Urine amylase

Urine amylase has shown high sensitivity in a diagnosis of acute pancreatitis in the past (Level 2b) [41]. However, comparison with blood amylase and other blood pancreatic enzymes found that, at present, measurements of urine amylase have no superiority in diagnostic ability to measurements of other blood pancreatic enzymes (Level 2b–3b) [42, 43].

Blood esterase 1

Esterase 1 is characterized by keeping an abnormal high level longer than any other pancreatic enzymes (Level 2b–3b) [44, 45], so its measurement is considered useful when medical examination is conducted after a long time has passed since the onset of the disease. A study reports that blood esterase 1 has no additional value in the diagnosis of acute pancreatitis and severity assessment (Level 2b) [46]. However, it is also reported that esterase 1 is as suitable as amylase and lipase in terms of clinical usefulness including sensitivity and specificity because rapid and simple measurement has recently become possible (Table 1) [10].

Other blood pancreatic enzymes

Trypsin is a key enzyme involved in the onset of acute pancreatitis and is inactivated rapidly by protease inhibitors in the blood, so determination of its enzymatic activity is difficult. However, it is determined as an antigen quantity by an immunological method. Measurement of the blood trypsin level in acute pancreatitis shows that it has high sensitivity for acute pancreatitis (Level 2b–3b) [39, 47]. Furthermore, there are reports that blood phospholipase A2 (PLA2) increases remarkably in acute pancreatitis and its level is correlated with the severity of the disease (Level 3b) [48, 49]. However, determination of both enzymes depends upon the immunological method, which makes rapid determination difficult. Therefore, their measurement is not suitable for making a diagnosis of acute pancreatitis in clinical settings.

Other urine pancreatic enzymes

Trypsinogen-2, one of the precursors of trypsin, belongs to the group of pancreatic enzymes and is excreted into the urine in the early phase of acute pancreatitis. Recently, there are several studies that reported a method that uses a stick resembling test paper to examine the presence or absence of an elevated level of urine trypsinogen-2 within 5 min or so (Level 2b) [5, 7–9, 35, 50, 51]. Clinical value of this method including its sensitivity and specificity is as high as that of amylase and lipase (Table 7). Particularly, recent studies report that sensitivity and negative predictive value (NPV) are both 100% [5, 12, 50]. This is a rapid and simple method, so its measurement is also a promising procedure for general clinicians.

Diagnostic imaging

Plain chest-abdominal roentgenography

CQ4 Is plain chest-abdominal roentgenography necessary for the diagnosis of acute pancreatitis?

Plain chest-abdominal roentgenography is necessary when acute pancreatitis is suspected (Recommendation A)

Because both plain chest and abdominal roentgenographic findings associated with acute pancreatitis are not specific, it is impossible to make a diagnosis of acute pancreatitis using this method (Level 4) [52]. However, plain chest and abdominal roentgenography is a crucial test in patients with acute pancreatitis for the differential diagnosis from other diseases such as alimentary tract perforation as well as for assessing the clinical course.

Findings in acute pancreatitis detected by plain X-ray examinations include images of ileus, colon cut-off signs, images of localized sentinel loop signs in the left upper abdomen, images of dilated duodenal loops and gas collection, and images of retroperitoneal gas collection. Colon cut-off signs are reported to be a result that the narrowing of the inner spaces of colon by the spread of inflammation arises from the extension of fluid collection and fat necrosis as far as the transverse mesocolon, phrenicocolic ligaments and the left or right anterior paranephric cavities, causes the dilatation of the mouth side of the colon [53–55] (Level 4). Most of the colon cut-off signs are observed in the splenic flexura or descending colon, followed by the transverse colon. Findings detected by plain chest and abdominal X-ray examinations include images suggesting the presence of such conditions as collection of pleural effusion, acute respiratory distress syndrome (ARDS) and pneumonia.

Ultrasonography

CQ5 Is ultrasonography necessary for the diagnosis of acute pancreatitis?

When acute pancreatitis is suspected, ultrasonography is necessary (Recommendation A)

Ultrasonography is one of the tests to be performed at first in every patient in whom acute pancreatitis is suspected.

Ultrasonography, which enables visualization of findings associated with acute pancreatitis such as pancreatic enlargement, inflammatory changes around the pancreas and ascites, is useful in making a diagnosis of acute pancreatitis. It is reported that the visualization rate of the pancreas by US is 62–90% and that of inflammatory changes around the pancreas are 62–90% for the anterior paraphrenic cavity, 90% for the lesser momentum, and 65% for the mesentery, respectively (Level 1b–2b) [56, 57]. Visualization of the pancreas and parapancreatic tissues may be poor in severe cases under the influence of images of intra-intestinal retention of gas bubbles (Level 1b–2b) [56, 57]. US is also effective in detecting biliary lithiasis responsible for acute pancreatitis and differentiating acute pancreatitis from other abdominal diseases.

CT

CQ6 Is CT useful in making a diagnosis of acute pancreatitis?

CT is useful when acute pancreatitis is suspected (Recommendation A)

CT should be performed aggressively when a definitive diagnosis of acute pancreatitis on the basis of clinical manifestations, hematological examination, urinalysis and US is impossible. CT enables visualization of objective local images of the pancreas free from the influence of gas bubbles in the alimentary tract and fatty tissues in the abdominal wall and cavity (Level 1b) [56, 58, 59], so it is the most useful imaging examination for making a diagnosis of acute pancreatitis. It is also useful in a differential diagnosis from other intra-abdominal diseases such as perforation associated with gastroduodenal ulcer.

CT findings useful in a diagnosis of acute pancreatitis include the enlargement of the pancreas, increased concentrations of adipose tissue in the parapancreatic and retroperitoneal cavities (mainly in an anterior pararenal space) and mesocolon and mesenteriolum, fluid collection, pseudocyst formation, uneven density of the pancreatic parenchyma, pancreatic necrosis, fatty necrosis in the retroperitoneal space and mesentery, hematoma, images of pancreatic fissure associated with trauma [60] (Figs. 1, 2, 3). Gas images in and around the pancreas are often caused by fistula formation between the intestinal tract and infections with gas-forming bacteria (Level 1c) (Fig. 4) [61].

CT also helps in assessing the severity of acute pancreatitis because a diagnosis that is important in deciding treatment policy has been made possible concerning complications accompanying pancreatitis and comorbidities in the intra-abdominal organs.

Table 7 Diagnostic ability of urine trypsinogen-2 measurement in acute pancreatitis

Author	Year	*n* (AP)	Methodology	Upper limit of normal	Unit	Cut-off value	Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC
Trypsinogen-2 (urinary)													
Jang et al. [5]	2007	191 (17)	Urine dipstick (immunochromatography)	50.0	μg/l		100.0	96.0			2.43	0.00	
Sankaralingam et al. [50]	2007	30 (5)	Urine dipstick (immunochromatography)	50.0	μg/l	(After 1 h)	100.0	91.0	66.0	100.0			
						(After 4 h)	100.0	96.0	80.0	100.0			
Raty et al. [12]	2007	50 (13)	Urine dipstick (immunochromatography)	50.0	μg/l		100.0	92.0	81.0	100.0			0.959
Sáez et al. [7]	2005	72 (50)	Urine dipstick (immunochromatography)	50.0	μg/l		68.0	86.4	91.9	54.3	5.00	0.37	
Chen et al. [8]	2005	165 (98)	Urine dipstick (immunochromatography)	50.0	μg/l		89.6	85.7	81.1	92.3	6.27	0.12	
Kylänpää-Bäck et al. [9]	2002	237 (29)	Urine dipstick (immunochromatography)	50.0	μg/l		93.0	92.0	63.0	99.0	11.63	0.08	
Kylänpää-Bäck et al. [35]	2000	525 (45)	Urine dipstick (immunochromatography)	50.0	μg/l		96.0	92.0	54.0	99.6	12.00	0.04	

AP Acute pancreatitis, *PPV* positive predictive value, *NPV* negative predictive value, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio, *AUC* area under the curve

MRI

CQ7 In which cases is MRI useful in making a diagnosis of acute pancreatitis?

MRI is useful in making a diagnosis of biliary stones causing pancreatitis and hemorrhagic pancreatic necrosis (Recommendation B)

A diagnosis of edematous pancreatitis by CT is difficult when it is not accompanied by enlargement of the pancreas but T2-enhanced MRI imaging enables visualization of the pancreas clearly in accordance with the severity of edema. Also, MRI has diagnostic ability similar to that of CT in making a diagnosis of parapancreatic fluid collection and hypertrophy of the anterior renal fascia [62, 63] (Fig. 5). Although differentiation by CT of parapancreatic fatty necrosis from fluid collection may be difficult in some cases, MRI enables clear differentiation of fatty necrosis from fluid according to signal strength (compared with fluid, fatty necrosis presents higher signals in T1-enhanced imaging and mildly low signals in T2-enhanced imaging) [62, 64, 65]. Hemorrhagic fatty necrosis that presents a high signal particularly in fat-saturation T1-enhanced imaging can be diagnosed relatively easily (Fig. 6). Gd-DTPA dynamic MRI imaging is able to depict foci of pancreatic necrosis as a hyperchromatic area [66, 67].

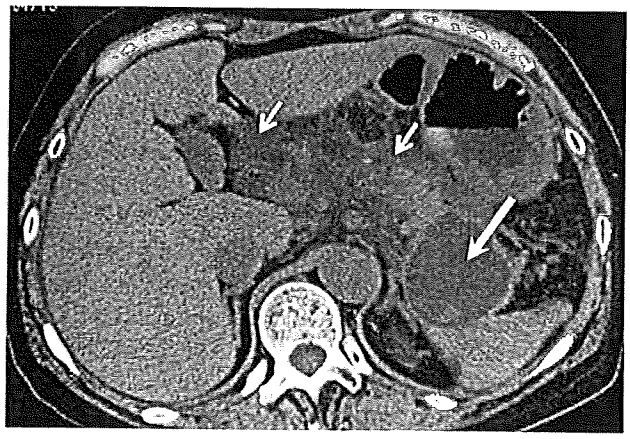

Fig. 1 Plain CT shows fluid in the parapancreatic cavities (*small arrows*) and pseudocyst formation in the pancreatic tail (*large arrow*)

Endoscopic retrograde cholangiopancreatography (ERCP)

CQ8 Is ERCP necessary for the diagnosis of acute pancreatitis?

ERCP is not used for the purpose of making a diagnosis of acute pancreatitis itself (Recommendation D) Note: As far as a disease such as gallstone-induced pancreatitis is

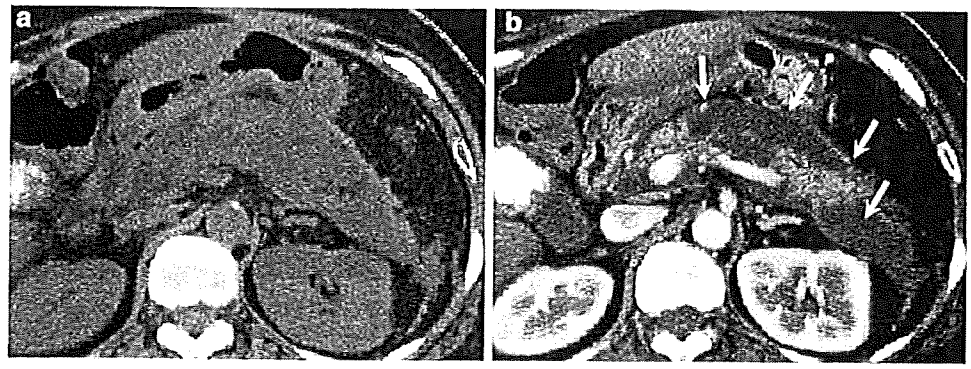

Fig. 2 Plain CT shows enlargement of the pancreatic body (**a**). Contrast-enhanced CT shows pancreatic necrosis as unenhanced area (*arrows*) (**b**)

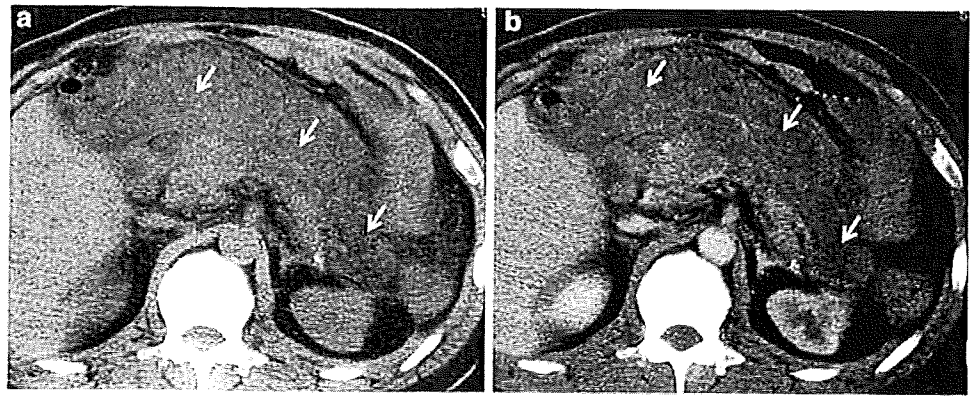

Fig. 3 Plain CT (**a**) and contrast-enhanced CT (**b**) show fatty necrosis (*arrows*) in mesentery

concerned, ERCP is often performed on the assumption that endoscopic treatment is to be delivered.

Adverse events associated with endoscopic retrograde cholangiopancreatography (ERCP) are reported, so ERCP is not used for the diagnosis of acute pancreatitis itself (Level 2b) [68, 69].

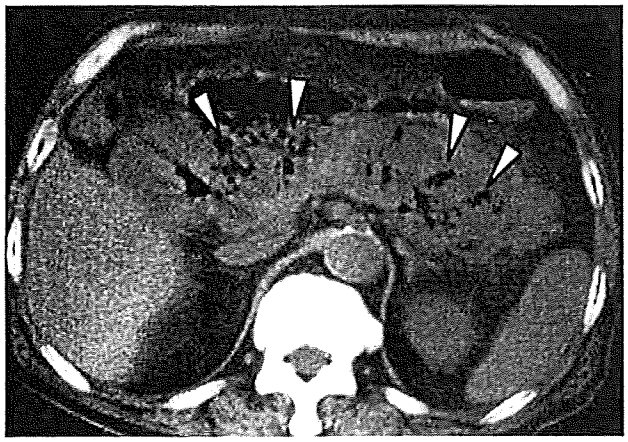

Fig. 4 Plain CT shows gas image caused by infection with gas-forming bacteria, in and around the pancreas

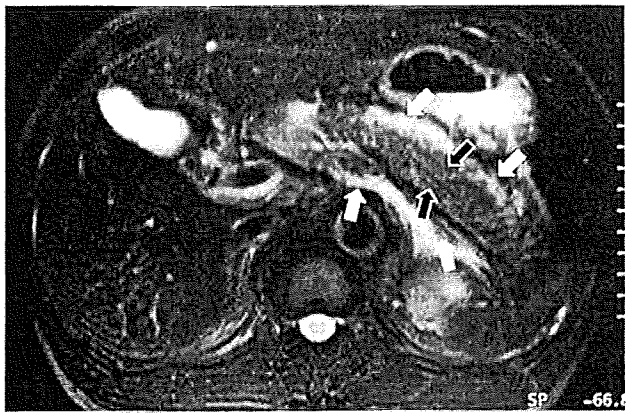

Fig. 5 T2-enhanced MRI imaging shows a mildly high signal of the pancreatic parenchyma (*black arrows*) and a high signal of parapancreatic fluid collection (*white arrows*), in edematous pancreatitis with mild enlargement of the pancreas

Etiologic diagnosis

Necessity and significance of etiologic diagnosis

CQ9 What is the purpose of etiologic diagnosis?

The purpose of etiologic diagnosis is deciding treatment policy in acute pancreatitis by elucidating causes of the disease condition. Treatments for these causes are also important in achieving resolution of acute pancreatitis and preventing recurrence of pancreatitis (Recommendation A)

As soon as a diagnosis of acute pancreatitis has been made, etiologic diagnosis should be made. Especially, the diagnosis of gallstone-induced pancreatitis should be given top priority as it is related closely to treatment policy including the assessment of whether endoscopic papillary treatment should be conducted or not. Etiologic diagnosis should be made immediately because treatment differs depending upon the causes of diseases including gallstone, hyperlipemia, trauma, incomplete fusion of the pancreatic duct, autoimmunity, hyperfunction of the parathyroid gland, and tumors of the pancreaticobiliary system. Pancreatic cancer and intrapancreatic papillary mucous tumor is likely to be associated with acute pancreatitis, so imaging examinations should be conducted.

CQ10 Which tests are necessary for the diagnosis of gallstone-induced acute pancreatitis?

Hematological examinations and ultrasonography should be performed in the first place (Recommendation A)

Presence of jaundice, elevated levels of ALP, γGTP and transamylase detected by blood tests and the presence of common bile duct stones and gallbladder stones visualized by extracorporeal US (EUS henceforth) lead to the suspicion of gallstone-induced acute pancreatitis. However, many of the stones in the common bile duct are small-sized 'passed stones' that induce acute pancreatitis and that have already been excreted from the papilla to the duodenum, so visualization of these stones by US may be difficult in

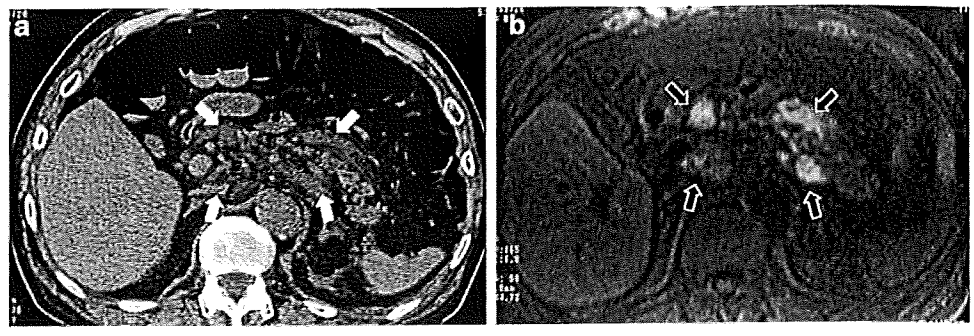

Fig. 6 Plain CT (**a**) and T1-enhanced MRI imaging (**b**). Parapancreatic fatty necrosis can be differentiated from fluid collection by fat-saturation T1-enhanced MRI imaging. Hemorrhagic fatty necrosis showed as fluid collection by plain CT (**a** *white arrows*) presents a high signal in fat-saturation T1-enhanced imaging (**b** *black arrows*)

some cases. This often makes difficult the diagnosis of gallstone-induced acute pancreatitis.

Combination of US and blood tests yields a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞ and negative likelihood ratio of 20.0–50.0, which enables the etiologic diagnosis of gallstone-induced acute pancreatitis (Level 2b) [70–72]. Not all cases involved are necessarily visualized by US, so US should be conducted repeatedly or MRCP, EUS, or ERCP (on the assumption that endoscopic papillary treatment is to be provided) should be conducted.

Personal and family history taking

Checking is necessary for past history of alcohol consumption, gallstone and hyperlipemia, and the presence or absence of tests and procedures involved in the onset of pancreatitis including ERCP, endoscopic papillary treatment, surgery and use of drugs.

Blood tests

Levels of bilirubin, transamylase (ALT, AST) and ALP should be measured in all cases to differentiate gallstone-induced acute pancreatitis from other acute pancreatitis [70]. There is a high possibility that gallstone-induced acute pancreatitis is present when blood ALT is over 150 IU/L (48–93% for sensitivity,34–96% for specificity, 1.4–12.0 for positive likelihood ratio, and 1.8–4.9 for negative likelihood ratio) (Level 1c–2b) [73, 74], or when abnormal values were detected by blood tests in more than three of the items including bilirubin, ALP, γGTP, ALT, ALT/AST (85% for sensitivity, 69% for specificity, 2.7 for positive likelihood ratio, and 4.6 for negative likelihood ratio) [71].

When the level of blood neutral fat exceeds 1000 mg/dL, there is a possibility that hyperlipemia is the cause of acute pancreatitis and when pancreatitis is accompanied by hypercalcemia, hyperfunction of the parathyroid gland is likely to be a cause [70].

Ultrasonography

Ultrasonography is useful in visualizing abnormal findings associated with the etiology of acute pancreatitis such as biliary stones and common bile duct dilatation. However, the ability of US to visualize the common bile duct decreases in acute pancreatitis due to intestinal gas imaging. The rate of US to visualize common bile duct stones differs from report to report (20–90%), so gallstone-induced pancreatitis should not be ruled out even if US has failed to detect biliary stones and bile duct dilatation (Level 1b–4) [75–77].

CT

CT is useful in the diagnosis of a pancreatic cancer and intrapancreatic papillary mucous tumor as a possible cause of acute pancreatitis along with acute worsening of chronic pancreatitis and traumatic pancreatitis. Because CT is not able to visualize biliary stones in many cases (40–53% for sensitivity), it is not suitable for diagnosing gallstone-induced acute pancreatitis (Level 1b) [71, 77].

MRI/MRCP

Compared with ERCP, MRCP enables visualization of, less invasively and without manipulation of the papilla and use of contrast media, the pancreatic duct and bile duct in a relatively early phase of the disease without carrying the risk of worsening the condition of acute pancreatitis. MRCP should be conducted aggressively when the presence of biliary stones is not certain according to US and CT (Level 3) [78–80]. The sensitivity to visualize common bile duct stones is 20% for CT, and 40% for MRCP, respectively, but it is 80% for MRI/MRCP. There is an opinion that recommends MRI/MRCP as a procedure for determining the indications for endoscopic papillary treatment (ERCP/ES) [69]. MRCP treated with MIP alone is likely to fail to detect small biliary stones, so the presence or absence of bile stones should be judged by all means, using as references original MRCP images and thin-sliced T2-enhanced images visualized from multiple directions. MRI/MRCP that visualizes an anomalous arrangement of the pancreaticobiliary tract and incomplete fusion of the pancreatic duct besides bile stones is useful in the etiologic diagnosis of acute pancreatitis (Level 4) [73, 81, 82].

EUS

EUS is superior to US in terms of the ability to visualize common bile duct stones (Level 1b–2b) [75, 83, 84]. EUS is indicated when extracorporeal US is not able to identify common bile duct stones after an attack has subsided. In cases where US has failed to elucidate the etiology, visualization of common bile duct stones is made possible by EUS in 59–78% of those cases (Level 1b–3b) [83, 85, 86]. There is a report showing that by performing EUS in cases where causes were not known by blood tests, US or CT, common bile duct stones were identified in 77.8% of those cases (Level 2b) [84]. Besides biliary stones, EUS is able to make a diagnosis of chronic pancreatitis, pancreatic cancer, intrapancreatic papillary mucous tumor, an anomalous arrangement of the pancreaticobiliary duct and incomplete fusion of the pancreatic duct. Therefore, this procedure is useful in making an etiologic diagnosis of acute pancreatitis (Level 1b–3b) [85, 86].

ERCP

ERCP performed at the time of an attack of acute pancreatitis carries a risk of worsening pancreatitis further. However, in gallstone-induced pancreatitis, when the presence of common bile duct stones is suspected along with jaundice and hepatic disorders, ERCP should be performed on the assumption of endoscopic treatment for biliary stones. When ERCP/ES is not available, patients should be transferred to a medical facility that is in a position to perform ERCP/ES. When gallstone-induced acute pancreatitis is suspected, elective ERCP should be conducted after recovery from pancreatitis because there is a possibility that common bile duct stones not visualized by other procedures are present (Level 3b) [87]. Besides bile stones, elective ERCP is also able to make an etiologic diagnosis of anatomic anomalies (an anomalous arrangement of the pancreaticobiliary duct, incomplete fusion of the pancreatic duct, obstruction of the accessory pancreatic duct, and long common channel [88]) and tumors.

References

1. Takeda K, Ohtuki K, Kitagawa M, et al. Final draft of the diagnostic criteria for and the criteria for severity assessment of acute pancreatitis; 2005 Report. Tokyo: The Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare; 2006. p. 27–34.
2. Steinberg WM, Goldstein SS, Davis ND, Shamma'a J, Anderson K. Diagnostic assays in acute pancreatitis. A study of sensitivity and specificity. Ann Intern Med. 1985;102:576–80.
3. Ventrucci M, Pezzilli R, Naldoni P, Montone L, Gullo L. A rapid assay for serum immunoreactive lipase as a screening test for acute pancreatitis. Pancreas. 1986;1:320–3.
4. Thomson HJ, Obekpa PO, Smith AN, Brydon WG. Diagnosis of acute pancreatitis: a proposed sequence of biochemical investigations. Scand J Gastroenterol. 1987;22:719–24.
5. Jang T, Uzbielo A, Sineff S, Naunheim R, Scott MG, Lewis LM. Point-of-care urine trypsinogen testing for the diagnosis of pancreatitis. Acad Emerg Med. 2007;14:29–34.
6. Petrov MS, Gordetzov AS, Emelyanov NV. Usefulness of infrared spectroscopy in diagnosis of acute pancreatitis. ANZ J Surg. 2007;77(5):347–51.
7. Sáez J, Martínez J, Trigo C, Sánchez-Payá J, Compañy L, Laveda R, et al. Clinical value of rapid urine trypsinogen-2 test strip, urinary trypsinogen activation peptide, and serum and urinary activation peptide of carboxypeptidase B in acute pancreatitis. World J Gastroenterol. 2005;11:7261–5.
8. Chen YT, Chen CC, Wang SS, Chang FY, Lee SD. Rapid urinary trypsinogen-2 test strip in the diagnosis of acute pancreatitis. Pancreas. 2005;30:243–7.
9. Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P, Hedström J, Haapiainen R, Korvuo A, et al. Comparison of urine trypsinogen-2 test strip with serum lipase in the diagnosis of acute pancreatitis. Hepatogastroenterology. 2002;49:1130–4.
10. Wilson RB, Warusavitarne J, Crameri DM, Alvaro F, Davies DJ, Merrett N. Serum elastase in the diagnosis of acute pancreatitis: a prospective study. ANZ J Surg. 2005;75:152–6.
11. Pace BW, Bank S, Wise L, Burson LC, Borrero E. Amylase isoenzymes in the acute abdomen: an adjunct in those patients with elevated total amylase. Am J Gastroenterol. 1985;80:898–901.
12. Raty S, Sand J, Nordback I. Detection of postoperative pancreatitis after pancreatic surgery by urine trypsinogen strip test. Br J Surg. 2007;94:64–9.
13. Koehler DF, Eckfeldt JH, Levitt MD. Diagnostic value of routine isoamylase assay of hyperamylasemic serum. Gastroenterology. 1982;82:887–90.
14. Malfertheiner P, Kemmer TP. Clinical picture and diagnosis of acute pancreatitis. Hepatogastroenterology. 1991;38:97–100.
15. Corsetti JP, Arvan DA. Acute pancreatitis. Diagnostic strategies for common medical problems. 2nd ed. Philadelphia: American College of Physician; 1999. p. 205.
16. Ohtsuki M, Kihara Y, Kikuchi K, et al. National epidemiological research of acute pancreatitis; 2004 Report. Tokyo: The Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare; 2005. p. 56–63.
17. Staniland JR, Ditchburn J, De Dombal FT. Clinical presentation of acute abdomen: study of 600 patients. Br Med J. 1972;3(823):393–8.
18. Read G, Braganza JM, Howat HT. Pancreatitis: a retrospective study. Gut. 1976;17:945–52.
19. Brewer BJ, Golden GT, Hitch DC, Rudolf LE, Wangensteen SL. Abdominal pain. An analysis of 1,000 consecutive cases in a University Hospital emergency room. Am J Surg. 1976;131(2):219–23.
20. Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. Scand J Gastroenterol Suppl. 1988;144:47–50.
21. de Dombal F. Acute abdominal pain: an O.M.G.E. survey. Scand J Gastroenterol. 1979;56(suppl):29–43.
22. de Dombal FT. Diagnosis of acute abdominal pain. 2nd ed. London: Churchill Livingstone; 1991. p. 19–30.
23. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut. 2005;54:1–9.
24. Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:25–32.
25. Sargent S. Pathophysiology, diagnosis and management of acute pancreatitis. Br J Nurs. 2006;15:999–1005.
26. Banks PA, Freeman ML, the Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379–400.
27. Smith RC, Southwell-Keely J, Chesher D. Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? ANZ J Surg. 2005;75:399–404.
28. Agarwal N, Pitchumoni CS, Sivaprasad AV. Evaluating tests for acute pancreatitis. Am J Gastroenterol. 1990;85:356–66.
29. Dervenis C, Johnson CD, Bassi C, Bradley E, Imrie CW, McMahon MJ, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini consensus conference. Int J Pancreatol. 1999;25:195–210.
30. Vissers RJ, Abu-Laban RB, McHugh DF. Amylase and lipase in the emergency department evaluation of acute pancreatitis. J Emerg Med. 1999;17:1027–37.
31. Nordestgaard AG, Wilson SE, Williams RA. Correlation of serum amylase levels with pancreatic pathology and pancreatitis etiology. Pancreas. 1988;3:159–61.
32. Apple F, Benson P, Preese L, Eastep S, Bilodeau L, Heiler G. Lipase and pancreatic amylase activities in tissues and in patients with hyperamylasemia. Am J Clin Pathol. 1991;96:610–4.
33. Orebaugh SL. Normal amylase levels in the presentation of acute pancreatitis. Am J Emerg Med. 1994;12:21–4.

34. Gumaste V, Dave P, Sereny G. Serum lipase: a better test to diagnose acute alcoholic pancreatitis. Am J Med. 1992;92:239–42.
35. Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P, Hedström J, Haapiainen R, Perhoniemi V, et al. Reliable screening for acute pancreatitis with rapid urine trypsinogen-2 test strip. Br J Surg. 2000;87:49–52.
36. Clavien PA, Robert J, Meyer P, Borst F, Hauser H, Herrmann F, et al. Acute pancreatitis and normoamylasemia. Not an uncommon combination. Ann Surg. 1989;210:614–20.
37. Eckfeldt JH, Kolars JC, Elson MK, Shafer RB, Levitt MD. Serum tests for pancreatitis in patients with abdominal pain. Arch Pathol Lab Med. 1985;109:316–9.
38. Ventrucci M, Pezzilli R, Naldoni P, Plate L, Baldoni F, Gullo L, et al. Serum pancreatic enzyme behavior during the course of acute pancreatitis. Pancreas. 1987;2:506–9.
39. Toskes PP. Hyperlipidemic pancreatitis. Gastroenterol Clin N Am. 1990;19:783–91.
40. Swensson EE, King ME, Malekpour A, Maull KI. Serum amylase isoenzyme alterations in acute abdominal conditions. Ann Emerg Med. 1985;14:421–3.
41. Holdsworth PJ, Mayer AD, Wilson DH, Flowers MW, McMahon MJ. A simple screening test for acute pancreatitis. Br J Surg. 1984;71:958–9.
42. Gunn IR, Faye S, Clayton MG. Prospective evaluation of urinary amylase test strip. Lancet. 1986;1:1161.
43. Werner M, Steinberg WM, Pauley C. Strategic use of individual and combined enzyme indicators for acute pancreatitis analyzed by receiver-operator characteristics. Clin Chem. 1989;35:967–71.
44. Buchler M, Malfertheiner P, Uhl W, Beger HG. Diagnostic and prognostic value of serum elastase 1 in acute pancreatitis. Klin Wochenschr. 1986;64:1186–91.
45. Flamion B, Delhaye M, Horanyi Z, Delange A, Demanet H, Quenon M, et al. Comparison of elastase-1 with amylase, lipase, and trypsin-like immunoreactivity in the diagnosis of acute pancreatitis. Am J Gastroenterol. 1987;82:532–5.
46. Millson CE, Charles K, Poon P, Macfie J, Mitchell CJ. A prospective study of serum pancreatic elastase-1 in the diagnosis and assessment of acute pancreatitis. Scand J Gastroenterol. 1998;33:664–8.
47. Ventrucci M, Pezzilli R, Gullo L, Plate L, Sprovieri G, Barbara L. Role of serum pancreatic enzyme assays in diagnosis of pancreatic disease. Dig Dis Sci. 1989;34:39–45.
48. Schroder T, Lempinen M, Kivilaakso E, Nikki P. Serum phospholipase A2 and pulmonary changes in acute fulminant pancreatitis. Resuscitation. 1982;10:79–87.
49. Nishijima J, Okamoto M, Ogawa M, Kosaki G, Yamano T. Purification and characterization of human pancreatic phospholipase A2 and development of a radioimmunoassay. J Biochem. 1983;94:137–47.
50. Sankaralingam S, Wesen C, Barawi M, Galera R, Lloyd L. Use of the urinary trypsinogen-2 dipstick test in early diagnosis of pancreatitis after endoscopic retrograde cholangiopancreatography. Surg Endosc. 2007;21:1312–5.
51. Warshaw AL, Fuller AF Jr. Specificity of increased renal clearance of amylase in diagnosis of acute pancreatitis. N Engl J Med. 1975;292:325–8.
52. Stein GN, Kalser MH, Sarian NN, Finkelstein A. An evaluation of the roentgen changes in acute pancreatitis: correlation with clinical findings. Gastroenterology. 1959;36:354–61.
53. Brascho DJ, Reynolds TN, Tanca P. The radiographic "colon cutoff sign" in acute pancreatitis. Radiology. 1962;79:763–8.
54. Meyers MA, Evans JA. Effect of pancreatitis on the small bowel and colon: spread along mesenteric planes. AJR. 1973;199:151–65.
55. Pickhardt PJ. The colon cutoff sign. Radiology. 2000;215:387–9.
56. Silverstein W, Isikoff MB, Hill MC, Barkin J. Diagnostic imaging of acute pancreatitis: prospective study using CT and sonography. AJR. 1981;137:497–502.
57. Jeffrey RB Jr, Laing FC, Wing VW. Extrapancreatic spread of acute pancreatitis: new observations with real-time US. Radiology. 1986;159:707–11.
58. Bollen TL, van Santvoort HC, Besselink MGH, et al. Update on acute pancreatitis: ultrasound, computed tomography, and magnetic resonance imaging features. Semin Ultrasound CT MRI. 2007;28:371–83.
59. Ichikawa K, Idoguachi K, Tanaka H, et al. Classification of acute pancreatitis based on retroperitoneal extension: application of the concept of interfascial planes. Eur J Radiol. 2006;20:445–52.
60. Balthazar EJ, Freeny PC, van Sonnenberg E. Imaging and intervention in acute pancreatitis. Radiology. 1994;193:297–306.
61. Alexander ES, Clark RA, Federle MP. Pancreatic gas: indication of pancreatic fistula. AJR. 1982;139:1089–93.
62. Miller FH, Keppke AL, Dalal K, Ly JN, Kamler VA, Sica GT. MRI of pancreatitis and its complications: part 1. Acute pancreatitis. AJR. 2004;183:1637–44.
63. Kim YK, Ko SW, Kim CS, Hwang SB. Effectiveness of MR imaging for diagnosing mild forms of acute pancreatitis: comparison with MDCT. J Magn Reson Imaging. 2006;24:1324–49.
64. Morgan DE, Baron TH, Smith JK, Robbin ML, Kenney PJ. Pancreatic fluid collection prior to intervention: evaluation with MR imaging compared with CT and US. Radiology. 1997;203:773–8.
65. Hirota M, Kimura Y, Ishiko T, Beppu T, Yamashita Y, Ogawa M. Visualization of the heterogeneous internal structure of so-called "pancreatic necrosis" by magnetic resonance imaging in acute necrotizing pancreatitis. Pancreas. 2002;25:63–7.
66. Ward J, Chalmers AG, Guthrie AJ, Larvin M, Robinson PJ. T2-weighted and dynamic MRI in acute pancreatitis: comparison with contrast enhanced CT. Clin Radiol. 1997;52:109–14.
67. Piironen A, Kivisaari R, Kemppainen E, Laippala P, Koivisto AM, Poutanen VP, et al. Detection of severe acute pancreatitis by contrast-enhanced magnetic resonance imaging. Eur Radiol. 2000;10:354–61.
68. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc. 1998;48:1–10.
69. British Society of Gastroenterology. United Kingdom guidelines for the management of acute pancreatitis. Gut. 1998;42(suppl 2):S1–13.
70. Pezzilli R, Uomo G, Zerbi A, et al. Diagnosis and treatment of acute pancreatitis: the position statement of the Italian Association for the study of the pancreas. Dig Liver Dis. 2008;40:803–8.
71. Wang SS, Lin XZ, Tsai YT, et al. Clinical significance of ultrasonography, computed tomography, and biochemical tests in the rapid diagnosis of gallstone-related pancreatitis: a prospective study. Pancreas. 1988;3:153–8.
72. Ammori BJ, Boreham B, Lewis P, et al. The biochemical detection of biliary etiology of acute pancreatitis on admission: a revisit in the modern era of biliary imaging. Pancreas. 2003;26:e32–5.
73. Liu CL, Fan ST, Lo CM, et al. Clinico-biochemical prediction of biliary cause of acute pancreatitis in the era of endoscopic ultrasonography. Aliment Pharmacol Ther. 2005;22:423–31.
74. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. Am J Gastroenterol. 1984;89:1863–6.
75. Liu CL, Lo CM, Chan HKF, et al. Detection of choledocholithiasis by EUS in acute pancreatitis: a prospective evaluation in 100 consecutive patients. Gastrointest Endosc. 2001;54:325–30.

76. Fogel EL, Sherman S. Acute biliary pancreatitis: when should the endoscopist intervene? Gastroenterology. 2003;125:229–35.
77. Moon JH, Cho YD, Cha SW, et al. The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US. Am J Gastroenterol. 2005;100:1051–7.
78. Saifuddin A, Ward J, Radgway J, Chalmers AG. Comparison of MR and CT scanning in severe acute pancreatitis: initial experiences. Clin Radiol. 1993;48:111–6.
79. Hallal AH, Amortegui JD, Jeroukhimov IM, et al. Magnetic resonance cholangiopancreatography accurately detects common bile duct stones in resolving gallstone pancreatitis. J Am Coll Surg. 2005;200(6):869–75.
80. Makary MA, Duncan MD, Harmon JW, et al. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. Ann Surg. 2005;241(1):119–24.
81. Lomas DJ, Bearcroft PWP, Gimsa AE. MR cholangiopancreatography: prospective comparison of a breath-hold 2D projection technique with diagnostic ERCP. Eur Radiol. 1999;9:1411–7.
82. Hirohashi S, Hirohashi R, Uchida H, et al. Pancreatitis: evaluation with MR cholangiopancreatography in children. Radiology. 1997;203:411–5.
83. Chak A, Hawes RH, Cooper GS, et al. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. Gastrointest Endosc. 1999;49:599–604.
84. Liu CL, Lo CM, Chan JKF, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc. 2000;51:28–32.
85. Norton SA, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. Br J Surg. 2000;87:1650–5.
86. Frossard JL, Sosa-Valencia L, Amouyal G, et al. Usefulness of endoscopic ultrasonography in patients with "idiopathic" acute pancreatitis. Am J Med. 2000;109:196–200.
87. Kamisawa T, Egawa N, Matsumoto G, et al. Pancreatographic findings in idiopathic acute pancreatitis. J Hepatobiliary Pancreat Surg. 2005;12:99–102.
88. Kamisawa T, Tu Y, Nakajima H, et al. Acute pancreatitis and a long common channel. Abdom Imaging. 2007;32:365–9.

J Hepatobiliary Pancreat Sci (2010) 17:37–44
DOI 10.1007/s00534-009-0213-4

Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading

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Received: 1 August 2009 / Accepted: 1 September 2009 / Published online: 11 December 2009

Abstract The assessment of severity at the initial medical examination plays an important role in introducing adequate early treatment and the transfer of patients to a medical facility that can cope with severe acute pancreatitis. Under these circumstances, "criteria for severity assessment" have been prepared in various countries, including Japan, and these criteria are now being evaluated. The criteria for severity assessment of acute pancreatitis in Japan were determined in 1990 (of which a partial revision was made in 1999). In 2008, an overall revision was made and the new Japanese criteria for severity assessment of acute pancreatitis were prepared. In the new criteria for severity assessment, the diagnosis of severe acute pancreatitis can be made according to 9 prognostic factors and/or the computed tomography (CT) grades based on contrast-enhanced CT. Patients with severe acute pancreatitis are expected to be transferred to a specialist medical center or to an intensive care unit to receive adequate treatment there. In Japan, severe acute pancreatitis is recognized as being a specified intractable disease on the basis of these criteria, so medical expenses associated with severe acute pancreatitis are covered by Government payment.

This article is based on the studies first reported in the JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.

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Keywords Acute pancreatitis · Severity assessment · Contrast-enhanced computed tomography · Prognostic factor

Introduction

The severity of acute pancreatitis differs widely, ranging from mild cases in whom short-time remission is achieved to severe cases that are accompanied by fatal complications such as shock, organ failure and/or sepsis with infected pancreatic necrosis. The severity of acute pancreatitis is also closely associated with the validity of treatment selection. The assessment of severity at the initial medical examination plays a useful role in terms of the criteria for introducing adequate early treatment and for the transfer of patients to a medical facility that can cope with severe acute pancreatitis. Under these circumstances, "criteria for severity assessment" are under preparation in various countries, including Japan, and these criteria are now being evaluated. The criteria for severity assessment of acute pancreatitis in Japan were prepared in 1990 (of which a partial revision was made in 1999) [1]. In 2008, an overall revision was made and New Japanese criteria for assessment of severity of acute pancreatitis were prepared. In the new severity assessment criteria, the diagnosis of severe acute pancreatitis can be made according to nine prognostic factors and/or the computed tomography (CT) grade, determined on the basis of contrast-enhanced CT. Patients with severe acute pancreatitis are expected be transferred to a specialist medical center or to an intensive care unit (ICU) to receive treatment there.

We present below a list of clinical questions (CQ) about the new criteria together with recommendation levels for their use.

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CQ1. Are clinical signs and symptoms, blood tests, and BMI useful for severity assessment of acute pancreatitis?

Clinical signs and symptoms alone are not reliable in severity assessment and they should be supported by objective measures (Recommendation A).

Acute pancreatitis presents with a wide spectrum of clinical signs and symptoms suggesting dysfunction of the major organs or abdominal complications. These signs and symptoms have also been used as factors in severity assessment in some criteria for reported to date [1–5]. On the other hand, United Kingdom guidelines (1988) [6] showed that clinical assessment alone is low in terms of reliability. The rate of occurrence of wrong assessment (classification) is about 50%. United Kingdom guidelines of 2005 also showed that severity assessment should be supplemented by laboratory data, because of low reliability of clinical assessment within 24 h following hospitalization [7]. Comprehensive assessment should be made for severity classification of acute pancreatitis.

The level of CRP is considered to be a reliable parameter that suggests the worsening of pancreatitis (Level 1c–2b) [8–10]. The Santorini consensus conference (1999) [11], the World Congress of Gastroenterology guidelines (2002) [12], and the United Kingdom guidelines (2005) [7] recommend as a prognostic factor a cut-off level of CRP of more than 15 mg/dl detected 48 h after onset of the disease. Also, in the New Japanese criteria for severity assessment, CRP of more than 15 mg/dl is used as the 7th prognostic factor (2008). Furthermore, there is a report showing that a combination of CRP with other types of diagnostic criteria leads to improvement in the reliability of severity assessment [8].

The level of procalcitonin (PCT) is a prognostic factor that is more effective than CRP in predicting the worsening of acute pancreatitis [13]. On the other hand, it is also reported (Level 2b) that the level of PCT is a sign that is particularly effective in predicting the occurrence of pancreatic infections [14].

Reports from Western countries show that obesity has a strong effect on the worsening of acute pancreatitis. Especially, obesity with a body mass index (BMI; body weight [kg]/height^2 [m^2]) of 30 kg/m^2 or more is associated with significantly large numbers of severe cases, cases of abscess formation, and cases of death compared with findings in those with a BMI of less than 30 kg/m^2 (Level 2c–4) [15, 16]. Meta-analyses of four prospective studies showed that obese patient with acute pancreatitis had a high risk of aggravation of pancreatitis. However, obesity had no effect on the risk of death in acute pancreatitis [17]. World Congress of Gastroenterology Guidelines (2002)

[12] and the United Kingdom Guidelines (2005) [7] show that obesity is a sign that leads most easily exacerbation of acute pancreatitis. A recent report shows that obese patients with a BMI of 30 Kg/m^2 or more have a tendency to be aggravated easily, resulting in systemic inflammatory response reactions [18]. However, analysis of the national epidemiological survey in Japan conducted in 1999 (Level 3b) [19] showed that there were only a few cases of BMI of 30 kg/m^2 or more (25/852 cases) and that death occurred in only one case; it was noted that no significant difference was found in the number of deaths among these groups and that the absence of this difference in Japan arose from a lack of differences in the type of obesity among people of different ethnicities and in the rate of extreme obesity being low.

CQ2. Are Contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) useful for the severity assessment of acute pancreatitis?

Accurate diagnosis of the presence and range of pancreatic ischemia or necrosis requires contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI). (Recommendation A)

Because the presence or absence of pancreatic necrosis and the extent of inflammatory changes are closely associated with various types of complications and life-related prognosis, an accurate diagnosis of pancreatic necrosis should be made [20–22]. The assessment of signs including pancreatic enlargement, extension of inflammation to the parapancreatic tissue, fluid collection, pseudocysts, calcified gallstones causing acute pancreatitis, and calcified common bile duct stones can be made using plain CT. However, the diagnosis of pancreatic ischemia or necrosis, as well as the assessment of its extent requires contrast-enhanced CT (Level 1c) [23].

Contrast-enhanced CT is the most useful procedure for the differentiation of necrotized pancreatitis from edematous pancreatitis (Level 1c) [23]. A report from Greece concludes that, irrespective of the early dysfunction of the organ, the risk of death is low even in severe pancreatitis when it is of edematous nature (Level 4) [24].

Although there are some experimental reports on the possibility that CT using contrast medium will lead to the exacerbation of acute pancreatitis, this has not been verified in clinical settings [25–28]. In Japan, the use of contrast medium has been contraindicated in principle in patients with acute pancreatitis since 1976; however, there are no reports to date showing that its use has resulted in the worsening of acute pancreatitis. As for circumstances in other countries, there are no countries where the use of contrast medium is contraindicated on principle in acute pancreatitis, except for Korea, where the use of some types of contrast medium is contraindicated on principle.

CT severity index (Level 2b) [29] is achieved by combining and scoring those factors associated closely with prognosis, including the presence or absence of pancreatic necrosis, the extent of necrosis, and the extent of inflammatory changes around the pancreas. Also in Japan, Matsuno et al. [28] and Takeda and Matsuno [30] proposed a method of severity assessment by contrast-enhanced CT from the same viewpoint and reported its usefulness (Level 2b). The classification of contrast-enhanced CT grade is included in the present revised edition of the Criteria for Severity Assessment of Acute Pancreatitis sponsored by the Japanese Ministry of Health, Labour and Welfare (2008) [45]. However, when contrast-enhanced CT is performed, note should be taken of its side effects. In the new criteria for severity assessment (2008), the classification of the contrast-enhanced CT grade is presented independently of prognostic factors, and severity assessment can be made without using contrast-enhanced CT, which is not indispensable in the early phase of management.

The diagnosis of pancreatic necrosis can be made in almost 100% of cases by performing contrast-enhanced CT 4–10 days after the onset of the disease (Level 1b–2b) [20, 21, 23, 31]. However, several studies conducted in Western countries also show the usefulness of early contrast-enhanced CT performed during the hospital stay (within 36 or 48 h after hospitalization) for the severity assessment of acute pancreatitis (Level 2b) [32, 33]. The use of contrast-enhanced CT is desirable in cases where worsening of pancreatic necrosis is suspected.

Furthermore, similar to contrast-enhanced CT, there are reports showing the usefulness of contrast-enhanced MRI for the detection of pancreatic necrosis and the understanding of the progression of inflammation in the tissue around the pancreas (Level 2b) [34–36]. MRI has benefits in that it can be used without causing exposure to X-rays and because it supplies information about the bile duct and the pancreatic duct. On the other hand, MRI has some weak points in that bringing in metal objects such as an artificial ventilator into the laboratory is prohibited and coping with an emergency examination is difficult.

CQ3. Are severity scoring systems useful for assessing the severity of acute pancreatitis?

The severity scoring system is useful for assessing the severity and for deciding the treatment strategy and the need for transfer to a specialist unit. (Recommendation A)

Symptoms and clinical findings of acute pancreatitis are various and the subjective assessment of its severity is

often difficult. Several forms of severity scoring criteria have been determined for assessing severity to date. Although the severity assessment based on the Ranson score and the Glasgow score requires 48 h, it is reported that prediction of the worsening of the disease can be made in 70–80% of cases by using a scoring system [37–39].

The Acute Physiology and Chronic Health Evaluation (APACHE) II score has been found to be useful for the assessment of acute pancreatitis. In the Atlanta symposium (1992) [5] and the World Congress of Gastroenterology Guidelines (2002) [12], cases with a score of above 8 points are classified into the grade of "severe". In the Santorini consensus conference [11], a score of above 8 points is classified into the grade of "severe". However, it is reported that, when the APACHE II score of above 6 points is classified into the grade of "severe", the sensitivity is assessed as being high (95%), but the positive predictive value is 40% [40]. Larvin has shown that the APACHE II score has a sensitivity of 65% and specificity of 76% during hospital stay, and a sensitivity of 76% and a specificity of 84% at 48 h after hospitalization, and that the difference between the Ranson score and the Glasgow score was not so large [41]. A detailed examination conducted on the basis of the total data of the national epidemiological research in Japan showed that the Japanese criteria have similar assessing ability to that of the Ranson score and the APACHE II score [42].

CQ4. Is the new Japanese severity scoring system useful for assessing the severity of acute pancreatitis?

The new Japanese severity scoring system is useful for assessing the severity of acute pancreatitis (Recommendation A)

The Japanese severity scoring system (1999) and the stage classification have been used widely in Japan because they reflect a good correlation between the classification of stage and the mortality rate. A rapid reduction in the mortality rate of acute pancreatitis has been achieved in recent years; the mortality rate of acute pancreatitis had fallen to 8.9% in the national survey of 2003 compared with 30% in the national survey of 1987 and 22% in the national survey of 1999. In Japan, severe acute pancreatitis is included in the category of a specified intractable disease and the medical expenses of severe acute pancreatitis are covered by government payment. In the Japanese old criteria, there were 18 items in the prognostic factors. This made the assessment based on those criteria extremely complicated and troublesome, which resulted in the overlap of similar prognostic factors. Shortcomings are also pointed out in that the CT grades do not reflect the prognosis of severe acute pancreatitis because the CT grades included in the prognostic factors were an assessment made by plain CT. For these reasons, the Research Committee for Intractable Disease of the Pancreas made a revision in the severity scoring system.

In the New Japanese criteria, prognostic factors and the contrast-enhanced CT grade are prepared so that severity assessment can be made according to both criteria (Table 1). Prognostic factors consist of the following 9 items: (1) base excess (BE) $\leqq -3$ mEq/L or shock: (systolic blood pressure <80 mmHg), (2) PaO_2 $\leqq 60$ mmHg (room air) or requiring respirator management, (3) blood urea nitrogen (BUN) $\geqq 40$ mg/dl (or creatinine [Cr] $\geqq 2.0$ mg/dl) or oliguria after fluid replacement, (4) lactic dehydrogenase (LDH) $\geqq 2$ times of upper limit of normal, (5) platelet count $\leqq 10 \times 10^4/mm^3$, (6) Ca $\leqq 7.5$ mg/dl, (7) CRP $\geqq 15$ mg/dl, (8) number of positive measures in SIRS criteria $\geqq 3$, and (9) age $\geqq 70$ years. Patients who satisfy more than 3 of the above 9 items are assessed as having severe acute pancreatitis. The contrast-enhanced CT grade is a classification for severity assessment made by the combination of 2 factors: the degree of extrapancreatic progression of inflammation and the extent of the poorly enhanced area that suggests the presence of pancreatic ischemia or necrosis, and cases of grade 2 or more are assessed as being severe (Table 1; Figs. 1, 2, 3).

A detailed examination of the new criteria conducted in 2006 according to the total data of the national survey of acute pancreatitis (including the data of cases from 1995 to 1998)found that the mortality rate was 29.3% in cases with a prognostic score of more than 3 points while it was 1.8% in cases with a prognostic score of under 2 points; a distinct difference was observed between the two categories. Furthermore, according to a report that assessed and examined the usefulness of the new assessment criteria by determining the area under curve by means of a receiver operating (ROC) analysis that used the mortality rate as a parameter, the new criteria (prognostic factors) were largely as useful as the old criteria, the Ranson Score, and the APACHE II score for severity assessment [43]. According to an examination of contrast-enhanced CT and the prognosis associated with its use, the mortality rate was 3.3% in cases of CT grade 1, 21.9% in cases of CT grade 2, and 33.3% in cases of CT grade 3 [44]. A prospective study conducted in 2007 showed that the mortality rate was 0% in cases with a prognostic score of under 2 points and 19.1% in cases with a prognostic score of more than 3 points. For contrast-enhanced CT, the mortality rate was 0% in cases of CT grade 1, 14.3% in cases of CT grade 2, and 15.4% in cases of CT grade 3. For complications of organ disorders, the rate was 4.3% in cases of CT grade1, 42.9% in cases of CT grade 2, and 46.2% in cases of CT grade 3. The mortality rate of cases that satisfied both the prognostic factors of more than 3 points and grade 2 of

Table 1 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 scores	
Total score = 0 or 1	Grade 1
Total score = 2	Grade 2
Total score = 3 or more	Grade 3
Assessment of severity	
(1) If prognostic factors are scored as 3 points or more, or (2) If CT Grade grade is judged as Grade 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	

contrast-enhanced CT was very high (30.8%) [45]. A prognostic score of 3 points in the new criteria is equivalent to that of 6–8 points in the old criteria [46]. The use of the new criteria for severity assessment resulted in a decrease by half in the number of cases of severe acute pancreatitis for which medical expenses are covered by Government payment [45, 46].

The new guidelines recommend that severity assessment is made at first on the basis of the prognostic factors that can be assessed at any time and everywhere, and that contrast-enhanced CT is performed in cases in which pancreatic necrosis is suspected by plain CT. It is also recommended that, in cases in which worsening of the disease is suspected, contrast-enhanced CT is performed even if the prognostic factor score is less than 2 points. Concerning advanced medical facilities that provide treatment for acute severe pancreatitis, it is recommended that the treatment policy is determined based on the understanding of the extent of the progress of inflammation and severity assessment.

CQ5. What are the indications for transferring patients with severe acute pancreatitis to a specialist unit?

Patients with severe acute pancreatitis (prognostic factor ≧3) assessed by the new Japanese criteria should be transferred promptly to a specialist medical institution.

As soon as the diagnosis of acute pancreatitis has been made, monitoring and fundamental treatment including adequate fluid replacement should be initiated. According to the guidelines of the British Society of Gastroenterology (1998) [6], when pancreatic necrosis of more than 50% or acute exudate collection is observed in multiple sites by contrast-enhanced CT, or when there is a complication of

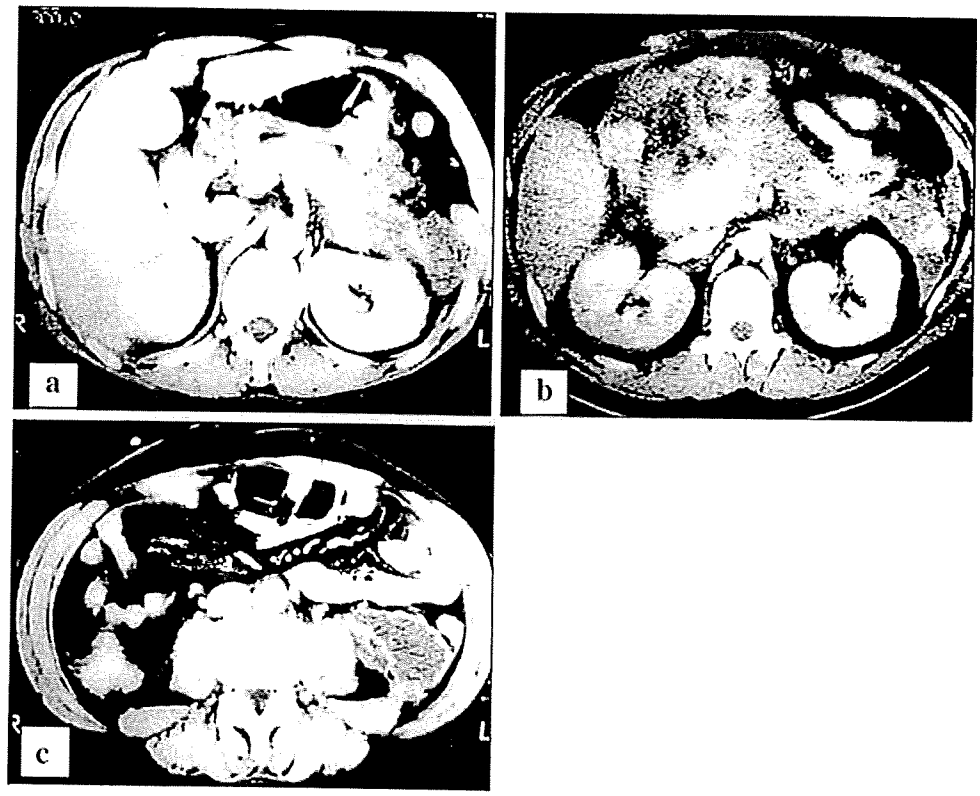

Fig. 1 Degree of extrapancreatic progression of inflammation in acute pancreatitis based on contrast-enhanced computed tomography. a Progression within anterior pararenal space (0 point), b progression to root of mesocolon (1 point), c progression to retroperitoneal space beyond lower pole of kidney (2 points)

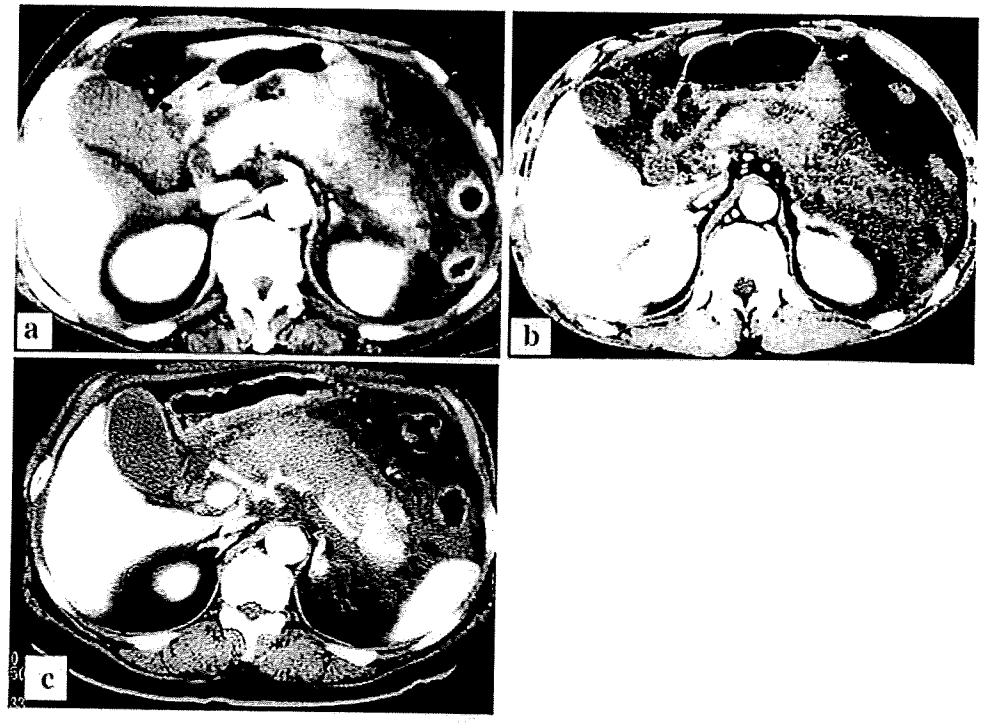

Fig. 2 Extent of hypoenhanced lesion of the pancreas based on contrast-enhanced computed tomography (*CT*). a Hypoenhanced lesion is localized in the tail of the pancreas (0 point), b hypoenhanced lesion is localized in the entire tail and part of the body of the pancreas (1 point), c hypoenhanced lesion is localized in the entire gland, except for part of the tail of the pancreas (2 points)

organ dysfunction, it is recommended that these criteria become criteria for patient transfer to a specialist medical facility.

The Santorini consensus conference (1999) [11] determined obesity (BMI >30 kg/m^2), collection of pleural effusion, APACHE II score of more than 6, APACHE O

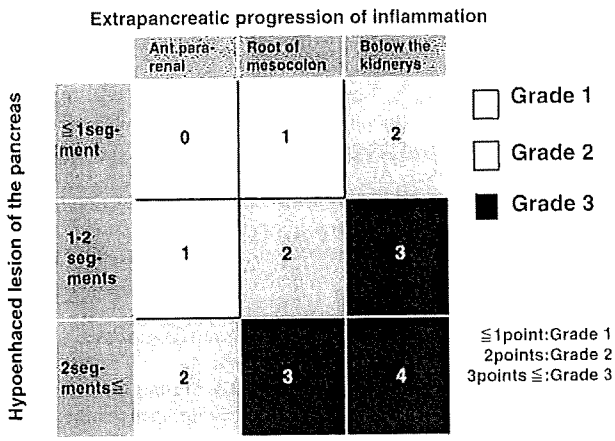

Fig. 3 Schematic matrix of progression of acute pancreatitis. CT Grade is a classification of severity assessment made by combining two factors: the degree of extrapancreatic progression of inflammation and the extent of hypoenhanced lesion of the pancreas based on contrast-enhanced CT. *Ant.*, Anterior

score (1 point is added to the APACHE II in cases of BMI of 25–30 kg/m^2 and 2 points in cases of BMI >30 kg/m^2, respectively) of more than 6, and CRP more than 15 mg/dL as the severity criteria and recommended these as the transfer criteria. The Practice Guidelines in Acute Pancreatitis (2006) [47] consider organ dysfunction as the most important reason for transfer and assess that patients with decreased blood pressure and renal failure(Cr >2.0 mg/dL)who show no response to hypoxia in particular and the initial fluid replacement should be transferred to the ICU immediately. In cases of acute pancreatitis in elderly patients with cardiac failure that require accurate determination of the fluid replacement dosage the Practice Guidelines also assess that those patients are indicated for transfer to achieve improvement in hemodynamic derangement. The Guidelines put forward ① BMI more than 30 kg/m^2, ② oliguria (<50 ml/h), ③ tachycardia (heart rate [HR], >120 bpm), ④ encephalopathy, and ⑤ increased dosage of sedatives as conditions that require attention, although emergency transfer is not needed.

Patients who have been assessed as having a prognostic score of more than 3 points (severe cases) according to the new Japanese criteria should be transferred to a medical facility or to an ICU that is in a position to cope with acute severe pancreatitis by providing ICU management, interventional radiology (IVR), continuous hemodiafiltration (CHDF), and/or endoscopic sphincterotomy (EST).

Because cases with a prognostic score of 2 points or less at the time of hospitalization often become worse depending upon the clinical course, those cases that have been assessed as being severe after repeated assessment of the prognostic score on the basis of the criteria for severity assessment, while receiving a sufficient dosage of fluid replacement and careful follow up, are indicated for transfer. Decision on the necessity for transfer should be made by taking into consideration the influence on the disease of the time spent for transfer.

References

1. Ogawa M, Hirota M, Hayasaka T, et al. Development and use of a new staging system for severe acute pancreatitis based on a nationwide survey in Japan. Pancreas. 2002;25:325–30.
2. Forell MM. Die konservative Behandulung der Pankreaserkrankungen. Der Internist. 1964;5:453–7.
3. Bank S, Wise L, Gersten M. Risk factors in acute pancreatitis. Am J Gastroenterol. 1983;78:637–40.
4. Imrie CW, Benjamin IS, Ferguson JC, et al. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. Br J Surg. 1978;65:337–41.
5. Bradley EL III. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993;128:586–90.
6. British Society of Gastroenterology. United Kingdom guidelines for the management of acute pancreatitis. Gut. 1998; 42 S2:1S–13S.
7. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut. 2005;54 Suppl III: iii1–iii9.
8. Viedma JA, Perez MM, Agullo J, et al. Inflammatory response in the early prediction of severity in human acute pancreatitis. Gut. 1994;35:822–7.
9. Pezzilli R, Billi P, Miniero R, et al. Serum interleukin-6, interleukin-8, and beta 2-microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. Dig Dis Sci. 1995;40:2341–8.
10. Uchikov PA, Sirakova IP, Murdjeva MA, Uchikov AP. Changes in plasma levels of acute phase proteins in pancreatitis. Folia Med (Plovdiv). 2000;42:23–30.
11. Dervenis C, Johnson CD, Bassi C, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini Consensus Conference. Int J Pancreatol. 1999;25:195–210.
12. Toouli J, Brooke-Smith M, Bassi C, et al. Working party of the program committee of the Bankok World Congress of Gastroenterology 2002. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol. 2002;17(Suppl):S15–39.
13. Skipworth RA, Pereira SP. Acute pancreatitis. Curr Opin Crit Care. 2008;14:172–8.
14. Rau BM, Kemppainen EA, Gumbs A, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenterstudy. Ann Surg. 2007;245:745–54.
15. Funnell IC, Bornman PC, Weakley SP, et al. Obesity: an important prognostic factor in acute pancreatitis. Br J Surg. 1993;80:484–6.
16. Martinez J, Sanchez PJ, Palazon JM, et al. Obesity: a prognostic factor of severity in acute pancreatitis. Pancreas. 1999;19:15–20.
17. Martinez J, Sanchez-Paya J, Palazon JM, et al. Is obesity a risk factor in acute pancreatitis? A meta-analysis. Pancreatology. 2004;4:42–8.
18. Sempere L, Martinez J, de Madaria E, et al. Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. Pancreatology. 2008;8:257–64.

19. Hirota M, Ogawa M. Obesity in acute pancreatitis. Kan-Tan-Sui. 2001;42:53–6. (in Japanese).
20. Vesentini S, Bassi C, Talamini G, et al. Prospective comparison of C-reactive protein level, Ranson score and contrast-enhanced computed tomography in the prediction of septic complications of acute pancreatitis. Br J Surg. 1993;80:755–7.
21. Kemppainen E, Sainio V, Haapiainen R, et al. Early localization of necrosis by contrast-enhanced computed tomography can predict outcome in severe acute pancreatitis. Br J Surg. 1996;83:924–9.
22. Bradley EL III, Murphy F, Ferguson C. Prediction of pancreatic necrosis by dynamic pancreatography. Ann Surg. 1989;210:495–503.
23. Larvin M, Chalmers AG, McMahon MJ. Dynamic contrast enhanced computed tomography: a precise technique for identifying and localizing pancreatic necrosis. BMJ. 1990;300:1425–8.
24. Lytras D, Manes K, Triantopoulou C, et al. Persistent early organ failure defining the high-risk group of patients with severe acute pancreatitis? Pancreas. 2008;36:249–54.
25. Carmona-Sanchez R, Uscanga L, Bezaury-Rivas P, et al. Potential harmful effect of Iodinated intravenous contrast medium on the clinical course of mild acute pancreatitis. Arch Surg. 2000;135:1280–4.
26. Hwang TL, Chang KY, Ho YP. Contrast-enhanced dynamic computed tomography does not aggravate the clinical severity of patients with severe acute pancreatitis. Reevaluation of the effect of intravenous contrast medium on the severity of acute pancreatitis. Arch Surg. 2000;135:287–90.
27. Uhl W, Roggo A, Kirschstein T, et al. Influence of contrast-enhanced computed tomography on course and outcome in patients with acute pancreatitis. Pancreas. 2002;24:191–7.
28. Matsuno S, Ogawa M, Takeda K et al. Annual report, 2001, Committee of Intractable Disease of the Pancreas, Japanese Ministry of Health, Labor and Welfare; 2001. p. 19–26 (in Japanese).
29. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990;174:331–6.
30. Takeda K, Matsuno S. Management of acute necrotizing pancreatitis based on CT grading. J Abdom Emerg Med. 1998;18:961–5. (in Japanese).
31. London NJ, Leese T, Lavelle JM, et al. Rapid-bolus contrast-enhanced dynamic computed tomography in acute pancreatitis: a prospective study. Br J Surg. 1991;78:1452–6.
32. Clavien PA, Hauser H, Meyer P, Rohner A. Value of contrast-enhanced computerized tomography in the early diagnosis and prognosis of acute pancreatitis. Am J Surg. 1988;155:457–66.
33. Rotman N, Chevret S, Pezet D, et al. Prognostic value of early computed tomographic scans in severe acute pancreatitis. J Am Coll Surg. 1994;179:538–44.
34. Hirota M, Kimura Y, Ishiko T, et al. Visualization of the heterogenous internal structure of so-called pancreatic necrosis by magnetic resonance imaging. Pancreas. 2002;25:63–7.
35. Ward J, Chalmers AG, Guthrie AJ, et al. T2-weighted and dynamic enhanced MRI in acute pancreatitis: comparison with contrast enhanced CT. Clin Radiol. 1997;52:109–14.
36. Lecesne R, Taourel P, Bret PM, et al. Acute pancreatitis: inter-observer agreement and correlation of CT and MR cholangiopancreatography with outcome. Radiology. 1999;211:727–36.
37. Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. Gut. 1984;25:1340–6.
38. Ranson JHC, Rifkind KM, Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Surg Gynecol Obstet. 1976;143:209–19.
39. Leese T, Shaw D. Comparison of three Glasgow multifactor prognostic scoring system in acute pancreatitis. Br J Surg. 1988;75:460–2.
40. Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. Br J Surg. 1990;77:1260–4.
41. Larvin M. Assessment of severity and prognosis in acute pancreatitis. Eur J Gastroenterol Hepatol. 1997;9:122–30.
42. Kitagawa M, Naruse T, Hayakawa T, et al. Prediction of exacerbation of acute pancreatitis. Suizou. 2005;20:17–30. (in Japanese).
43. Matsuno S, Takeda K, Kitagawa M et al. Annual report, 2005, Committee of Intractable Disease of the Pancreas, Japanese Ministry of Health, Labor and Welfare; 2005. p. 32–8 (in Japanese).
44. Matsuno S, Takeda K, Ogawa M, et al. Re-evaluation of CT Grade in acute pancreatitis. Suizou. 2002;7:93–9. (in Japanese).
45. Takeda K, Ootsuki M, Kihara Y et al. Annual report, 2008, Committee of Intractable Disease of the Pancreas, Japanese Ministry of Health, Labor and Welfare; 2008. p. 43–7 (in Japanese).
46. Yokoe M, Mayumi T, Hayashi K. Clinical evaluation of the revised staging system for acute pancreatitis in Japan. Suizou. 2009;24:140–6. (in Japanese).
47. Bank PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379–400.

J Hepatobiliary Pancreat Sci (2010) 17:45–52
DOI 10.1007/s00534-009-0210-7

Fundamental and intensive care of acute pancreatitis

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Received: 1 August 2009 / Accepted: 1 September 2009 / Published online: 12 December 2009

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

This article is based on the studies first reported in the JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.

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therapy and nutritional support are available. The disease condition in acute pancreatitis changes every moment and even symptoms that are mild at the time of diagnosis may become severe later. Therefore, severity assessment should be conducted repeatedly at least within 48 h following diagnosis. An adequate dose of fluid replacement is essential to stabilize cardiovascular dynamics and the dose should be adjusted while assessing circulatory dynamics constantly. A large dose of fluid replacement is usually required in patients with severe acute pancreatitis. Prophylactic antibiotic administration is recommended to prevent infectious complications in patients with severe acute pancreatitis. Although the efficacy of intravenous administration of protease inhibitors is still a matter of controversy, there is a consensus in Japan that a large dose of a synthetic protease inhibitor should be given to patients with severe acute pancreatitis in order to prevent organ failure and other complications. Enteral feeding is superior to parenteral nutrition when it comes to the nutritional support of patients with severe acute pancreatitis. The JPN Guidelines recommend, as optional continuous regional arterial infusion and blood purification therapy.

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

Introduction

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

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

Principles of medical management for acute pancreatitis

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

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

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

Calcium and potassium chloride should be replaced if deficiencies arise. Hyperglycemia is managed with insulin as needed. In patients with severe acute pancreatitis, continuous monitoring of central venous pressure or pulmonary wedge pressure, blood gas analysis, and electrolyte measurement is crucial to determining the adequate volume that must be replaced. Oxygen is administered as needed to maintain at least 95% oxygen saturation.

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

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

CQ 2. Is pain control by analgesia necessary?

The pain associated with acute pancreatitis is severe and persistent, so pain control is crucial in the management of acute pancreatitis. (Recommendation A)

The pain associated with acute pancreatitis may cause anxiety in patients and adversely affect their clinical course; this may include respiratory distress, which should be relieved shortly after it develops. The nonnarcotic analgesic buprenorphine has an effect superior to procaine, and, unlike procaine, it does not exacerbate the pathology of acute pancreatitis by including contracting of the sphincter of Oddi (Level 1b) [3]. Pentazocine has an analgesic effect superior to that of procaine (Level 1b) [4]. According to an randomized controlled trial (RCT) comparing metamizole and morphine, the analgesic effect was similar for both agents (Level 2b) [5].

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

Nasogastric suction is not necessary in mild acute pancreatitis except for cases that are accompanied by paralytic ileus and frequent vomiting. H_2 blockers are not required in an acute pancreatitis except for cases accompanying acute gastric mucosal lesion and hemorrhagic ulcer. On the contrary, H_2 blockers may increase the incidence of complications and prolong the duration of pain. (Recommendation D)

There are no definitive studies in humans to support the opinion that nasogastric suction is useful to the pancreas at rest in patients with acute pancreatitis. RCTs in patients with mild to moderate acute pancreatitis have shown no ameliorating effect of gastric suction on the clinical course by, for example, alleviating pain or shortening the hospital stay (Level 1b) [6–13]. Rather, there are some reports claiming that nasogastric suction may prolong the period of abdominal pain and nausea (Level 1b) [9–12]. The placement of a nasogastric tube in patients with acute pancreatitis is unnecessary unless the disease is associated with paralytic ileus and/or frequent vomiting.

There are no reports suggesting that cimetidine, an H_2 blocker, might ameliorate the clinical course of acute pancreatitis (Level 1b) [12–16]. According to a systematic review (Level 1a) [17], use of cimetidine resulted in a tendency to increase the incidence of complications associated with acute pancreatitis and to prolong the duration of pain. There are no reports of RCTs to date that examined the efficacy of proton pump inhibitors (PPI) in acute pancreatitis.

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

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

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

Pancreatic and extrapancreatic infections are a determining factor leading to death in severe acute pancreatitis. The mortality rate of patients with infected pancreatic necrosis or sepsis is extremely high, and antibiotic prophylaxis has been recommended to prevent infectious complications in severe acute pancreatitis. Three RCTs of the antibiotic ampicillin conducted in the 1970s showed that it did not reduce the frequency of infectious complications (Level 1b) [18–20]. A human study investigating pancreatic tissue penetration by antibiotics such as ciprofloxacin, ofloxacin, imipenem, and pefloxacine (pefloxacin) provided sufficient tissue concentration in the pancreas [21]. Four RCTs (Level 1b) [22–25] of the prophylactic effect of antibiotics demonstrated that broad-spectrum antibiotics with good pancreatic tissue penetration decreased the incidence of infectious complications and the mortality rate. RCTs investigating the prophylactic effects of imipenem demonstrated that imipenem decreased the occurrence of infectious pancreatic complications (Level 1b) [26, 27]. Two RCTs (Level 1b) [28, 29] that investigated the prophylactic effects of meropenem also showed a decrease in the occurrence of infectious complications and the occurrence of pancreatic infections, complications, or mortality was similar as that of imipenem [28].

On the other hand, a placebo-controlled, double-blind trial of ciprofloxacin + metronidazole in patients with predicted severe acute pancreatitis showed that prophylactic administration of these antibiotics did not prevent pancreatic infection (Level 1b) [30]. According to an RCT that examined the prophylactic effects of meropenem in patients with necrotizing pancreatitis, the incidence and mortality rates of pancreatic infections and the rate of cases that required surgical intervention were not different from those in a placebo-controlled group (Level 1a) [31].

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

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

Selective digestive decontamination (SDD) has also been reported as a means of antibiotic prophylaxis in severe acute pancreatitis (Level 1b) [38]. Although SDD was reported in the 1980s as a method of preventing respiratory tract infection in patients with multiple trauma [39], only one RCT assessed SDD in severe acute pancreatitis (Level 1b) [38]. In that trial, antibiotics were given orally, enterally, and intravenously, as well as being applied topically to the gums and tracheotomy site. SDD significantly reduced the frequency of infectious pancreatic complications compared with that in the control groups, and multivariate analysis with severity assessment demonstrated a reduced mortality rate for SDD. In principle, SDD offers comprehensive infection management, not only by the enteral administration of nonabsorptive agents but also by the prevention of systemic infection through sterilization of the oral cavity, as well as by intravenous antibiotic administration and continuous surveillance cultures of the oral cavity and rectum.

Although the prophylactic application of broad-spectrum antibiotics reduces the incidence of infectious complications in severe acute pancreatitis, fungal infection in pancreatic necrosis is increasing (Level 2b) [40–45]. The mortality rate of infected pancreatic necrosis complicated by fungal infection is higher than the mortality rate in the absence of fungal infection (Level 2b) [40–45]. A human study reported that the antifungal agent fluconazole had good penetration into pancreatic tissue (Level 2b) [46], and clinical studies have demonstrated that the prophylactic administration of fluconazole reduced the incidence of fungal infection in patients with severe acute pancreatitis (Level 2b) [44–47]. However, there have been no reliable RCTs of the prophylactic administration of antifungal agents in patients with pancreatic necrosis, and the efficacy of antifungal agents has yet to be investigated in an RCT.

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

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

In the 1960s, the protease inhibitor aprotinin was widely used to treat severe acute pancreatitis, but the drug failed to demonstrate clinical efficacy in three RCTs (Level 1b) [48–50]. The efficacy of the synthetic protease inhibitor gabexate mesilate was investigated in five RCTs (Level 1b) [51–55], but a meta-analysis of four of them [51–54] showed no reduction in the frequency of surgical intervention or in the mortality rate, although the incidence of complications was reduced (Level 1a) [56]. However, the remaining RCT (Level 1b) [55], the results of which were published in 2000, showed that continuous intravenous administration of gabexate mesilate (2400 mg/day) for 7 days significantly reduced the frequency of complications and the mortality rate. According to a meta-analysis (Level 1a) [57] of ten RCTs (6 trials of gabexate mesilate [51–53, 55, 58, 59] and 4 trials of aprotinin [49, 50, 60, 61]) reported in 2004, use of protease inhibitors did not lead to a decreased mortality rate in patients with acute pancreatitis. On the other hand, a meta-analysis concerning the data sampled from patients with moderate ~ severe acute pancreatitis showed that the mortality rate decreased significantly owing to the infusion of protease inhibitors.

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

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

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

Clinical trials of nutritional management in acute pancreatitis have shown that enteral nutrition is more useful than total parenteral nutrition in terms of ability to alleviate the inflammatory response and reduce the incidence of infection, frequency of surgery, and medical costs. A meta-analysis (Level 1a) [62] of six RCTs (263 cases; Level 1b) [63–68]—which compared two methods of nutritional management of acute pancreatitis (total parental nutritional and enteral nutrition)—showed that enteral nutrition reduced the frequency of infection, surgery, and the length of hospital stay. However, there was no difference in the mortality rate or incidence of complications other than infection.

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