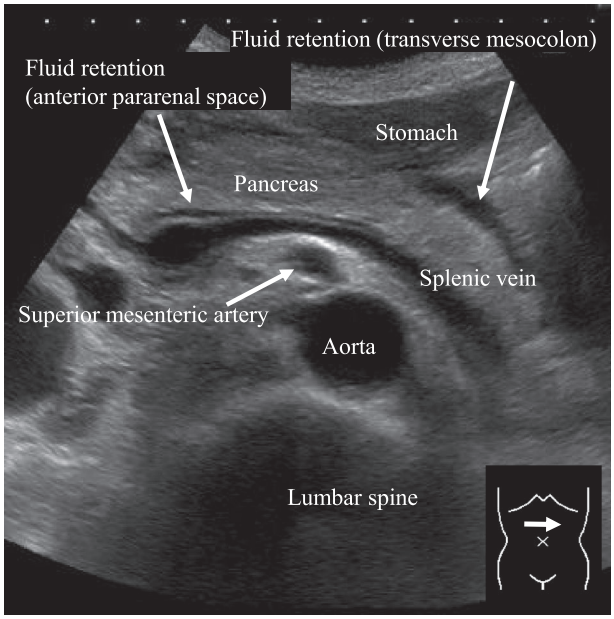

Fig. 1 Ultrasonography. Mild pancreatic enlargement and fluid accumulation in the anterior pararenal space, transverse mesocolon and bursa omentalis can be observed

<Comment> The differentiation of acute necrotizing pancreatitis from acute edematous pancreatitis is important in determining the treatment strategy. The evaluation of acute edematous pancreatitis and acute necrotizing pancreatitis is difficult with the non-contrast CT, and thus an angiographic evaluation of the pancreas using contrast-enhanced dynamic CT is needed [21, 63]. In many cases of early-onset pancreatitis (less than 1 week), the differentiation of acute peripancreatic fluid collection (APFC) associated with edematous pancreatitis from acute necrotic collection (ANC) can be difficult. In the early phases of acute pancreatitis, the poorly defined pancreas in the arterial phase of dynamic CT imaging can be reversible ischemia, and cannot be conclusively identified as necrosis of the pancreatic parenchyma. However, necrotizing pancreatitis is strongly suspected if a poorly contrasted area is observed by dynamic CT more than 2 weeks after onset [64] (Fig. 3).

4–2: Can walled-off necrosis (WON) be differentiated from pancreatic pseudocyst (PPC) using imaging diagnosis?

By referring to the shape, extent and internal characteristics (CT contrast level and magnetic resonance imaging (MRI) signal intensity), PPC and WON can be differentiated. This can be useful in determining a treatment regime.

(**C**)

<Comment> About 4 weeks after the onset of ANC, a capsule-like rim appears around the fatty necrotic focus, forming a shape called WON (Fig. 4). It is important to differentiate pseudocysts that form by encapsulating fluid collection due to edematous pancreatitis from WON that is formed by encapsulating necrotic substances due to necrotizing pancreatitis [63, 65]. WON has an irregular shape, and not only extends to peripancreatic tissues and mesocolon, but also to the paracolic gutter [63, 65, 66]. Inside WON, there is a mixture of fluid, necrotic substances and fat tissues, making the CT contrast level higher than water concentration and, in many cases, inhomogeneous. By referring to the shape, extent and internal characteristics (CT contrast level and MRI signal intensity), PPC and WON can be differentiated in many cases.

CQ5 In which cases is MRI useful for the diagnosis of acute pancreatitis?

MRI is more useful than CT in diagnosing bile duct stones causing pancreatitis and hemorrhagic necrotizing pancreatitis.

(**2C**)

<Comment> Although it can be difficult in some cases to differentiate parapancreatic fatty necrosis from fluid collection by CT, an MRI enables the clear differentiation of fatty necrosis from fluid based on the signal strength. Compared with fluid, fatty necrosis presents higher signals in T1-enhanced imaging and mildly lower signals in T2-enhanced imaging [67–69], and GdDTPA dynamic MRI imaging can depict the foci of necrotizing pancreatitis as a poorly contrasted area [70, 71].

CQ6 Is contrast-enhanced CT useful for the diagnosis of vascular complication associated with acute pancreatitis?

Contrast-enhanced CT is useful for the diagnosis of active hemorrhage and thrombosis associated with pancreatitis.

(**1C**)

<Comment> In acute pancreatitis, bleeding can occur in the areas from the peripancreatic tissues to the mesentery and mesocolon. Contrast-enhanced CT is necessary when there is a need to evaluate the presence of persistent bleeding

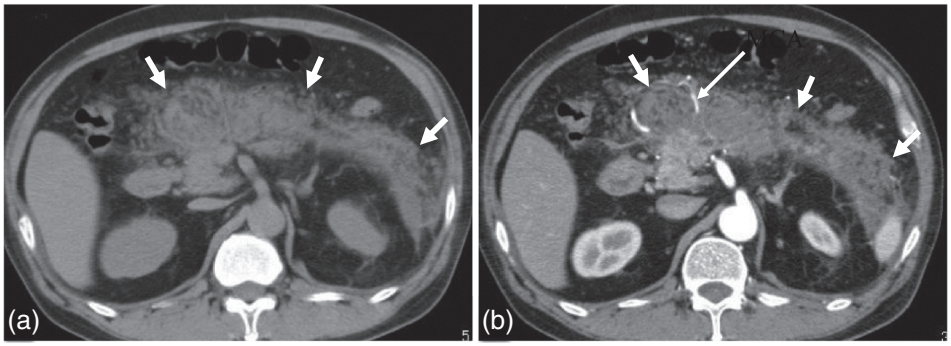

Fig. 2 Acute necrotic collection (ANC). In non-contrast computed tomography (CT) (**a**), inhomogeneous fluid retention (indicated by the arrow) can be observed from the transverse mesocolon to the left paracolic gutter, accompanied with internal fat accumulation. Although it is poorly contrasted by contrast-enhanced CT (**b**), middle colic artery (MCA) running inside can be observed. This can be diagnosed as acute necrotic collection (ANC) in the transverse mesocolon

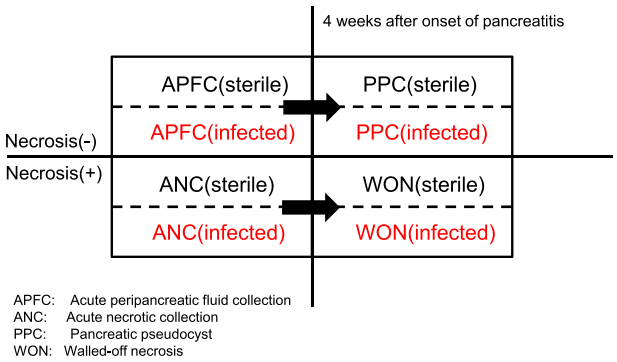

Fig. 3 Classification of pancreatic fluid collection by the revised Atlanta classification. *AFPC* acute peripancreatic fluid collection, *ANC* acute necrotic collection, *PPC* pancreatic pseudocyst, *WON* walled-off necrosis

[72]. Also, a peripancreatic arterial rupture can occur in acute pancreatitis, accompanied by acute peripancreatic fluid collection, causing internal bleeding (known as pseudoaneurysm) [73, 74] (Fig. 5). Contrast-enhanced CT and color Doppler ultrasonography is necessary to accurately diagnose venous thrombus [75].

Etiology

CQ7 Which pathological conditions should be considered as priority issues during etiological diagnosis?

During etiological diagnosis, the diagnosis of gallstone-induced acute pancreatitis should be determined as the most important and urgent issue, as this greatly affects the treatment, such as endoscopic papillary treatment.

(**1A**)

<Comment> Bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) values and an ultrasonography should be examined in all cases to diagnose the presence of gallstone-induced acute pancreatitis [76]. MRI/magnetic resonance cholangiopancreatography (MRCP) can visualize common bile duct stones, an anomalous arrangement of pancreaticobiliary ducts, and pancreas divisum, and is useful for the etiological diagnosis of acute pancreatitis [77–79]. Endoscpic ultrasonography (EUS) has a better capacity for visualizing common bile duct stones compared to ultrasonography [80–82]. It can diagnose bile duct stones, chronic pancreatitis, pancreatic cancer and intraductal papillary mucinous tumor, and is useful for the etiological diagnosis of acute pancreatitis [83, 84].

Severity assessment

CQ8 When should a severity assessment be performed?

In principle, it is recommended that a severity assessment be made immediately after diagnosis and repeated over time (especially within 48 h of the diagnosis).

(**1C**)

<Comment> Severity assessments for acute pancreatitis are useful for the appropriate introduction of initial treatment, and, when necessary, transfer to facilities where treatment for severe acute pancreatitis can be provided [85–87]. A severity assessment at the time of the diagnosis of acute pancreatitis can increase the possibility of accurate treatment for the patient and an improved prognosis. Repeated severity assessments may be small in cost. Members of the Revision Committee of JPN Guidelines 2015 reached the consensus that sequentially repeated severity assessments are highly beneficial for patients. The revised edition of the Atlanta Classifications (2012) [21] also state that "the severity of acute pancreatitis can be reassessed on a daily basis while the pancreatitis is still evolving, and in particular re-evaluations should be made 24 h, 48 h and 7 days after admission to the hospital."

CQ9 Is a scoring system useful for severity assessments?

It is recommended that a scoring system is used for severity assessments.

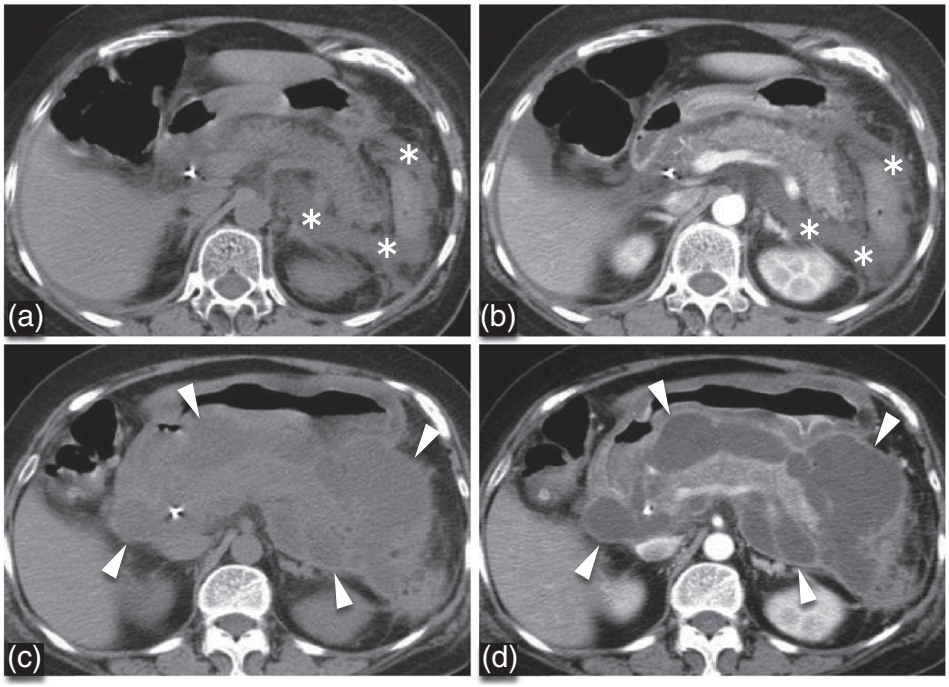

Fig. 4 Acute necrotic collection (ANC) and walled-off necrosis (WON). In the non-contrast computed tomography (CT) (**a**) and contrast-enhanced CT (**b**), a high level of fluid concentration (*) was observed around the enlarged pancreatic parenchyma, and acute necrotic collection (ANC) was suspected. In a non-contrast CT (**c**) and contrast-enhanced CT (**d**) carried out 4 weeks after onset, an enlarged necrosis was encapsulated (indicated by arrowheads) with an irregular shape. This was diagnosed as walled-off necrosis (WON) and a drainage operation was performed

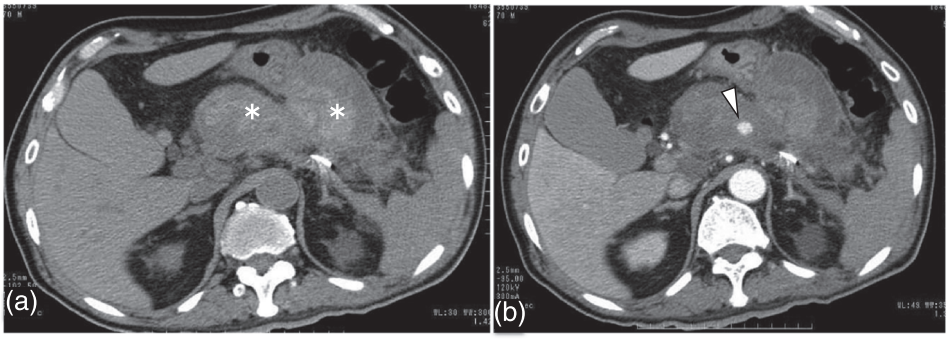

Fig. 5 Bleeding in acute pancreatitis. In the non-contrast computed tomography (CT) (**a**), hemorrhagic fat necrosis can be observed in the pancreas, peripancreatic tissues, lesser sac space and transverse mesocolon. High density areas (*) can be partly observed, accompanied by a bleeding mass. In the dynamic CT (**b**), contrast agent leakage (pseudoaneurysm, indicated by the arrowheads) inside the bleeding mass can be observed, indicating persistent bleeding

(**1B**)

<Comment> Various scoring systems have been proposed and are used at clinical sites for severity assessments of acute pancreatitis. The Ranson score [88] was reported in 1974, the Glasgow score [89] in 1984, the APACHE-II [87] in 1989, and the systemic inflammatory response syndrome (SIRS) [90] in 2006, all of which are used as scoring systems. In terms of new scoring systems, the Panc 3 score [91] and POP score [92] were proposed in 2007, the BiSAP score [93] in 2008, and the HAPS score [94] in 2009.

The JPN Severity Score (JSS) was revised in 2008 [14] (Table 4), and it has been reported that the best predictors of organ failure are the JSS and BiSAP scores [95]. Also, according to a report by Mounzer et al., in comparison to the Ranson, Glasgow, APACHE-II, SIRS, POP, BiSAP, JSS and HAPS scoring systems, the JSS had the best scoring capacity for AUC at 48 h after admission [96].

CQ10 Is contrast-enhanced CT useful for severity assessments of acute pancreatitis that is suspected to increase in severity?

(At facilities where treatment for acute pancreatitis is provided,) Contrast-enhanced CT is recommended for identifying poorly contrasted areas of acute pancreatitis and is also useful in the diagnosis of complications. However, the possibility of exacerbating pancreatitis and renal function and allergic reactions associated with the contrast must be considered.

(**2B**)

<Comment> The presence of necrotizing pancreatitis and the extension of inflammatory changes are closely related to various complications and prognosis [97–99], and accurate diagnosis is necessary. The evaluation of an enlarged pancreas, inflammatory extension to

peripancreatic fat tissue, fluid collection, pseudocyst, and fat necrosis are generally possible with non-contrast CT. However, the diagnosis and evaluation of necrotizing pancreatitis and its scope needed for severity assessments is not possible with non-contrast CT, and contrast-enhanced CT is required for this [100] (Figs 6–8). If contrast-enhanced CT is taken within 4 to 10 days of onset, the diagnosis of necrotizing pancreatitis can be made with an accuracy of almost 100% [97, 98, 100, 101].

Transfer indication

CQ11 When should patients with acute pancreatitis be transferred to specialized hospital?

Severe cases should be treated immediately at a facility capable of providing treatment for severe acute pancreatitis. Where such treatment is difficult at the facility, it is strongly recommended that the consideration be given to the immediate transfer of the patient. Even where the case is mild in the early stages, severity assessments should be carried out repeatedly over time, and when the criteria are met, transfer should be considered.

(**1C**)

<Comment> It has been reported that hospitals with a large number of cases of acute pancreatitis have good clinical outcomes [102–104]. According to a report by Murata et al. using Japan's Diagnosis Procedure Combination (DPC)* data, good clinical outcomes were achieved in hospitals receiving a large number of patients annually [103].

For cases considered "severe" according to the JSS, patients should be transferred to a facility where ICU management, IVR, continuous hemodiafiltration (CHDF), endoscopic treatment for cholelithiasis, surgical treatment, a

Table 4 JPN Severity Score (JSS)

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≦−3 mEq/L or shock (systolic blood pressure < 80 mmHg)	
2. PaO_2≦60 mmHg (room air) or respiratory failure (respirator management is needed)	
3. BUN≧40 mg/dL (or Cr≧2.0 mg/dL) or oliguria (daily urine output < 400 mL even after IV fluid resuscitation)	
4. LDH≧2 times of upper limit of normal	
5. Platelet count≦100,000/mm^3	
6. Serum Ca≦7.5 mg/dL	
7. CRP≧15 mg/dL	
8. Number of positive measures in SIRS criteria≧3	
9. Age≧70 years	
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 score	
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 as "severe".	

Measures in SIRS diagnostic criteria: (1) Temperature > 38 °C or <36 °C, (2) Heart rate > 90 beats/min, (3) Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr, (4) WBC > 12,000 cells/mm^3,<4,000 cells/mm^3, or > 10% immature (band) forms
Modified from Ref. [14]

nutritional support team (NST) and other measures for severe acute pancreatitis are available.

*The Diagnosis Procedure Combination (DPC) is a case-mix system, which is similar to the diagnosis-related groups (DRGs) used in Medicare in the United States.

Fluid therapy

CQ12 What should be used as initial infusion solution?

An extracellular solution (Ringer's Lactate solution, etc.) is recommended as the initial infusion solution for acute pancreatitis.

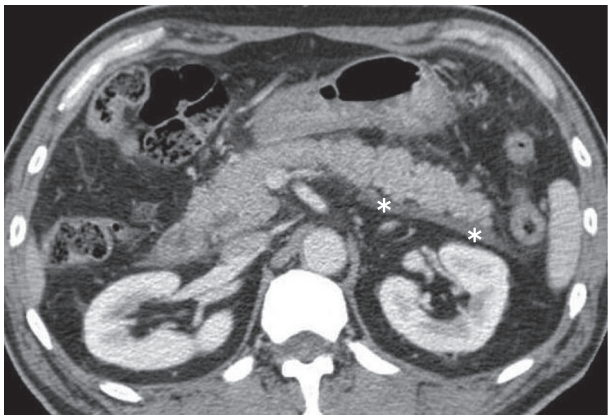

Fig. 6 Computed tomography (CT) Grade 1 (JSS). In the contrast-enhanced CT, the mild enlargement of the entire pancreas can be observed with no noticeable poorly contrasted areas. Since fluid collection (*) can be observed in the left anterior pararenal space and the root of the transverse mesocolon, this can be diagnosed as CT Grade 1 acute pancreatitis

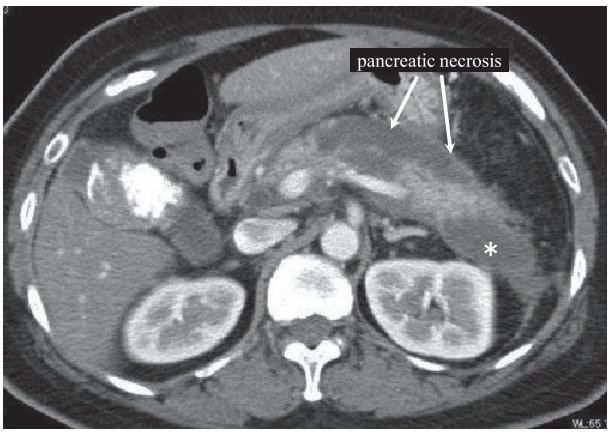

Fig. 7 Computed tomography (CT) Grade 2 (JSS). In the contrast-enhanced CT, poorly contrasted fat necrosis can be observed in the lesser sac, left anterior pararenal space and transverse mesocolon. This was diagnosed as CT Grade 2 according to the necrosis level of the pancreas (1/3-1/2) and due to the fat necrosis observed in the root of the transverse mesocolon

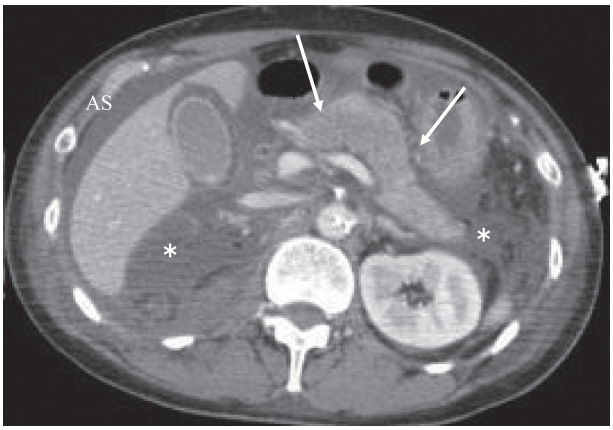

Fig. 8 Computed tomography (CT) Grade 3 (JSS). In the contrast-enhanced CT, a large amount of ascites (AS) was observed. The enlargement of the pancreatic body and a poorly contrasted area (indicated by the arrows) were observed. Significant fat necrosis (*) reaching the transverse mesocolon and left posterior peritoneal cavity space was observed. This was diagnosed as CT Grade 3 severe acute pancreatitis

(**1C**)

<Comment> According to two RCTs, Ringer's Lactate solution was found to be more effective in reducing inflammation than saline. At the same time, colloid solution HES was found to have the same reductive effect on inflammation as Ringer's Lactate solution, with a mild increase in abdominal muscle pressure [105, 106]. In an observational study of patients with severe acute pancreatitis admitted to an ICU, the volume of extracellular solution infused into survivors within 48 h of admission was reported to be significantly higher than that for non-survivors [107]. Also, in a prospective study of patients with severe acute pancreatitis who exhibited shock and oliguria at the time of admission, significantly higher values for the rates of mechanical ventilation and incidences of ACS and lethal rates were obtained in the rapid fluid expansion group [108]. Although there is not sufficient reliable evidence regarding what should be used as the initial infusion solution for acute pancreatitis [109, 110], the benefits to patients when using an extracellular solution, especially Ringer's lactate solution, are considered to sufficiently outweigh the risks.

CQ13 What is the optimal initial infusion rate at the onset of acute pancreatitis?

For patients in shock or with dehydration in the early phases of acute pancreatitis, short-time rapid fluid resuscitation (150–600 mL/h: depending on the presence of shock and the dehydration level) is recommended. However, this should be carried out with great care in order to avoid excessive fluid infusion. For patients without dehydration, they

should be monitored closely with an appropriate amount of fluid infusion (130–150 mL/h). Particularly for patients with comorbidities such as cardiac or renal failure, the circulating blood volume should be careful evaluated to determine the rate of fluid infusion.

(**1C**)

<Comment> The results of the studies regarding the initial fluid infusion rate vary according to dehydration levels. Patients with unstable circulation dynamics should be recognized as being in a severe condition with a high mortality rate, and their circulation dynamics should be more carefully evaluated and monitored. For such patients, the introduction of colloid solution infusion, catecholamine administration, and in some cases, blood purification therapy may be considered [21, 49–51, 105, 108, 109, 111–116].

CQ14 What are the indications for the termination of initial rapid fluid infusion for acute pancreatitis?

If a mean arterial pressure of 65 mmHg or more and a urine output of 0.5 mL/kg per hour or more has been secured in patients with acute pancreatitis, rapid fluid infusion should be discontinued and a reduction of the rate of fluid infusion is suggested. The volume of infusion should be adjusted to maintain these levels.

(**2C**)

<Comment> There are few reports on the usefulness of indicators for the termination of rapid fluid infusion. Decreases in BUN, hematocrit (Ht), and CVP have been studied, but these did not serve as useful indicators [105, 107, 110, 117]. In the Pancreatitis Bundles, one item states, "For acute pancreatitis, a sufficient amount of fluid replacement and monitoring should be performed within 48 h of onset, and mean arterial pressure (MAP) should be maintained at 65 mmHg or more and urinary output at 0.5 ml/kg per hour or more, respectively [20]." The results of a nationwide survey of patients who developed acute pancreatitis throughout the year of 2011 in Japan showed a significantly low mortality rate of 9.5% in patients in compliance with these levels, while the mortality rate of those in non-compliance was 19.4%. This showed that compliance with the Bundles can improve the life prognosis of patients [118].

Nasogastric tube

CQ15 Is a nasogastric tube useful for the remedy of acute pancreatitis?

No remedial effect of nasogastric tube insertion has been observed for mild acute pancreatitis. Therefore, the routine use of nasogastric suction tubes is not required.

(**1A**)

<Comment> At least eight RCTs [119–126] have been performed on nasogastric suction tube for mild to moderate pancreatitis. However, no beneficial effects such as reduced pain or shortened periods of hospitalization were reported. Rather, the duration of abdominal pain and nausea was prolonged with use of nasogastric tube [122, 125].

Pain control

CQ16 Is pain relief necessary for acute pancreatitis?

Pain associated with acute pancreatitis is severe and persistent, raising the need of sufficient pain control.

(**1A**)

<Comment> The appropriate use of analgesics was found to be effective in reducing pain. It was further found that this does not inhibit diagnosis or treatment [127]. A consensus has not yet been reached as to which analgesics are useful in reducing pain from acute pancreatitis [128–131].

Antibiotics prophylaxis

CQ17 Is the prophylactic administration of antibiotics effective in improving acute pancreatitis?

The prophylactic administration of antibiotics is not necessary in mild acute pancreatitis, since the incidence and mortality rates of infectious complications from mild acute pancreatitis are low.

(**1A**)

The prophylactic administration of antibiotics in severe acute pancreatitis and necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset).

(**2B**)

<Comment> Although a number of meta-analyses have been performed on the prophylactic administration of antibiotics used for acute pancreatitis, the results have not been consistent [132–160]. Many recent reports have shown that it is ineffective. However, the Meta-Analysis team for JPN Guidelines focused on the timing for starting antibiotic administration and the patients who received such treatments, and performed a meta-analysis [44] using six RCTs conducted on patients with severe acute pancreatitis or necrotizing pancreatitis within 48 and 72 h of onset [132, 133, 136, 137, 139, 141]. As a result, mortality and infectious pancreatic complication rates were significantly reduced. However, to meet the conditions of the timing to start antibiotic

administration, the type of antibiotics and the selection of subjects, a large scale RCT is considered necessary [49]. Although no clear understanding has been obtained regarding the period of prophylactic antibiotic administration, continuous administration for more than 2 weeks should be avoided in patients with no signs of infection [161]. A possible increase in complications such as fungal infections due to the use of broad-spectrum antibiotics has also been reported [162].

CQ18 Is the prophylactic administration of antifungal agents effective for acute pancreatitis?

No remedial effect of the prophylactic administration of antifungal agents for acute pancreatitis has been observed. Therefore, routine administration is not recommended.

(**1C**)

<Comment> Recently, no large scale RCTs have been performed on the preventive effects of antifungal administration for acute pancreatitis, and it is uncertain if such administration can reduce mortality rates or shorten the period of hospitalization [163–168].

Protease inhibitor

CQ19 Is the intravenous administration of protease inhibitor effective for acute pancreatitis?

The effectiveness of intravenous administration of protease inhibitor (gabexate mesilate) for improving the life prognosis and the rate of complications of acute pancreatitis has not been clearly proven. Further consideration of the efficacy of continuous high-dose intravenous administration for severe cases is required.

(**ungraded B**)

<Comment> In 17 reports [89, 169–185] on the meta-analysis of RCTs [186] published in 2014 no significant reduction in mortality rates was achieved by the administration of protease inhibitor.

Nutritional support

CQ20 Is intravenous hyperalimentation useful for acute pancreatitis?

Intravenous hyperalimentation is not recommended for mild cases.

(**1B**)

Total parenteral nutrition (not performed with oral or enteral nutrition) should be avoided if possible.

(**1B**)

<Comment> In two RCTs, no efficacy was observed from intravenous high calorie infusion for mild acute pancreatitis [187, 188]. In RCT conducted for severe acute pancreatitis, the medical cost of enteral nutrition for each patient was shown to be one-third of that for intravenous alimentation [189]. Also, the SIRS positive rate, CRP value and APACHE II scores were significantly lower in patients receiving enteral nutrition 7 days after admission. However, it has been also reported that these indicators did not decrease in patients receiving intravenous alimentation [190]. Furthermore, a significant decrease, not only in the rate of incidence of infectious necrotizing pancreatitis, but also in the infection rate of multiple organ failure and mortality rates were reported with enteral nutrition for severe acute pancreatitis, when compared with total parenteral nutrition [191].

CQ21 What are the significance and indications of enteral nutrition?

In severe cases, it is more significant as a measure to prevent infection rather than as a route of nutrition support. It can be applied and implemented for severe cases which do not have accompanying intestinal complications.

(**1A**)

<Comment> A number of RCTs have been performed in the past, in which comparisons were made between enteral nutrition and intravenous alimentation as treatments for acute pancreatitis [188–196]. A systematic review [197, 198] of these tests reported that enteral nutrition was associated with a significantly lower incidence of infection, reduced surgical intervention and a reduced length of hospital stay in comparison with total parenteral nutrition (without enteral nutrition) [197]. Therefore, enteral nutrition for severe cases is significant as an infection prevention measure, and is considered to contribute to the improvement of life prognosis.

CQ22 When is the optimal timing to start enteral nutrition?

If initiated in the early phase, enteral nutrition can reduce the incidence of complications and can contribute to an increased rate of survival. Therefore, it is desirable that it be started within at least 48 h of admission.

(**2A**)

<Comment> The efficacy of enteral nutrition, and a decrease in mortality rates have been demonstrated [191, 199]. Enteral nutrition can be started in the early phases of severe pancreatitis, with great care for severe ileus, intestinal ischemia and intestinal necrosis. For severe pancreatitis, enteral nutrition should be started early and at a low dose. If possible, it should begin within 48 h of admission.

CQ23 Which administration method should be used for enteral nutrition?

In principle, it is recommended that enteral feeding tubes be inserted into the jejunum through the Treitz ligament. However, if a feeding tube cannot be inserted into the jejunum, nutrients can be infused into the duodenum or stomach instead.

(**2B**)

<Comment> The low executing rate of early enteral nutrition has been a major issue [200]. The difficulty of inserting alimentation tubes into the jejunum may be one cause. It has been reported that enteral nutrition with gastric tube is not inferior to that with jejunal nutrition in terms of safety and complications [201–203]. Therefore, intragastric alimentation can be also used as an alternative means of administration.

23–1: What should be used to provide enteral nutrition?

Enteral nutrition can be provided from among digestible nutrients, semi-digestible nutrients and component nutrients, considering the viscosity and osmotic pressure.

(**B**)

<Comment> No characteristic trend has been found in analysis of the efficacy of the components of enteral nutrition, and there is not believed to be any significant difference between components [204–210].

CQ24 When should oral administration be started?

The initiation of oral administration should be determined using indicators such as the subsidence of abdominal pain and the serum pancreatic enzyme (especially serum lipase) level, etc.

(**2B**)

<Comment> Although abdominal pain after oral administration has not been studied in detail, D in Balthazar's CT score, duration of sustained pain, high serum lipase concentration [211] and high CRP value, high serum amylase concentration, and high serum lipase concentration in mild pancreatitis [212] are reported to be associated with the relapse of abdominal pains. The use of serum pancreatic enzymes (especially serum lipase) as an indicator to determine the timing of the start of oral administration after acute pancreatitis is considered appropriate. In mild pancreatitis, results have been reported, which support active early oral administration [213, 214].

A flowchart for the management of acute pancreatitis is shown in Figure 9.

Intensive care

CQ25 Can peritoneal lavage (PL) for acute pancreatitis improve prognosis?

No life-saving effect has been observed from peritoneal lavage for acute pancreatitis, and therefore it is not recommended.

(**2B**)

<Comment> Twelve RCTs [215–226] and one meta-analysis [227] of peritoneal lavage have been performed, but the diagnostic methods, severity assessment and treatment methods for acute pancreatitis are inconsistent, resulting in differing evaluations.

In both existing meta-analysis [228] and the new meta-analysis performed by the Meta-Analysis team for JPN Guidelines 2015, no effect was observed in the survival rate, incidence of complications or length of hospital stay, and therefore it was concluded that PL is not recommended.

CQ26 When and for what types of pancreatitis should CHF/CHDF be introduced?

For severe cases where circulation dynamics are not stable with anuria even after sufficient initial fluid infusion or cases with abdominal compartment syndrome (ACS), continuous hemofiltration (CHF)/CHDF should be introduced.

(**1C**)

The efficacy of CHF/CHDF in cases of severe acute pancreatitis not mentioned above is uncertain. Therefore, routine use is not recommended.

(**2C**)

<Comment> In a report by Pupelis et al., it was concluded that the early application of continuous venovenous hemofiltration (CVVH) facilitates the reduction of intra-abdominal hypertension (IAH) [229]. Xu et al. also reported that as a result of CVVH carried out for cases of severe acute pancreatitis with complications ACS, intra-abdominal pressure (IAP) and tumor necrosis factor-α (TNF-α) were significantly decreased 24 h after CVVH commenced [230].

CQ27 Is the continuous regional arterial infusion of protease inhibitors and antibiotics effective for acute necrotizing pancreatitis?

Continuous regional arterial infusion therapy is reported to be effective in reducing pancreatic infection and mortality rates for severe acute pancreatitis and acute necrotizing pancreatitis, but its efficacy has not been confirmed.

(**ungraded B**)

<Comment> A number of observational studies have concluded that the continuous regional arterial infusion of

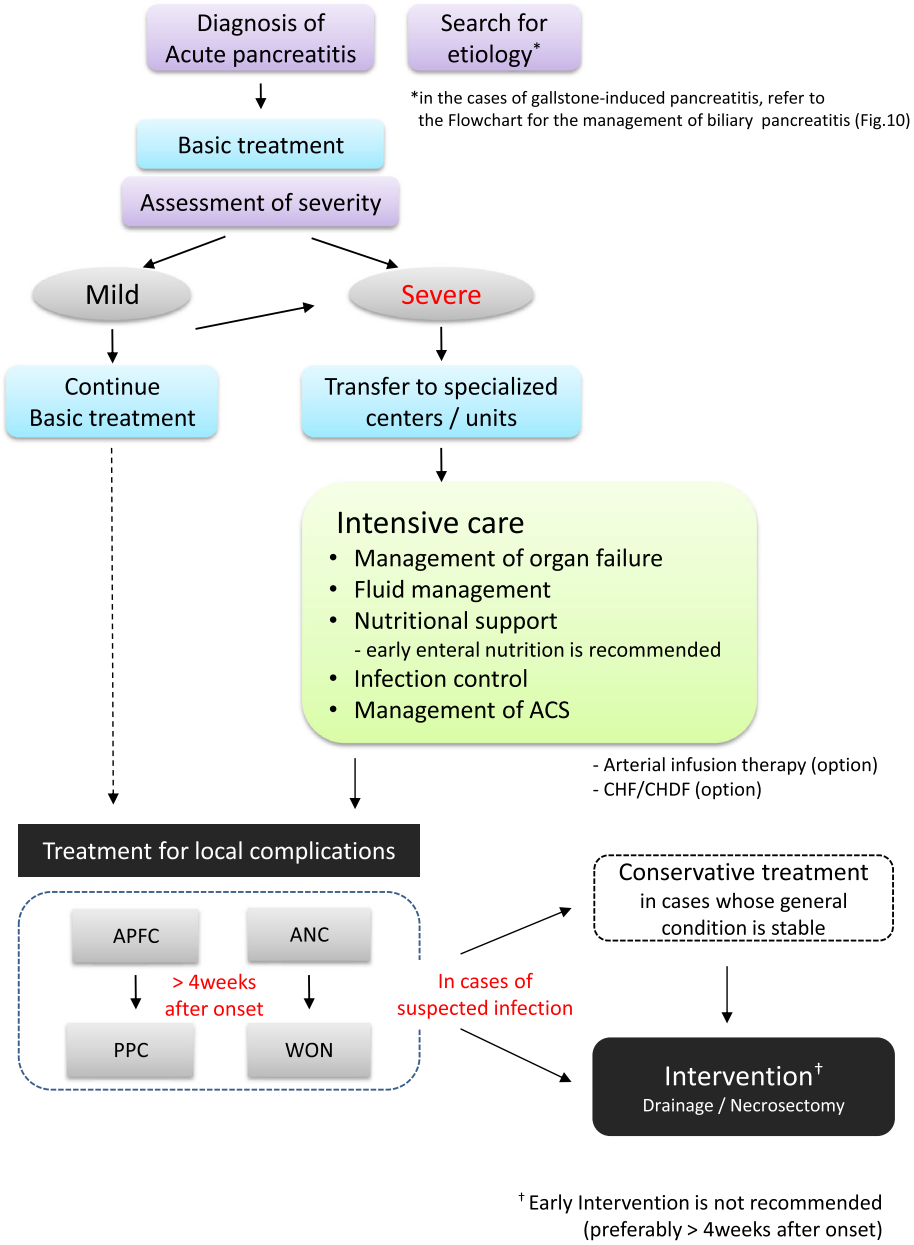

Fig. 9 Flowchart for the management of acute pancreatitis. *ACS* abdominal compartment syndrome, *ANC* acute necrotic collection, *APFC* acute peripancreatic fluid collection, *CHF/CHDF* continuous hemo (dia)filtration, *PPC* pancreatic pseudocyst, *WON* walled-off necrosis

protease inhibitors and antibiotics is effective [231–235]. In one RCT, additional antibiotics, urgent surgical frequencies and mortality rates were significantly lower in a group treated with regional pancreatic-arterial infusion than in a group not treated with such a method [236]. However, it was pointed out that bias could not be ruled out in the case of this RCT [237]. The results of propensity score matching analysis using the Diagnosis Procedure Combination (DPC) database showed no significant differences between these two groups regarding the hospital mortality rate and infection rate of complications [238].

Management of biliary pancreatitis

CQ28 For what types of gallstone-induced acute pancreatitis can early ERCP/ES be carried out?

Early ERCP/ES should be performed in gallstone-induced acute pancreatitis when complications of cholangitis or prolonged passage disorder of the biliary tract are suspected. (**1A**)

<Comment> Four RCTs [239–242] were performed on early endoscopic retrograde cholangiopancreatography

(ERCP) with and without endoscopic sphincterotomy (ES) for acute pancreatitis. A meta-analysis [243] conducted for these tests concluded that both the incidence rate of complications and the mortality rate were low in the group treated with ERCP/ES. At present, early ERCP/ES should be performed for acute pancreatitis, which is diagnosed or suspected as gallstone-induced pancreatitis, in cases of: (1) complications of cholangitis; or (2) suspected prolonged passage disorder such as in the development and/or deterioration of jaundice (Fig. 10).

CQ29 Is cholecystectomy recommended to prevent the recurrence of gallstone-induced acute pancreatitis?

To prevent the recurrence of gallstone-induced acute pancreatitis, cholecystectomy is recommended for cases where such surgery is possible.

(**1B**)

<Comment> Cholecystectomy is considered a first choice treatment for preventing the recurrence of gallstone-induced acute pancreatitis. ES + cholecystectomy is very likely to be the most effective method of preventing the recurrence of pancreatitis and biliary tract complications. The rate of recurrence of biliary tract complications was high in the group treated solely with ERCP + ES, and where there is no reason not to perform a cholecystectomy, ERCP + ES should not be considered on its own. The rate of recurrence of pancreatitis was high in the group with no treatment, and some types of radical treatment were required [244–258].

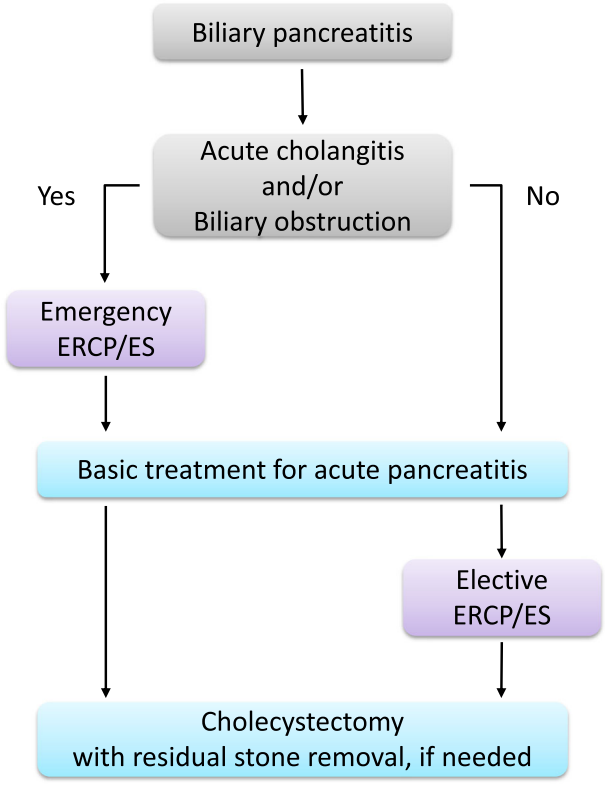

Fig. 10 Flowchart for the management of biliary pancreatitis. *ERCP/ES* endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy

CQ30 What is the appropriate timing to perform cholecystectomy for gallstone-induced pancreatitis?

A cholecystectomy should be performed as soon as the gallstone-induced acute pancreatitis has been resolved.

(**1B**)

<Comment> The rate of recurrence of pancreatitis during the recovery period after discharge is reported to be 32–61%. This rate is said to be particularly high within 6 weeks after discharge [259–261]. In a systematic review of the timing of cholecystectomy for mild biliary pancreatitis, it was reported that there was no readmission when cholecystectomy was performed on patients at the time of first admission [262]. A meta-analysis on the safety of cholecystectomy within 48 h of admission has also been conducted [263].

Management of abdominal compartment syndrome

CQ31 For what types of acute pancreatitis patients is IAP measurement necessary?

The sequential measurement of IAP is recommended for cases with excessive fluid infusion, high severity, renal and respiratory complications, and fluid accumulation in multiple areas as observed by CT, since the onset of ACS increases the mortality rate in such cases.

The measurement of IAP repeated over time is recommended for cases with excessive fluid infusion, high severity, complications of renal and respiratory disorders, and fluid accumulation in multiple areas as observed by CT, given that the onset of ACS increases the mortality rate of such cases.

(**2C**)

<Comment> In acute pancreatitis, complications can be induced by increased IAP. The World Society of Abdominal Compartment Syndrome (WSACS) defines this as where intra-abdominal hypertension (IAH) persists at levels of IAP≧12 mmHg [264, 265]. Moreover, IAH with a series of pathological conditions including organ failure caused by ischemia in intra-abdominal and retroperitoneal organs, and circulatory failure associated with respiratory failure and anomalous venous return caused by diaphragmatic eventration and increased intrathoracic pressure and is referred to as ACS. ACS is defined as cases with

IAP > 20 mmHg accompanied by new organ disorder/failure [264, 265].

The mortality rate of acute pancreatitis with complication of ACS varies depending on the report [266–275], but a systematic review by van Brunschot et al. showed a high mortality rate of 47.5% [276]. Also, a large number of complications from organ disorder/failure have been shown. The mortality rate of regional pancreatic infection complicated with ACS is reported to be 24.0–66.7% [267, 268, 272, 275, 276]. Acute pancreatitis with excessive fluid infusion, high severity, renal disorders, creatinine levels, complications of respiratory disorders, tachypnea, and fluid collection in multiple areas, as observed by CT, is likely to develop IAH/ACS [108, 266, 277, 278], and the measurement of IAP over time is necessary.

CQ32 How should IAH/ACS be treated?

When there is persistent or recurrent IAP≧12 mmHg, conservative treatment (gastrointestinal decompression, intra-abdominal decompression, improvement of abdominal wall compliance, appropriate fluid infusion and circulation management) should be initiated. The goal should be to manage for IAP≦15 mmHg. Surgical decompression should be considered only when internal treatment is not effective for patients with IAP > 20 mmHg and where the additional complication of organ failure is of concern.

(**2D**)

<Comment > In 2013, WSASC recommended that conservative treatment for IAH be carried out first [279]. The proposed procedure for treatment is the step-wise implementation of gastrointestinal decompression, intra-abdominal decompression, improvement of abdominal wall compliance, and appropriate fluid infusion and circulation management for the entire body and local areas. Also, the implementation of surgical decompression is suggested when internal treatment is not effective for patients with IAP > 20 mmHg and when new organ disorders appear. Chen et al. reported a success rate of medical treatment of 75.0% [268]. Also, Boone et al. reported the performance of surgical depression for all cases with ACS complications [280].

Interventions for local complications

CQ33 What are the indications for therapeutic intervention in local pancreatic complications?

In principle, conservative treatments should first be performed for necrotizing pancreatitis. The best indication for intervention is applied to cases of infected necrotizing pancreatitis with suspected or confirmed infection accompanying an aggravated general condition.

(**1C**)

<Comment > Given that the mortality rate from early operations (within 72 h of onset) is very high [281], conservative treatment should be first performed for necrotizing pancreatitis. High mortality rates of 12–26% are observed for ANC or WON accompanying infections [282–284], and intervention treatment is recommended for infectious necrotizing pancreatitis with suspected or confirmed infection accompanying an aggravated general condition [47, 285, 286]. However, conservative treatments such as antibiotic administration can be prioritized for stable general conditions, even if a diagnosis of infectious necrotizing pancreatitis has been made [284, 287]. Rare indications include closed gastric drainage due to PPC [288–291], or a restricted or closed pancreatic duct or intrapancreatic bile duct due to necrosis of pancreatic parenchyma, etc. [292, 293].

CQ34 How should infected pancreatic necrosis be diagnosed?

Infected pancreatic necrosis should be suspected when clinical symptoms and blood test findings deteriorate. Routine use of fine needle-aspiration (FNA) is not required for diagnosis, and clinical signs and CT should be used for a comprehensive determination. If an aggravated general condition is observed, percutaneous drainage or endoscopic drainage should be given for diagnosis and treatment.

(**1C**)

<Comment > Findings suggestive of infected pancreatic necrosis are a deterioration of clinical symptoms and blood test results, a positive bacterial blood culture test, a positive endotoxin test and increased procalcitonin values [294, 295], as well as CT-identified gas in the pancreas or peripancreatic tissues. As direct diagnostic methods for infectious necrotizing pancreatitis, CT or US guided FNA can be used for bacteriological examination [296, 297]. In the past, the routine use of FNA was recommended when infectious necrotizing pancreatitis was suspected, but this indication has become more limited recently [282, 298–300].

CQ35 When should therapeutic intervention for infected pancreatic necrosis be carried out?

If possible, therapeutic intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off, or in other words, during the WON period.

(**2C**)

<Comment > The mortality rate of necrotizing pancreatitis is significantly high from necrosectomy in the early phases [281, 301, 302] and thus it is recommended to perform necrosectomy after at least 4 weeks after the onset of acute pancreatitis when necrosis has been sufficiently walled off

[47, 287, 303]. When infectious necrotizing pancreatitis is suspected, postponing intervention treatment is recommended until 4 weeks after onset when ANC becomes WON.

CQ36 How should the therapeutic intervention for infected pancreatic be selected?

During therapeutic intervention for infected pancreatic necrosis, percutaneous (retroperitoneal) drainage or endoscopic transluminal drainage should be first given, and if no improvement is achieved, necrosectomy should then be performed. Necrosectomy by endoscopic or retroperitoneal approach is recommended.

(**2B**)

<Comment> As intervention treatment for infectious necrotizing pancreatitis, a step-wise approach has been proposed [304], and the selection of minimally invasive method such as percutaneous (retroperitoneal) drainage or endoscopic transluminal drainage has been recommended [47, 287, 304–307]. Necrosectomy should be considered necessary in cases where drainage is not effective. Regarding the methods of necrosectomy, the efficacy of video-assisted retroperitoneal debridement (VARD) and endoscopic necrosectomy has been shown [284, 305, 308]. Regarding approach methods, the retroperitoneal approach has fewer complications than the laparotomy approach [309, 310].

Post-ERCP pancreatitis

CQ37 Which endoscopic procedure is effective for the prevention of post-ERCP pancreatitis?

Prophylactic temporary pancreatic stent placement is useful as an effective endoscopic procedure for the prevention of post-ERCP pancreatitis. This should only be performed in the high-risk groups* for post-ERCP pancreatitis given the risks and cost.

(**2A**)

The guidewire method is very likely to reduce the incidence of post-ERCP pancreatitis.

(**2A**)

<Comment> A number of RCTs and meta-analyses have been performed on prophylactic temporary pancreatic stent placement for high-risk groups of post-ERCP pancreatitis. In most studies stent placement is reported to be effective for the prevention of pancreatitis [311–329]. Meta-analysis was conducted on cannulation methods using contrast agent infusion and guidewires. As a result, a significant reduction of post-ERCP pancreatitis was observed in the group treated with the guidewire method. Therefore, the guidewire method can be used as a first choice therapy [330].

*The high-risk group for post-ERCP pancreatitis refers to patients with confirmed or suspected Sphincter of Oddi dysfunction, patients for whom cannulation is difficult, patients for whom pre-cut sphincterotomy has been performed, or patients for whom balloon dilatation has been provided.

CQ38 Which drug therapy is effective for the prevention of post-ERCP pancreatitis? What are the indications for this?

For the prevention of post-ERCP pancreatitis, the intrarectal administration of NSAIDs should be carried out for all cases undergoing ERCP with no contraindications.

(**2A**)

Other drugs should not be used as routine preventive measures, since their efficacy has been refuted or is uncertain.

<Comment> NSAIDs administration significantly inhibited the onset of post-ERCP pancreatitis [331–334]. Regarding modes of administration, intrarectal administration significantly inhibited the onset of post-ERCP pancreatitis [335, 336].

Clinical indicators

CQ39 Can compliance with the guidelines and bundles improve patient prognosis?

A high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis.

(**1C**)

<Comment> Patients who received treatment, report greater satisfaction in more than eight items of the Pancreatitis Bundles (2010) and showed significantly lower mortality rates than patients who received treatments that satisfied seven items or less [118].

In a questionnaire conducted in Germany, it was reported that although surgeons in Germany were aware of the guidelines for the management of acute pancreatitis, approximately 50% performed treatments that varied from the guidelines [337]. It has been reported, however, that since the publication of the French guidelines, treatments that are more in line with the guidelines have been carried out in France [338]. It is also reported that in Britain, the introduction of Pathway improved the performance rates of CT, severity assessments and ICU admission [339]. From the above reports, compliance with the guidelines and Bundles may lead to the improvement of prognosis, but further consideration is still required (Table 5).

Table 5 Pancreatitis Bundles 2015

In principle, compliance with all of the items is recommended for acute pancreatitis, except under special circumstances. Whether or not compliance with the items has been carried out should be detailed on the medical record.

1. When a diagnosis of acute pancreatitis is made, repeated severity assessments should be carried out at diagnosis, and within 24 h, and 24–48 h after diagnosis based on the JPN Severity Score (JSS).
2. For patients with severe acute pancreatitis, transfer to an appropriate medical facility should be considered within 3 h after diagnosis has been made.
3. For patients with acute pancreatitis, causes of pancreatitis should be differentiated within 3 h after diagnosis, using medical records, hematological examination and imaging studies.
4. For gallstone-induced pancreatitis, early ERC + ES should be considered in patients with accompanying cholangitis and/or prolonged passage disorder of the biliary tract including the occurrence or aggravation of jaundice.
5. At a medical facility where treatment for severe acute pancreatitis is performed, abdominal contrast-enhanced CT studies should be performed within 3 h after initial treatment. A non-enhanced area and the extent of the disease should be examined, and severity should be assessed on the basis of the CT grades of acute pancreatitis.
6. For acute pancreatitis, sufficient amounts of fluid replacement and monitoring should be performed within 48 h of onset, and mean arterial pressure (MAP): diastolic blood pressure + (systolic blood pressure-diastolic blood pressure)/3 should be maintained at 65 mmHg or more and urinary output at 0.5 ml/kg per h or more, respectively.
7. Pain control should be provided for acute pancreatitis.
8. Prophylactic wide-spectrum antibiotics should be administered for severe acute pancreatitis within 72 h of onset.
9. Even if intestinal peristalsis is not present, enteral nutrition should be started in small amounts (jejunal administration is desirable) within 48 h of diagnosis.
10. Cholecystectomy should be performed after the subsiding of symptoms of pancreatitis for gallstone-induced pancreatitis accompanied by cholecystolithiasis.

Conclusion

The latest evidence-based guidelines for the management of acute pancreatitis have been prepared with a clearly described scope and purpose using the GRADE system. For subject areas where no results have been obtained, new meta-analysis was conducted for the grading of recommendations. Also, the Pancreatitis Bundles 2015 was established, which can enhance awareness for improvements in the quality of treatment. Furthermore, the JPN Guidelines 2015 provide a mobile application that can be used easily in a daily clinical situation. Effort has been made to maintain transparency and neutrality during the preparation of these guidelines. The most up-to-date preparation methods and recommendations were used. In this way, we are confident that clinicians will be able to easily follow these guidelines and that these guidelines will contribute to improve the treatment of acute pancreatitis. Above all, it is hoped that the JPN Guidelines 2015 will be used to determine treatments for patients and will contribute to optimal support for them.

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Prior to the preparation of these medical guidelines, all members of the Guidelines Revision Committee declared any conflicts of interest (COI). Effort was made to avoid biases in the guidelines with regard to economic issues. Effort was also made to create a cooperative system with a number of relevant academic societies and research organizations, in order to avoid academic conflicts of interest among individual academic societies.

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The QR codes (for iPhone and Android) to download the mobile application can be found at http://www.jshbps.jp/en/guideline/jpn-guideline2015.html.

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