for acute gallstone pancreatitis. Br J Surg. 1993;80:247. (Level of treatment/prevention 4).
54. Tate JJ, Lau WY, Li AK. Laparoscopic cholecystectomy for biliary pancreatitis. Br J Surg. 1994;81:720–2. (Level of treatment/prevention 4).
55. Ballestra-Lopez C, Bastida-Vila X, Bettonica-Larranaga C, et al. Laparoscopic management of acute biliary pancreatitis. Surg Endosc. 1997;11:718–21. (Level of treatment/prevention 4).
56. Ricci F, Castaldini G, de Manzoni G, et al. Minimally invasive treatment of acute biliary pancreatitis. Surg Endosc. 1997;11: 1179–82. (Level of treatment/prevention 4).
57. Uhl W, Muller CA, Krahenbuhl L, et al. Acute gallstone pancreatitis: timing of laparoscopic cholecystectomy in mild and severe disease. Surg Endosc. 1999;13:1070–6. (Level of treatment/prevention 4).
58. Chang L, Lo S, Stabile BE, et al. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: a prospective randomized trial. Ann Surg. 2000;231:82–7. (Level of treatment/prevention 1b).
59. Rijna H, Borgstein PJ, Meuwissen SG, et al. Selective preoperative endoscopic retrograde cholangiopancreatography in laparoscopic biliary surgery. Br J Surg. 1995;82:1130–3. (Level of treatment/prevention 4).
60. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol. 2007;102:1781–8. (Level of etiology/adverse effects 4).
61. Griniatsos J, Karvounis E, Isla A. Early versus delayed single-stage laparoscopic eradication for both gallstones and common bile duct stones in mild acute biliary pancreatitis. Am Surg. 2005;71(8):682–6. (Level of treatment/prevention 4).
62. Campbell-Lloyd AJ, Martin DJ, Martin IJ. Long-term outcomes after laparoscopic bile duct exploration: a 5-year follow up of 150 consecutive patients. ANZ J Surg. 2008;78:492–4.

J Hepatobiliary Pancreat Sci (2010) 17:70–78
DOI 10.1007/s00534-009-0220-5

Post-ERCP pancreatitis

Shinju Arata · Tadahiro Takada · Koichi Hirata · Masahiro Yoshida · Toshihiko Mayumi · Morihisa Hirota · Masamichi Yokoe · Masahiko Hirota · Seiki Kiriyama · Miho Sekimoto · Hodaka Amano · Keita Wada · Yasutoshi Kimura · Toshifumi Gabata · Kazunori Takeda · Keisho Kataoka · Tetsuhide Ito · Masao Tanaka

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

Abstract Pancreatitis remains the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP). Detailed information about the findings of previous studies concerning post-ERCP pancreatitis has not been utilized sufficiently. The purpose of the present article was to present guidelines for the diagnostic criteria of post-ERCP pancreatitis, and its incidence, risk factors, and prophylactic procedures that are supported by evidence. To achieve this purpose, a critical examination was made of the articles on post-ERCP pancreatitis, based on the data obtained by research studies published up to 2009. At present, there are no standardized diagnostic criteria for post-ERCP pancreatitis. It is appropriate that post-ERCP pancreatitis is defined as acute pancreatitis that has

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.

S. Arata (✉)
Critical Care and Emergency Center, Yokohama City University School of Medicine, 4-57 Urafune, Minami, Yokohama 232-0024, Japan
e-mail: s_arata@yokohama-cu.ac.jp

T. Takada · H. Amano · K. Wada
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

K. Hirata · Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University Graduate School of Medicine, Sapporo, Japan

M. Yoshida
Department of Hemodialysis and Surgery, Clinical Research Center, Kaken Hospital, International University of Health and Welfare, Chiba, Japan

T. Mayumi
Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

Morihisa Hirota
Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

M. Yokoe
General Internal Medicine, Japanese Red Cross Society Nagoya Daini Hospital, Nagoya, Japan

Masahiko Hirota
Department of Surgery, Kumamoto Regional Medical Center, Kumamoto, Japan

S. Kiriyama
Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

M. Sekimoto
Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan

T. Gabata
Department of Radiology, Graduate School of Medical Science, Kanazawa University, Ishikawa, Japan

K. Takeda
Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai, Japan

K. Kataoka
Otsu Municipal Hospital, Otsu, Japan

T. Ito
Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

M. Tanaka
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

developed following ERCP, and its diagnosis and severity assessment should be made according to the diagnostic criteria and severity assessment of the Japanese Ministry of Health, Labour and Welfare. The incidence of acute pancreatitis associated with diagnostic and therapeutic ERCP is 0.4–1.5 and 1.6–5.4%, respectively. Endoscopic papillary balloon dilation is associated with a high risk of acute pancreatitis compared with endoscopic sphincterotomy. It was made clear that important risk factors include dysfunction of the Oddi sphincter, being of the female sex, past history of post-ERCP pancreatitis, and performance of pancreaticography. Temporary prophylactic placement of pancreatic stents in the high-risk group is useful for the prevention of post-ERCP pancreatitis [odds ratio (OR) 3.2, 95% confidence interval (CI) 1.6–6.4, number needed to treat (NNT) 10]. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduction in the development of post-ERCP pancreatitis (OR 0.46, 95% CI 0.32–0.65). Single rectal administration of NSAIDs is useful for the prevention of post-ERCP pancreatitis [relative risk (RR) 0.36, 95% CI 0.22–0.60, NNT 15] and decreases the development of pancreatitis in both the low-risk group (RR 0.29, 95% CI 0.12–0.71) and the high-risk group (RR 0.40, 95% CI 0.23–0.72) of post-ERCP pancreatitis. As for somatostatin, a bolus injection may be most useful compared with short- or long-term infusion (OR 0.271, 95% CI 0.138–0.536, risk difference 8.2%, 95% CI 4.4–12.0%). The usefulness of gabexate mesilate was not apparent in any of the following conditions: acute pancreatitis (control 5.7 vs. 4.8% for gabexate mesilate), hyperamylasemia (40.6 vs. 36.9%), and abdominal pain (1.7 vs. 8.9%). Formulation of diagnostic criteria for post-ERCP pancreatitis is needed. Temporary prophylactic placement of pancreatic stents in the high-risk group offers the most promise as a means of preventing post-ERCP pancreatitis. As for pharmacological attempts, there are high expectations concerning NSAIDs because they are excellent in terms of cost-effectiveness, ease of use, and safety. There was no evidence of effective prophylaxis with the use of protease inhibitors, especially gabexate mesilate.

Keywords Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis · Pancreatitis · Guidelines · ERCP · Complications

Introduction

The first edition of the Guidelines for the Management of Acute Pancreatitis that was based on evidence was published in 2003 with the cooperation of the Japanese Society of Abdominal Emergency Medicine, the Japan Pancreas Society, and a Research Group of the Ministry of Health, Labour and Welfare of Japan. An English-language version of the Guidelines was published in 2006 [1]. A revised second edition was published in 2007 on the basis of a detailed examination mainly of new related studies that had been reported since 2003. In 2008, a revision was made of the Japanese diagnostic criteria and the criteria for severity assessment. Accordingly, a third Japanese edition that included the latest evidence was prepared [2].

Pancreatitis remains the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP) and there are many studies that report on its incidence, risk factors, and prophylactic procedures. However, detailed information about previous reports has not been utilized sufficiently in Japan. There is a possibility that diagnostic examinations will be insufficient or that adequate prophylactic treatment may not be delivered to high-risk patients. A chapter on the management of post-ERCP pancreatitis was included de novo in the third edition of the Guidelines for the Management of Acute Pancreatitis [2].

In the present article, we present the results of a search for references, mainly of studies published until January 2009, through PubMed and the internet edition of the Japana Centra Revuo Medicina; we collected and included references concerning the diagnostic criteria, incidence, risk factors, and prevention of post-ERCP pancreatitis. Further search for references was conducted in a manual fashion as needed. Critical appraisals of references obtained through these procedures were made. Evidence obtained was put in order and recommended management procedures were formulated taking into account the opinions of specialists and actual medical circumstances. The evidence obtained from each item was evaluated in accordance with the scientific classification method used at the Cochrane Library (Level and Recommendation) [3]. The recommendation grades were classified in A, B, C1, C2, D [4].

Diagnosis of post-ERCP pancreatitis

CQ1: Are there any diagnostic criteria for post-ERCP pancreatitis ?

There are no standardized diagnostic criteria.

Post-ERCP pancreatitis refers to a condition that presents with clinical signs of acute pancreatitis following ERCP and is accompanied by elevated levels of pancreatic enzymes, although, according to present knowledge, there are no standardized criteria for the timing of blood collection and the cutoff values of pancreatic enzymes. As for the diagnostic criteria, the severity classification by Cotton et al. [5] (Table 1; Level 5) is generally used, although there are problems associated with promptness in diagnosis and inability of severity assessment to be made in the early phase of the disease.

Table 1 Severity classification of post-ERCP pancreatitis by Cotton et al.

Mild	Moderate	Severe
Clinical pancreatitis, amylase at least 3 times normal at more than 24 h after the procedure, requiring admission or prolongation of planned admission to 2–3 days	Pancreatitis requiring hospitalization of 4–10 days	Hospitalization for more than 10 days, or hemorrhagic pancreatitis, necrosis, or pseudocyst, or intervention (percutaneous drainage or surgery)

From Ref. [5] with some modification

ERCP Endoscopic retrograde cholangiopancreatography

According to present knowledge, post-ERCP pancreatitis is defined as acute pancreatitis that has occurred de novo following ERCP. The diagnosis and severity assessment of post-ERCP pancreatitis in Japan should be made according to the diagnostic criteria for acute pancreatitis and the criteria for severity assessment of the Japanese Ministry of Health, Labour and Welfare. Prior endoscopic procedures that induce pancreatitis include endoscopic sphincterotomy (ES) and endoscopic papillary balloon dilation (EPBD).

Incidence of post-ERCP pancreatitis

There are several reports on the incidence of complications associated with diagnostic ERCP and therapeutic ERCP in which ES or EPBD is undertaken simultaneously. The incidence of acute pancreatitis associated with the use of diagnostic ERCP is reported to be 0.4–1.5% (Level 2b) [6–8]. The incidence of acute pancreatitis induced by therapeutic ERCP is high compared with that induced by diagnostic ERCP (Level 1b–2b) [9, 10] at 1.6–5.4% (Level 1b–2b) [6, 7, 9–11] and that of severe acute pancreatitis induced by diagnostic ERCP is 0.4–0.7% (Level 2b–4) [8, 12]. The risk of acute pancreatitis associated with EPBD is high compared with that associated with ES [relative risk (RR) 1.98, 95% confidence interval (CI) 1.35–2.90] (Level 1a) [13].

According to studies of 21 medical facilities in Japan, acute pancreatitis occurred in 166 (1.1%) of 14,947 cases in which diagnostic and/or therapeutic ERCP was performed during the 4 years, 1995–1998. The incidence of acute pancreatitis was 0.8% with diagnostic ERCP and 1.9% with therapeutic ERCP. On the other hand, the incidence of severe acute pancreatitis was 0.07% with diagnostic ERCP and 0.1% with therapeutic ERCP. There was 1 case of death with therapeutic ERCP and the overall mortality rate was 0.007%. The mortality rate was 0.02% when the cases involved were limited to therapeutic ERCP (Level 4) [14]. The incidence of acute pancreatitis was reported to be 5–20% in cases in which EPBD was undertaken in operations for common bile duct stones (Level 4) [15].

Risk factors of post-ERCP pancreatitis

A meta-analysis of 15 prospective cohort studies and 52 retrospective cohort studies that examined the risk factors of post-ERCP pancreatitis found that the risk factors for acute pancreatitis associated with ERCP included dysfunction of the Oddi sphincter (RR 4.09, 95% CI 3.37–4.96), being of the female sex (RR 2.23, 95% CI 1.75–2.84), and a past history of pancreatitis (RR 2.46, 95% CI 1.93–3.12; Level 2a) [16]. It was also reported that the absence of bile duct dilation (Level 2b) [6], bile duct diameter of <1 cm (Level 2b) [11, 17–19], Younger age (Level 2b) [6, 20], difficult cannulation (Level 1b–2b) [11, 21, 22], and performance of pancreatography (Level 1b–4) [6, 18, 23–25] were risk factors for acute pancreatitis.

Prevention of post-ERCP pancreatitis

CQ2. Are there any preventive procedures for post-ERCP pancreatitis ?

Prophylactic pancreatic stent placement is useful in the high-risk group* of post-ERCP pancreatitis. (Recommendation B)

As for pharmacological prophylaxis, there is a possibility that nonsteroidal anti-inflammatory drugs (NSAIDs) will be useful. (Recommendation C1)

There is insufficient evidence supporting the usefulness of combined use of pancreatic stent placement and NSAIDs.

There is a possibility that bolus injection of somatostatin will be useful.**

*Cases with a definitive diagnosis of dysfunction of the Oddi sphincter or suspected cases, cases in which cannulation is difficult, cases with EPBD, and cases with precut sphincterotomy (refer to the following text and Tables 1, 2).

**Note: In Japan, somatostatin is not on the market, but octreotide (Sandostatin®, Novartis, East Hanover, NJ, USA), an analogue of somatostatin, is on the market. For details, refer to the following text.

Prophylactic endoscopic procedures

Prophylactic temporary placement of pancreatic stents

As far as prophylactic temporary placement of pancreatic stents in the high-risk group of post-ERCP pancreatitis is

Table 2 Effects of prophylactic pancreatic stent placement in post-ERCP pancreatitis

Reference	Number of cases	Age (years; SEM)	Proportion of females (%)	Reasons for indicated stent placement				Cases of occurrence of pancreatitis		OR (95% CI)	*P* value
				SOD suspected	Difficult cases of cannulation	Precut	EBD	Placement group	No-placement group		
Smithline et al. [27]	93	47	38	+	+	+	−	6/43	9/50	0.73 (0.25, 2.27)	0.60
Sherman et al. [28]	104			+	+	+	−	1/46	8/58	0.13 (0.017, 1.15)	0.03
Tarnasky et al. [29]	80	45.7 ± 2.2	73	+	+	−	−	3/41	10/39	0.07 (0.01, 0.59)	0.003
Aizawa and Ueno [30]	130	68.21 ± 4	43	−	−	−	+	0/38	6/92	0.17 (0.009, 3.14)	0.18
Fazel et al. [31]	74	44.6 ± 2.2	86	+	+	−	−	2/38	10/36	0.14 (0.02, 0.71)	0.009

From Ref. [26] with some modification

SOD Sphincter of Oddi dysfunction, *EBD* endoscopic balloon dilatation

concerned, there is a meta-analysis of 5 prospective studies including 4 randomized controlled trials (RCTs; 481 cases; Level 1a) [26] (Table 2) [27–31] (Level 1a–2b). Included in the high risk group in the 5 studies were cases with a definitive diagnosis of dysfunction of the sphincter of Oddi or suspected cases, those in which cannulation was difficult, those with EPBD, and those with precut sphincterotomy. The incidence of post-ERCP pancreatitis was 5.8% in the group in which stents were placed and 15.5% in the group in which no stent was placed, showing that pancreatic stent placement was useful [odds ratio (OR) 3.2, 95% CI 1.6–6.4]. As for the incidence of post-ERCP pancreatitis according to severity, the incidence of mild to moderate post-ERCP pancreatitis was lower in the stent group (12/206 vs. 36/275) and no significant difference was observed between the 2 groups, although there were no severe cases in the stent placement group (0/206 vs. 7/275). The ARR (absolute risk reduction) was 0.1 and the number needed to treat (NNT) was 10, which means that 10 cases of pancreatic stent placement are required to prevent 1 case of post-ERCP pancreatitis.

A review (Level 5) [32] concerning the reports published between January 1966 and January 2004 expressed almost the same opinions as those in the above-quoted meta-analysis. Cost-effectiveness, risks, and clinical benefits should be taken into account when pancreatic stents are placed.

An RCT (Level 1b) [33] published in 2007 reported on 201 cases in which spontaneous stent dislodgement occurred found that the incidence of post-ERCP pancreatitis was 3.2% in the group in which stents were placed and 13.6% in the group in which no stent was placed ($P = 0.019$), and that there was also a significant reduction in the development of hyperamylasemia. An RCT conducted in Japan in 2007 asserted that there was a tendency similar to that reported in the previous studies, but failed to show a significant difference between stented and unstented groups because the number of cases (64 cases) was small (Level 1b) [34].

Table 3 Indications for pancreatic stent placement to reduce risk of post-ERCP pancreatitis

Generally recommended indications
SOD (suspected or documented)
Previous post-ERCP pancreatitis
Difficult cannulation involving pancreatic instrumentation or injection
Precut sphincterotomy starting at orifice (after pancreatic instrumentation)
Pancreatic sphincterotomy (major or minor papilla)
Aggressive instrumentation of pancreatic duct (such as brush cytology)
Balloon dilatation of intact sphincter
Endoscopic ampullectomy
Not generally recommended indications
Low-risk patients (older, obstructive jaundice, obstructed pancreatic duct)
Needle-knife precut or fistulotomy starting above orifice, in absence of other risks
Pancreatic duct not injected with contrast, and limited pancreatic guidewire manipulation in otherwise low-risk patient
Doubtful feasibility of successful pancreatic wire access and stent placement

From Ref. [35] with some alterations

SOD Sphincter of Oddi dysfunction

In 2007, Freeman [35] asserted the usefulness of prophylactic pancreatic stent placement on the basis of a detailed examination of the previous reports, and summarized its indications (Table 3) (Level 5).

Other endoscopic procedures

There are reports of several RCTs concerning endoscopic procedures other than prophylactic pancreatic stent placement. According to studies of conventional cannulation using contrast medium and cannulation using a guidewire, there was no significant difference between the 2 methods in terms of the development of post-ERCP pancreatitis (Level 1b) [36, 37]. Some RCTs (Level 1b) [38, 39] have asserted the usefulness of a procedure that uses a needle knife.

The evidence is weak that supports the recommendation of the use of a single procedure, so a safe procedure should be selected by taking into account the equipment at facilities and the skills of the operators.

Pharmacological prophylaxis

There are many studies of pharmacological prophylaxis of post-ERCP pancreatitis. According to a detailed examination of the above review [32] reported in 2004 (Level 5), most of the studies failed to show clearly the usefulness of prophylactic use of drugs (Table 4). Important factors responsible for this result are pointed out, including the lack of a high-risk group in patient selection, the case mix, and/or the variety of criteria used to define post-ERCP pancreatitis. Even with the 2 most promising agents for the prevention of post-ERCP at that time, gabexate mesilate and somatostatin, problems were pointed out, such as the long time required for administration and the cost-effectiveness (the NNT is 35 for gabexate mesilate), especially in outpatients.

Discussion follows concerning the results of examinations of individual drugs based mainly on the data in meta-analyses and RCTs that were reported recently.

NSAIDs

According to a meta-analysis of 6 RCTs concerning the administration of NSAIDs in a total of 1,300 patients, post-ERCP pancreatitis was significantly lower in the group in which NSAIDs were administered (652 cases, including 271 cases in which diclofenac was used and 381 cases in which indomethacin was used; 8.9 vs. 16.8%; OR 0.46, 95% CI 0.32–0.65, $P < 0.0001$; Level 1a) [40]. There were no side effects associated with the use of NSAIDs. Of these 6 RCTs, a meta-analysis of 4 RCTs evaluating a rectally administered drug involving a total of 912 patients (456 patients received a placebo, 160 patients received diclofenac 100 mg, and 296 received indomethacin 100 mg) reported that the single use of NSAIDs just before or after ERCP was useful in preventing post-ERCP pancreatitis (4.4 vs. 12.5%; RR 0.36, 95% CI 0.22–0.60, NNT 15; Level 1a) [41]. A subgroup analysis of the same 4 RCTs reported that, in the group in which NSAIDs were administered, there was a significant decrease in post-ERCP pancreatitis in both the low-risk group (RR 0.29, 95% CI 0.12–0.71, $P = 0.006$) and the high-risk group (RR 0.40, 95% CI 0.23–0.72, $P = 0.002$; Level 1a) [42]. Of the 4 RCTs, 2 studies referred to pancreatic stent placement. In one study, prophylactic pancreatic stents were not placed in either group; in the other study, stents were placed in 13 patients in the drug administration group and in 12 patients in the placebo group, although subgroup analysis was not conducted. The reason that stent placement was indicated was not mentioned.

Table 4 Pharmacological attempts to reduce risk of post-ERCP pancreatitis

Medication	Assessment	Results of meta-analyses since 2007	Results of recent RCTs
Calcium inhibitors	Ineffective		
Lidocaine (local administration)	Ineffective		
Nitroglycerin	Possibly effective		
Antibiotics	Possibly effective		
Nonionic contrast medium	Ineffective		
Steroid	Ineffective	Ineffective	
PAF inhibitors	Ineffective		
IL-10	Ineffective		
Heparin	Ineffective		
NSAID	Possibly effective	Effective	
Gabexate mesilate			
Short-term infusion	Ineffective	Ineffective	Effective
Long-term infusion	Effective	Ineffective	
Octreotide	Ineffective	Ineffective	
Somatostatin			
Short-term infusion	Ineffective	Ineffective	
Long-term infusion	Possibly effective	Possibly effective	
Bolus injection		Effective	
Allopurinol	Ineffective	Ineffective	
N-acetylcysteine			Ineffective
Ulinastatin			Possibly ineffective
Semapimod			Possibly effective

From Ref. [32] with alterations

RCT Randomized controlled trial, *PAF* Platelet activating factor, *IL* interleukin, *NSAID* nonsteroidal anti-inflammatory drug

In Western countries, a 100-mg suppository and a 100-mg tablet of both diclofenac and indomethacin are on the market and the maximum dosage per administration is 100 mg. In Japan, only medication with a maximum dose of 50 mg is on the market and the ordinary dosage is 25–50 mg per administration. At present, the prophylactic effect of the use of 50 mg of such medication against post-ERCP pancreatitis is not known. According to the sales data of a company concerning the use of Voltaren®, Novartis, East Hanover, NJ, USA (diclofenac) suppositories, the incidence of side effects caused by the administration of 25–50 mg/was 1.76% (301/17,094) and the incidence of side effects caused by the administration of 50–100 mg was 0.52% (1/191). However, side effects of other types of NSAIDs (phenylbutazone and oxyphenbutazone) were reported in many countries in 1984, so the dosage was re-examined and the upper dosage/administration limit was reduced in 1985 in Japan. Consideration of the dosage for prophylactic use is needed in Japan.

Gabexate mesilate

A meta-analysis of 4 RCTs on gabexate mesilate concluded that gabexate mesilate was ineffective in the prevention of post-ERCP pancreatitis, (OR 0.67, 95% CI 0.31–1.47) and it failed to show usefulness in the prevention of severe pancreatitis, death, hyperamylasemia, and abdominal pain (Level 1a) [43]. According to a meta-analysis that took note of the administration schedule (Level 1a) [44], the incidence of post-ERCP pancreatitis after long-term infusion (12 h) was decreased by 5.2% (95% CI 1.1–9.4%, $P = 0.01$), but a significant difference was not observed in the development of hyperamylasemia. An examination of short-term infusion (within 12 h) failed to show usefulness both in post-ERCP pancreatitis (difference in the incidence −1.1%, 95% CI −3.8 to 1.6%) and in hyperamylasemia.

A third meta-analysis (Level 1a) [45] of the 5 RCTs including all of the RCTs examined by two meta-analyses mentioned already (Level 1a) [43, 44] found that the incidence of post-ERCP pancreatitis was 5.7% in the control group vs. 4.8% in the administration group and concluded that gabexate mesilate was not useful in the prevention of post-ERCP pancreatitis and also in reducing hyperamylasemia (40.6% vs. 36.9%) and abdominal pain (1.7% vs. 8.9%). A meta-analysis of long-term infusion of gabexate mesilate conducted by 2 RCTs also failed to show its usefulness in the prevention of post-ERCP pancreatitis. According to a recent report (Level 1b) [46], the incidence of post-ERCP pancreatitis was 3.9% (8/203) in the group in which 500 mg/6 h of gabexate mesilate was administered prior to ERCP (preoperative group), 3.4% (7/203) in the group in which 500 mg/6 h of gabexate mesilate was administered after ERCP (post-operative group), and 9.4% (19/202) in the control group, showing that a significant decrease was observed in the group (3.7%; 15/406) in which gabexate mesilate was administered compared with the control group ($P < 0.01$). There was no significant difference between the preoperative group and the post-operative group, so gabexate mesilate administration is recommended post-operatively only in patients with a high risk.

Somatostatin and octreotide

According to a meta-analysis (Level 1a) [44] that paid attention to the administration schedule of somatostatin, long-term infusion (12 h) was associated with a decrease of post-ERCP pancreatitis by 7.7% (95% CI 3.4–12.0%, $P < 0.0001$), and somatostatin was also found to be useful in hyperamylasemia ($P = 0.017$). Short-term infusion (within 12 h) failed to show usefulness either in post-ERCP pancreatitis (difference in the incidence −2.3%, 95% CI −5.2 to 0.5%) or in hyperamylasemia. The examination of 670 cases in which bolus injection was conducted (4 μg/kg or 250 μg just before catheter insertion or just after diagnostic ERCP; 337 vs. 333) found that bolus injection reduced post-ERCP pancreatitis by 8.2% (95% CI 4.4–12.0%, $P < 0.0001$) and that it was also useful in hyperamylasemia ($P = 0.001$). The study asserted that bolus injection was most likely to be useful in consideration of its practical utility in clinical settings. According to a meta-analysis (Level 1a) [45] of 9 RCTs that included all RCTs contained in the meta-analysis mentioned above [44], the incidence of acute pancreatitis was 7.3% (96/1,309) in the control group and 5.3% (72/1,349) in the treatment group (OR 0.73, 95% CI 0.54–1.006, RR 0.734, 95% CI 0.535–1.006), showing that there was no significant difference between the 2 groups. An examination of 4 RCTs of short-term infusion and 3 RCTs of long-term infusion found that the incidence of post-ERCP pancreatitis in the control group vs. the treatment group was 6.4 vs. 11.8% and 6.4 vs. 2.9%, respectively, showing that there was no significant difference. Similar to the meta-analyses mentioned already, a study of the bolus injection group in 3 RCTs showed that the bolus injection was useful in the prevention of post-ERCP pancreatitis (OR 0.271, 95% CI 0.138–0.536, difference in incidence 8.2%, 95% CI 4.4–12.0, NNT 12, 95% CI 8–23) and hyperamylasemia. Another RCT was also conducted in 2008 (Level 1b) [47]. A study of 391 cases in which therapeutic ERCP was undertaken showed that the incidence of post-ERCP pancreatitis was significantly lower in the group in which somatostatin administration continued for 12 h starting from 30 min before ERCP (3.6% in the treatment group vs. 9.6% in the placebo group, $P = 0.02$). As far as octreotide is concerned, there is a meta-analysis of 15 RCTs. The overall examination of a total of 2,621 cases failed to show the usefulness of

octreotide in the prevention of post-ERCP pancreatitis (OR 0.78, 95% CI 0.57–1.08; Level 1a) [48]. However, when the analysis was limited to a total of 1,714 cases including cases in 5 RCTs that studied more than 200 cases, it was found that post-ERCP pancreatitis was decreased significantly by octreotide (OR 0.50, 95% CI 0.32–0.79, $P = 0.003$, NNT 31).

Allopurinol

An examination concerning allopurinol was conducted in a total of 1,554 cases; 783 cases in the treatment group and 771 cases in the control group, based on 6 RCTs but the study failed to show treatment effects on any of the following conditions: post-ERCP pancreatitis (OR 0.74, 95% CI 0.37–1.48, $P = 0.40$), severe post-ERCP pancreatitis (OR 0.87, 95% CI 0.33–2.28, $P = 0.78$), or hyperamylasemia (OR 0.88, 95% CI 0.37–2.11, $P = 0.78$), or death (OR 0.19, 95% CI 0.01–3.91, $P = 0.28$; Level 1a) [49]. Furthermore, an examination of 4 RCTs, including an RCT reported in 2008, also failed to show a significant difference in the incidence of post-ERCP pancreatitis between allopurinol-treated and allopurinol-untreated groups (8.9 vs. 9.7%, $P = 0.68$, RR 0.86, 95% CI 0.42–1.77; Level 1a) [50].

Steroids

There is a meta-analysis of 7 RCTs concerning steroid use, which concluded that steroid use had no effect on post-ERCP pancreatitis (OR 1.13, 95% CI 0.89–1.44, $P = 0.32$), severe acute pancreatitis (OR 1.61, 95% CI 0.74–3.52, $P = 0.23$), or hyperamylasemia (OR 0.92, 95% CI 0.57–1.48, $P = 0.73$), and that prophylactic use of steroid cannot be recommended (Level 1a) [51].

N-acetylcysteine

According to 2 RCTs, the use of *N*-acetylcysteine, which was expected to act as a free radical scavenger, was found to be ineffective in preventing post-ERCP pancreatitis (Level 1b) [52, 53].

Ulinastatin

A report from Japan on a multicenter RCT concerning ulinastatin found a significantly lower incidence of post-ERCP pancreatitis in the treatment group compared with the control group [2.9% (6/204) vs. 7.4% (15/202), $P = 0.041$; Level 1b] [54]. The report defined post-ERCP pancreatitis as a condition that is accompanied by abdominal pain continuing for more than 24 h following ERCP, or elevated levels of pancreatic enzymes (amylase or lipase) of more than 3 times the upper limit of normal at 18 h after ERCP, but a significant difference was not observed in the incidence of abdominal pain [8.8% (18/204) vs. 14.4% (29/202)]. An RCT reported in 2006 compared a group with a high dosage of ulinastatin (450,000 units), a group with low dosage (150,000 units), and a group treated with gabexate mesilate (900 mg) and found that the incidence of post-ERCP pancreatitis was 3/46 (6.5%), 4/47 (8.5%), and 2/46 (4.3%), respectively, showing that a difference was not observed among the groups (Level 1b) [55]. Furthermore, an RCT was reported in 2007 comparing a group with ulinastatin administration (150,000 units) and a group with gabexate mesilate administration (600 mg); that study found that the incidence of post-ERCP pancreatitis was similar in both groups [2.9% (1/34); Level 1b] [56]. Neither the 2006 report [55] nor the 2007 report [56] found any superiority of gabexate mesilate over ulinastatin, and the effectiveness of gabexate mesilate is being denied according to present knowledge. According to an RCT of 227 cases limited to a high-risk group by considering cost-effectiveness, post-ERCP pancreatitis occurred in 6.7% of patients in the treatment group (100,000 units of ulinastatin) and in 5.6% in the placebo group. Accordingly, the RCT concluded that ulinastatin was not useful in the prevention of post-ERCP pancreatitis (Level 1b) [57].

Mitogen-activated protein kinase inhibitor

An RCT of 242 patients treated with semapimod, a synthetic guanylhydrazone that inhibits the phosphorylation of p38 mitogen-activated protein kinase, found a significant reduction of post-ERCP hyperamylasemia in the group that underwent a single use of semapimod (29.8% in the placebo group vs. 18.4% in the treatment group, $P = 0.031$), but failed to detect a significant difference in the incidence of post-ERCP pancreatitis (14.9% in the placebo group vs. 9.1% in the treatment group, $P = 0.117$). There were no serious side effects associated with the use of semapimod (Level 1b) [58].

Conclusion

The formulation of reliable and standardized diagnostic criteria for post-ERCP pancreatitis is needed (Level 5) [59]. As far as the prevention of post-ERCP pancreatitis is concerned, placement of pancreatic stents in the high-risk group would be useful according to present knowledge. Concerning pharmacological prophylaxis, NSAIDs are most strongly recommended in terms of cost-effectiveness, ease of use, and safety. Because studies that have been carried out to date concern only a small number of cases,

further studies are required. Bolus injection of somatostatin is expected to be useful, although the number of cases that have been studied is also small. The usefulness of protease inhibitors, which are used widely in Japan, gabexate mesilate in particular, is equivocal. So it is thought that the cost-effectiveness would be low, unless such agents are used only in limited cases.

References

1. Takada T, Kawarada Y, Hirata K, et al. JPN Guidelines for the management of acute pancreatitis: cutting-edge information. J Hepatobiliary Pancreat Surg. 2006;13:2–6.
2. Takada T, Hirata K, Mayumi T, Yoshida M, Tanaka M, Shimosegawa T, et al. JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.
3. Centre for Evidence-based Medicine Homepage. Levels of evidence and grades of recommendations. http://www.cebm.net/levels_of_evidence.asp#levels)2009.
4. Takada T, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, et al. Cutting-edge information for the management of acute pancreatitis. J Hepatobiliary Pancreat Surg. 2009. doi:10.1007/s00534-009-0216-1.
5. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37:383–93. (Diagnostic level 5).
6. Loperfido S, Angelini G, Benedetti G, et al. Major early complications from diagnostic and therapeutic ERCP: prospective multicenter study. Gastrointest Endosc. 1998;48:1–10. (Treatment level 2b).
7. Lenriot Aurc JP, Le Neel JC. Catheteisme retrograde et sphincterotomie endoscopique: evaluation prospective en milieu chirurgical (in French). Gastroenterol Clin Biol. 1993;17:244–50. (Treatment level 2b).
8. Reiertsen O, Skjoto J, Jacobsen CD, Rossel AR. Complications of fiberoptic gastrointestinal endoscopy—five years' experience in a central hospital. Endoscopy. 1987;19:1–6. (Treatment level 2b).
9. Sherman S, Hawes RH, Rathgaber SW, et al. Post-ERCP pancreatitis: randomized, prospective study comparing a low-and high-osmolality contrast agent. Gastrointest Endosc. 1994;40:422–7. (Etiologic level 1b).
10. Johnson GK, Geenen JE, Bedford RA, et al. A comparison of nonionic versus ionic contrast media: results of retrospective, multicenter study. Midwest Pancreaticobiliary Study Group. Gastrointest Endosc. 1995;42:312–6. (Etiologic level 1b).
11. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335:909–18. (Etiologic level 2b).
12. Escourrou J, Cordova JA, Lazorthes F, Frexinos J, Ribet A. Early and late complications after endoscopic sphincterotomy for biliary lithiasis with and without the gall bladder in situ. Gut. 1984;25:598–602. (Etiologic level 4).
13. Weinberg BM, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Database Syst Rev. 2006;18:CD004890. PMID17054222 (Etiologic level 1a).
14. Atomi Y, Saisyo H, Hayakawa T, Akashi R, Kumada T, Shiratori K, et al. A study of endoscopic papillary treatment: a research study of intractable pancreatic diseases, vol. 12. Study by the Ministry of Health, Labour and Welfare of Heisei; 2001, p. 47–53 (Etiologic level 4).
15. Tsujino T, Isayama H, Komatsu Y, et al. Risk factors for pancreatitis in patients with common bile duct stones managed by endoscopic papillary balloon dilation. Am J Gastroenterol. 2005;100(1):38–42. (Etiologic level 4).
16. Masci E, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. Endoscopy. 2003;35(10):830–4. (Etiologic level 2a).
17. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. Gastroenterology. 1991;101(4):1068–75. (Etiologic level 2b).
18. Chen YK, Foliente RL, Santoro MJ, Walter MH, Collen MJ. Endoscopic sphincterotomy-induced pancreatitis: increased risk associated with nondilated bile ducts and sphincter of Oddi dysfunction. Am J Gastroenterol. 1994;89(3):327–33. (Etiologic level 2b).
19. Dickinson RJ, Davies S. Post-ERCP pancreatitis and hyperamylasaemia: the role of operative and patient factors. Eur J Gastroenterol Hepatol. 1998;10(5):423–8. (Etiologic level 2b).
20. Deans GT, Sedman P, Martin DF, et al. Are complications of endoscopic sphincterotomy age related? Gut. 1997;41(4):545–8. (Etiologic level 2b).
21. De Palma GD, Catanzano C. Use of corticosteroids in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. Am J Gastroenterol. 1999;94(4):982–5. (Etiologic level 1b).
22. Poon RT, Yeung C, Lo CM, Yuen WK, Liu CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. Gastrointest Endosc. 1999;49(5):593–8. (Etiologic level 1b).
23. Roszler MH, Campbell WL. Post-ERCP pancreatitis: association with urographic visualization during ERCP. Radiology. 1985;157:595–8. (Etiologic level 4).
24. Johnson GK, Geenen JE, Johanson JF, Sherman S, Hogan WJ, Cass O. Evaluation of post-ERCP pancreatitis: potential causes noted during controlled study of differing contrast media. Midwest Pancreaticobiliary Study Group. Gastrointest Endosc. 1997;46:217–22. (Etiologic level 1b).
25. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. Gabexate in digestive endoscopy—Italian Group. N Engl J Med. 1996;335(13):919–23. (Etiologic level 1b).
26. Singh P, Das A, Isenberg G, Wong RC, et al. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. Gastrointest Endosc. 2004;60:544–50. (Treatment/prevention level 1a).
27. Smithline A, Silverman W, Rogers D, et al. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. Gastrointest Endosc. 1993;39:652–7. (Treatment/prevention level 1b).
28. Sherman S, Bucksot EL, Esber E, et al. Does leaving a main pancreatic duct stent in place reduce the incidence of precut biliary sphincterotomy-induced pancreatitis? Randomized prospective study. Am J Gastroenterol. 1995;90:241. (Treatment/prevention level 1b).
29. Tarnasky PR, Palesch YY, Cunningham JT, et al. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology. 1998;115:1518–24. (Treatment/prevention level 1b).
30. Aizawa T, Ueno N. Stent placement in the pancreatic duct prevents pancreatitis after endoscopic sphincter dilation for removal of bile duct stones. Gastrointest Endosc. 2001;54:209–13. (Treatment/prevention level 2b).

31. Fazel A, Quadri A, Catalano MF, et al. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc. 2003;57:291–4. (Treatment/prevention level 1b).
32. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc. 2004;59:845–64. (Treatment/prevention level 5).
33. Sofuni A, Maguchi H, Itoi T, et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol. 2007;5:1339–46. (Treatment/prevention level 1b).
34. Tsuchiya T, Itoi T, Sofuni A. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. J Hepatobiliary Pancreat Surg. 2007;14:302–7. (Treatment/prevention level 1b).
35. Freeman ML. Pancreatic stents for prevention of post-endoscopic cholangiopancreatography pancreatitis. Clin Gastroenterol Hepatol. 2007;5:1354–65. (Treatment/prevention level 5).
36. Bailey AA, Bourke MJ, Williams SJ, et al. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. Endoscopy. 2008;40:296–301. (Treatment/prevention level 1b).
37. Katsinelos P, Paroutoglou G, Kountouras J, et al. A comparative study of standard ERCP catheter and hydrophilic guide wire in the selective cannulation of the common bile duct. Endoscopy. 2008;40:302–7. (Treatment/prevention level 1b).
38. Varadarajulu S, Wilcox CM. Randomized trial comparing needle-knife and pull-sphincterotome techniques for pancreatic sphincterotomy in high-risk patients. Gastrointest Endosc. 2006; 64:716–22. (Treatment/prevention level 1b).
39. Khatibian M, Sotoudehmanesh R, Ali-Asgari A, et al. Needle-knife fistulotomy versus standard method for cannulation of common bile duct: a randomized controlled trial. Arch Iran Med. 2008;11:16–20. (Treatment/prevention level 1b).
40. Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. Hepatobiliary Pancreat Dis Int. 2009;8:11–6. (Treatment/prevention level 1a).
41. Elmunzer BJ, Waljee AK, Elta GH, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut. 2008;57:1262–7. (Treatment/prevention level 1a).
42. Zheng MH, Xia HH, Chen YP. Rectal administration of NSAIDs in the prevention of post-ERCP pancreatitis: a complementary meta-analysis. Gut. 2008;57:1632–3. (Treatment/prevention level 1a).
43. Zheng M, Chen Y, Yang X, et al. Gabexate in the prophylaxis of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2007;7:6–13. (Treatment/prevention level 1a).
44. Rudin D, Kiss A, Wetz RV, et al. Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. J Gastroenterol Hepatol. 2007;22:977–83. (Treatment/prevention level 1a).
45. Andriulli A, Leandro G, Federici T, et al. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. Gastrointest Endosc. 2007;65:624–32. (Treatment/prevention level 1a).
46. Manes G, Ardizzone S, Lombardi G, et al. Efficacy of postprocedure administration of gabexate mesylate in the prevention of post-ERCP pancreatitis: a randomized, controlled, multicenter study. Gastrointest Endosc. 2007;65:982–7. (Treatment/prevention level 1b).
47. Lee KT, Lee DH, Yoo BM. The prophylactic effect of somatostatin on post-therapeutic endoscopic retrograde cholangiopancreatography pancreatitis: a randomized, multicenter controlled trial. Pancreas. 2008;37:445–8. (Treatment/prevention level 1b).
48. Bai Y, Gao J, Zou DW, et al. Prophylactic octreotide administration does not prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. Pancreas. 2008;37:241–6. (Treatment/prevention level 1a).
49. Zheng M, Chen Y, Bai J, et al. Meta-analysis of prophylactic allopurinol use in post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas. 2008;37:247–53. (Treatment/prevention level 1a).
50. Bai Y, Gao J, Zhang W, et al. Meta-analysis: allopurinol in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis. Aliment Pharmacol Ther. 2008;28:557–64. (Treatment/prevention level 1a).
51. Zheng M, Bai J, Yuan B, et al. Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis. BMC Gastroenterol. 2008;8:6. (Treatment/prevention level 1a).
52. Katsinelos P, Kountouras J, Paroutoglou G, et al. Intravenous *N*-acetylcysteine does not prevent post-ERCP pancreatitis. Gastrointest Endosc. 2005;62:105–11. (Treatment/prevention level 1b).
53. Milewski J, Rydzewska G, Degowska M, Kierzkiewicz M, Rydzewski A. *N*-acetylcysteine does not prevent post-endoscopic retrograde cholangiopancreatography hyperamylasemia and acute pancreatitis. World J Gastroenterol. 2006;12:3751–5. (Treatment/prevention level 1b).
54. Tsujino T, Komatsu Y, Isayama H, et al. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. Clin Gastroenterol Hepatol. 2005;3:376–83. (Treatment/prevention level 1b).
55. Fujishiro H, Adachi K, Imaoka T, et al. Ulinastatin shows preventive effect on post-endoscopic retrograde cholangiopancreatography pancreatitis in a multicenter prospective randomized study. J Gastroenterol Hepatol. 2006;21:1065–9. (Treatment/prevention level 1b).
56. Ueki T, Otani K, Kawamoto K, et al. Comparison between ulinastatin and gabexate mesylate for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized trial. J Gastroenterol. 2007;42:161–7. (Treatment/prevention level 1b).
57. Yoo JW, Ryu JK, Lee SH, et al. Preventive effects of ulinastatin on post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a prospective, randomized, placebo-controlled trial. Pancreas. 2008;37:366–70. (Treatment/prevention level 1b).
58. van Westerloo DJ, Rauws EA, Hommes D, et al. Pre-ERCP infusion of semapimod, a mitogen-activated protein kinase inhibitor, lowers post-ERCP hyperamylasemia but not pancreatitis incidence. Gastrointest Endosc. 2008;68:246–54. (Treatment/prevention level 1b).
59. Mine T, Akashi R, Ito T, et al. Progress of a prospective study concerning post–ERCP pancreatitis and its diagnostic criteria; 2008 Report. Tokyo: The intractable pancreatic disease investigation and research group of the Japanese Ministry of Health, Labour and Welfare. 2008. p. 37–43. (Diagnosis level 5).

J Hepatobiliary Pancreat Sci (2010) 17:79–86
DOI 10.1007/s00534-009-0218-z

Treatment strategy for acute pancreatitis

Keita Wada · Tadahiro Takada · Koichi Hirata · Toshihiko Mayumi · Masahiro Yoshida · Masamichi Yokoe · Seiki Kiriyama · Masahiko Hirota · Yasutoshi Kimura · Kazunori Takeda · Shinju Arata · Morihisa Hirota · Miho Sekimoto · Shuji Isaji · Yoshifumi Takeyama · Toshifumi Gabata · Nobuya Kitamura · Hodaka Amano

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

Abstract When a diagnosis of acute pancreatitis (AP) is made, fundamental medical treatment consisting of fasting, intravenous (IV) fluid replacement, and analgesics with a close monitoring of vital signs should be immediately started. In parallel with fundamental medical treatment, assessment of severity based on clinical signs, blood test, urinalysis and imaging tests should be performed to determine the way of treatment for each patient. A repeat evaluation of severity is important since the condition is unstable especially in the early stage of AP. At the time of initial diagnosis, the etiology should be investigated by means of blood test, urinalysis and diagnostic imaging. If a biliary pancreatitis accompanied with acute cholangitis or

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.

K. Wada (✉) · T. Takada · H. Amano
Department of Surgery, Teikyo University School of Medicine, 2-11-1, Kaga-cho, Itabashi, Tokyo 173, Japan
e-mail: wada@med.teikyo-u.ac.jp

K. Hirata · Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University Graduate School of Medicine, Sapporo, Japan

T. Mayumi
Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Yoshida
Department of Hemodialysis and Surgery, Clinical Research Center Kaken Hospital, International University of Health and Welfare, Chiba, Japan

M. Yokoe
General Internal Medicine, Japanese Red Cross Society Nagoya Daini Hospital, Nagoya, Japan

S. Kiriyama
Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

Masahiko Hirota
Department of Surgery, Kumamoto Regional Medical Center, Kumamoto, Japan

K. Takeda
Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai, Japan

S. Arata
Critical Care and Emergency Center, Yokohama City University Medical Center, Yokohama, Japan

Morihisa Hirota
Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

M. Sekimoto
Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan

S. Isaji
Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine, Mie, Japan

Y. Takeyama
Department of Surgery, Kinki University School of Medicine, Osaka, Japan

T. Gabata
Department of Radiology, Graduate School of Medical Science, Kanazawa University, Ishikawa, Japan

N. Kitamura
Department of Emergency and Critical Care Medicine, Kimitsu Chuo Hospital, Chiba, Japan

biliary stasis is diagnosed or suspected, an early endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES) is recommended in addition to the fundamental medical treatment. In mild cases, the fundamental medical treatment should be continued until clinical symptom is subsided with normal laboratory data. In cases with severe acute pancreatitis (SAP) referral should be considered to medical centers experienced in the treatment of SAP, and intensive care is recommended for preventing both organ failures and infectious complications. Hemodynamic stabilization with vigorous fluid resuscitation, respiratory support and antibiotics are the major parts of intensive care in the early period of SAP. Continuous hemodiafiltration (CHDF) and continuous regional arterial infusion (CRAI) of protease inhibitor and/or antibiotics may be effective to improve pathophysiology of AP especially in the early stage of the disease. In the late stage of AP, infectious complications are critical. If an infectious complication is suspected based on clinical signs, blood test and imaging, a fine needle aspiration (FNA) is recommended to establish a diagnosis. The accuracy of FNA is reported to be 89 ~ 100%. For patients with sterile pancreatitis, non-surgical treatment should be indicated. For patients with infected pancreatic necrosis, therapeutic intervention either by percutaneous, endoscopic, laparoscopic or surgical approach are indicated. The most preferred surgical intervention is necrosectomy, however, non-surgical treatment with antibiotics is still the treatment of choice if the general condition is stable. Necrosectomy should be performed as late as possible. For patients with pancreatic abscess, drainage is recommended.

Keywords Acute pancreatitis · Guidelines · Gallstone pancreatitis · Intensive care · Interventional treatment

Introduction

Acute pancreatitis (AP) is a disease showing wide range in severity from mild to severe, and severe acute pancreatitis (SAP) has a potential of leading to death. As a result of recent advances in diagnostic imaging and intensive care, the outcome of acute pancreatitis is being improved, nevertheless, high mortality is still reported in the most serious cases [1–6]. So far, clinical practice guidelines (CPG) for acute pancreatitis have been developed in many countries and regions [7–13]. The first Japanese CPG for acute pancreatitis (JPN guidelines) was published in Japanese in 2003, and in English in 2006 [14–20]. Subsequently, the mortality of SAP improved dramatically from 21.4 to 8.9% in Japan, however, the most severe cases of SAP still have a high mortality rate of 30%. In 2008, the Japanese Ministry of Health, Labour and Welfare devised new diagnostic criteria and the severity scoring system of acute pancreatitis and Japanese CPG were revised and published (Tables 1, 2). In this article, the treatment strategy for acute pancreatitis in new Japanese Guidelines (JPN guidelines 2010) is described.

Flowchart for the management of acute pancreatitis (Fig. 1)

A patient who is diagnosed as acute pancreatitis should be hospitalized, and a fundamental medical treatment consisting of fasting, giving intravenous (IV) fluid replacement, oxygen and analgesics (if necessary) under an adequate vitals monitoring should be immediately started. At the same time, establishment of the etiology based on blood tests and imaging, and assessment of the severity based on the severity scoring system should be conducted (Table 2). It is advisable to conduct the assessment of the severity within 3 h after diagnosis. As the condition is unstable in the early stage of acute pancreatitis, repeated assessment of the severity is important even after admission. Particularly, repeated assessment of the severity within 48 h after admission is strongly recommended.

Medical treatment

In the early stage of acute pancreatitis, it is important to stabilize the hemodynamics with sufficient IV fluid resuscitation. Prolongation of shock due to insufficient fluid replacement may cause organ failure, which has strong relation to early mortality due to acute pancreatitis [21, 22]. Vigorous IV fluid resuscitation should be applied to maintain a mean blood pressure of 65 mmHg and urine volume of 0.5 mL/kg/h while monitoring pulse, blood pressure, urine volume, oxygen saturation, and blood test data. For severe cases, if necessary, a central venous line is secured to monitor central venous pressure (CVP) (Recommendation A).

The pain caused by acute pancreatitis is severe and persistent, and therefore it is important that it should be fully controlled (Recommendation A) [23, 24].

Nasogastric suction is not always necessary because previous randomized controlled trials (RCTs) showed no clinical efficacy such as relief of pain or shortening of hospital stay (Recommendation D) [25–32]. Therefore, nasogastric suction should be selectively used for patients with bowel obstruction or severe nausea.

Administration of H_2-blockers has no direct effectiveness on acute pancreatitis. Rather, it may exacerbate the incidence of the complications or duration of the pain (Recommendation D) [27, 29, 31, 33–36]. Moreover, there are no reports demonstrating the effectiveness of proton

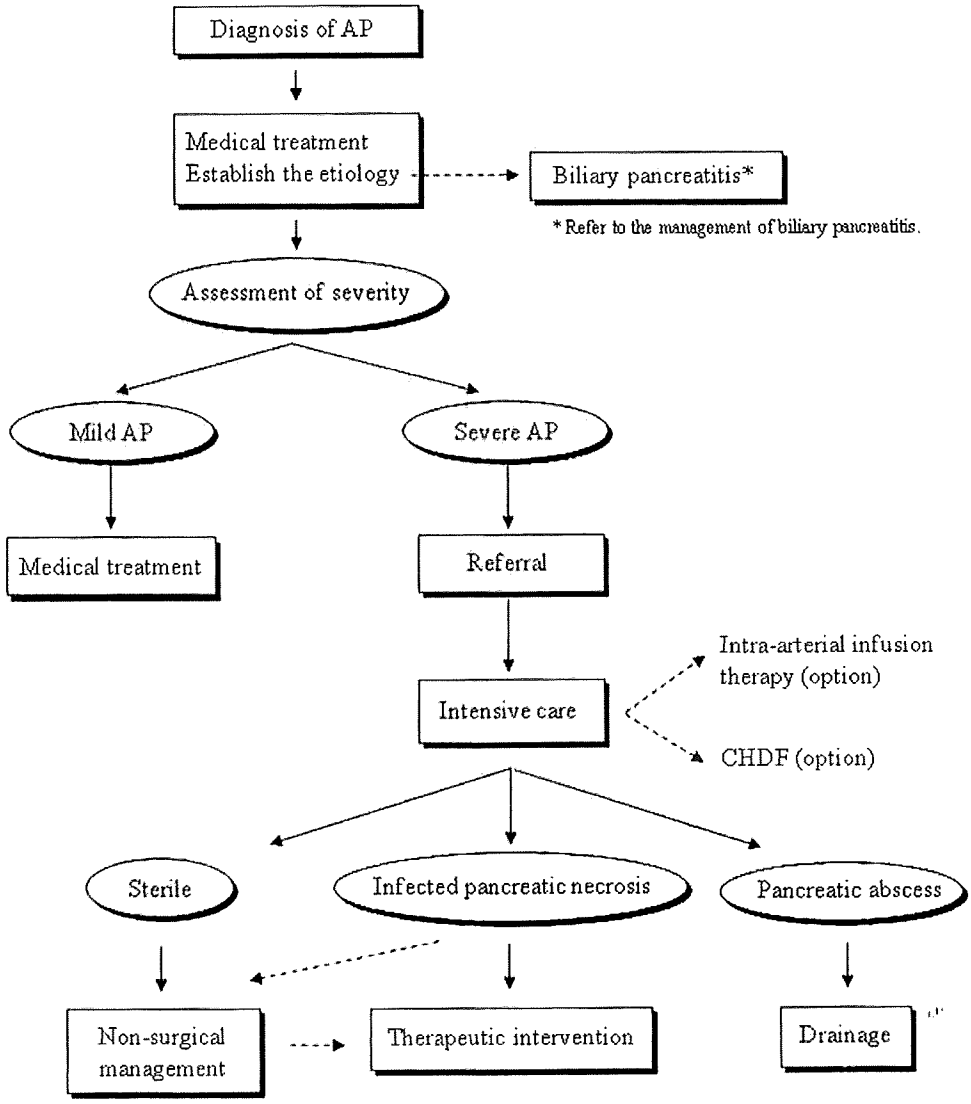

Fig. 1 Flowchart for the management of acute pancreatitis

pump inhibitors (PPI) on acute pancreatitis. Administering H_2-blockers and PPIs should be considered for those with acute gastric mucosal lesions or with gastrointestinal bleeding.

The use of prophylactic antibiotics should not be routinely used for acute pancreatitis. Some systematic reviews showed that the prophylactic antibiotics for acute pancreatitis improve the incidence of infectious complications and mortality [37, 38], while others reported no improvement [39, 40], which makes it difficult to obtain a solid conclusion. In mild cases, incidences of infectious complications themselves are low, and thus routine use of prophylactic antibiotics is not recommendable; however, its efficacy on SAP is expected in terms of lowering of incidences of infectious complications and mortality (Recommendation B) [41–46]. Thus, concerning prophylactic antibiotics, it is advisable to select antibiotics having a broad spectrum and good penetration to the pancreatic and peripancreatic tissues and not to use them beyond 2 weeks. Moreover, the effect of prophylactic antifungal agents remains to be established currently (Recommendation C2) [47–50].

The clinical usefulness of protease inhibitors for acute pancreatitis to decrease incidences of complications and mortality is unknown still now. Although studies so far have not demonstrated clinical usefulness in mild cases, part of the studies in serious cases and sub-analysis based on the severity in meta-analysis have reported decreases in mortality and incidences of complications (Recommendation C1) [51, 52].

Establishing the etiology

Acute pancreatitis develops due to various causes and clarification of its etiology is important for deciding the treatment plan and preventing recurrence. Particularly,

making the diagnosis of biliary acute pancreatitis is most important and of the highest priority because it is greatly related to the treatment plan, including urgent endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES). To make a diagnosis of biliary pancreatitis, medical history, blood test and external ultrasonography are useful (Recommendation A). When the blood ALT is higher than 150 IU/L [sensitivity 48 ~ 93%, specificity 34 ~ 96%, positive likelihood ratio (PLR) 1.4 ~ 12.0, negative likelihood ratio (NLR) 1.8 ~ 4.9] [53, 54] or when the blood test shows abnormalities in more than three of the five measures including bilirubin, ALP, γ-GTP, ALT and ALT/AST ratio (sensitivity 85%, specificity 69%, PLR 2.7, NLR 4.6) [55], biliary pancreatitis is greatly suspected.

Referral and intensive care

A frequent complication of SAP is organ failure, which is a significant prognostic factor. According to the reports since 2000, about half of the deaths due to acute pancreatitis occur early, i.e., within 2 weeks after onset, and a main cause of death is organ failure associated with circulatory failure [21, 22]. In contrast, the main causes of death in those who died in the late stage include infectious complications, especially, infected pancreatic necrosis [56–58]. Thus, in the diagnosis of acute pancreatitis, it is strongly recommended to immediately (within 3 h) judge the severity according to the severity scoring system (Table 2). Furthermore, referral should be made to the institutions having various experiences in the treatment of SAP when the diagnosis of SAP is established (Recommendation A).

Intensive care includes hemodynamic stabilization by vigorous fluid management, respiratory management, nutrition, prevention of infected complications, and, if necessary, CVP and pulmonary arterial monitoring are performed. For cases that show unstable hemodynamics and have no diuresis in spite of sufficient IV fluid resuscitation, introduction of continuous hemodiafiltration (CHDF) should be considered (Recommendation B). CHDF with a polymethylmethacrylate (PMMA) membrane also may remove various cytokines, and potentially have an advantage in preventing systemic inflammation and organ failure (Recommendation C1) [59].

In SAP, the energy requirement increases. So, when oral nutrition is impossible for a long period, nutritional support should be indicated. In cases with SAP, application of early enteral alimentation with careful attention to ileus or enteric ischemia/necrosis decreases the incidence of infectious complications and helps to shorten hospital stay and reduce medical costs (Recommendation B) [60–63].

If possible, contrast enhanced computed tomography (CECT) should be applied to those with SAP. The findings such as pancreatic swelling, peripancreatic inflammatory changes, fluid collection, pseudocyst, fat necrosis, calcified gallstone, etc. are evaluable by a plain CT. However, diagnosis of pancreatic necrosis and related evaluations are difficult by plain CT, and CECT is necessary [64]. The CECT is useful to identify hypoenhanced lesions in pancreatic parenchyma suggestive of necrotizing pancreatitis and is also useful to identify pancreatitis-related complications (bleeding in pseudocyst, and portal thrombosis) and the concomitance of pancreatic cancer.

Necrotizing pancreatitis develops in 10 ~ 20% of the patients with acute pancreatitis and the mortality is unfavorable, reaching 15 ~ 20%. The prognosis after complications of organ failure or infections with necrotizing pancreatitis is further worse. Because in the cases with necrotizing pancreatitis pancreatic ischemia and disturbance of the pancreatic microcirculation are observed from the early stage, it is difficult for an intravenously administered drug to reach the pancreatic tissue. Continuous regional arterial infusion (CRAI) of protease inhibitors and/or antibiotics in the early stage of onset potentially decreases the mortality of acute necrotizing pancreatitis and the incidence of infectious complications (Recommendation C1) [65–68].

Surgical management

Most of the late death in cases of acute pancreatitis is caused by infectious complications. Particularly, the mortality of infected pancreatic necrosis is high [56–58]. High fever, leukocytosis, marked elevation of CRP, positive blood culture, endotoxicemia, intra-abdominal gas in the pancreas and peripancreatic soft tissue on CT scan, etc. are the findings suggestive of infected pancreatic necrosis. Fine needle aspiration (FNA) is useful for diagnosing infectious pancreatic necrosis

Table 1 The diagnostic criteria of acute pancreatitis of the Japanese Ministry of Health, Labour and Welfare (2008)

1. Presence of acute abdominal pain and tenderness in the epigastric region
2. Elevation of the pancreatic enzymes in the blood or urine
3. Presence of abnormal findings associated with acute pancreatitis in the pancreas on ultrasonography, CT or MRI

The patients who show more than two among the above three conditions and who have no other pancreatic diseases or acute abdominal diseases are diagnosed as having acute pancreatitis. Exacerbating chronic pancreatitis is included in acute pancreatitis

Measurement of the pancreatic enzymes highly specific for the pancreas (pancreatic amylase, lipase, etc.) is advisable

Table 2 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 mg/dL) or oliguria (daily urine output <400 mL even after IV fluid resuscitation)	
4. LDH ≧2× 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 old	
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 is judged as Grade 2 or more, the severity grading is evaluated to be "severe"	

Measures in SIRS diagnostic criteria: (1) Temperature >38 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

(Recommendation A) [2, 69]. For sterile pancreatic necrosis, non-surgical management is the rule (Recommendation B). For infectious pancreatic necrosis, therapeutic interventions including percutaneous, endoscopic, laparoscopic and surgical interventions should be applied (Recommendation B) [7, 13, 70]. In cases of a stable general condition, a follow-up of conservative therapies with antimicrobial agents is applicable (Recommendation C1) [71–73]. Early surgery is not recommended for necrotic pancreatitis due to high mortality (Recommendation D) [74]. The surgery should be performed as late as possible (Recommendation C1) [13, 75]. As for the operative method for infectious pancreatic necrosis, necrosectomy is recommended (Recommendation A) [76].

As the treatment of pancreatic abscess, drainage either by percutaneous, endoscopic or surgical means is recommended (Recommendation B) [77, 78]. If no improvements in clinical findings are observed by percutaneous or endoscopic drainage, surgical drainage is advisable.

In cases with symptoms, complications or enlargement of pancreatic pseudocyst, therapeutic interventions should be performed (Recommendation A) [79, 80]. In cases with pancreatic pseudocyst, any treatment should be selected case by case depending on communication between the cyst and pancreatic duct and positional relationship with the gastrointestinal wall (Recommendation A).

Flowchart for the management of biliary pancreatitis (Fig. 2)

In cases with biliary pancreatitis accompanied by acute cholangitis and/or persistent biliary stasis, early endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy (ERCP/ES) should be conducted (Recommendation B) [81–83]. When a gallbladder

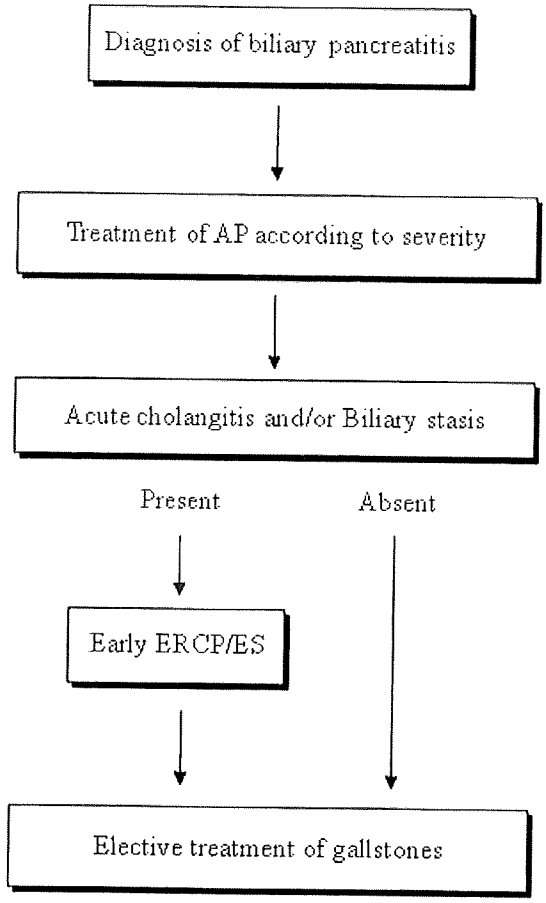

Fig. 2 Flowchart for the management of biliary pancreatitis

stone complicates biliary pancreatitis, cholecystectomy should be performed immediately after remission of pancreatitis (Recommendation B) [84–86].

References

1. Andersson R, Andersson B, Haraldsen P, Drewsen G, Eckerwall G. Incidence, management and recurrence rate of acute pancreatitis. Scand J Gastroenterol. 2004;39:891–4.
2. Banks PA, Gerzof SG, Langevin RE, Silverman SG, Sica GT, Hughes MD. CT-guided aspiration of suspected pancreatic infection: bacteriology and clinical outcome. Int J Pancreatol. 1995;18:265–70.
3. Corfield AP, Cooper MJ, Williamson RC. Acute pancreatitis: a lethal disease of increasing incidence. Gut. 1985;26:724–9.
4. Mann DV, Hershman MJ, Hittinger R, Glazer G. Multicentre audit of death from acute pancreatitis. Br J Surg. 1994;81:890–3.
5. McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984–1995. Br J Surg. 1999;86:1302–5.
6. Perez A, Whang EE, Brooks DC, Moore FD Jr, Hughes MD, Sica GT, et al. Is severity of necrotizing pancreatitis increased in extended necrosis and infected necrosis? Pancreas. 2002; 25:229–33.
7. UK guidelines for the management of acute pancreatitis. Gut 2005; 54 Suppl 3:iii1–9.
8. Consensus on the diagnosis and treatment of acute pancreatitis. Chin J Dig Dis 2005; 6:47–51.
9. AGA Institute medical position statement on acute pancreatitis. Gastroenterology 2007; 132:2019–21.
10. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379–400.
11. Meier R, Beglinger C, Layer P, Gullo L, Keim V, Laugier R, et al. ESPEN guidelines on nutrition in acute pancreatitis. European Society of Parenteral and Enteral Nutrition. Clin Nutr. 2002;21:173–83.
12. Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol. 2002;17(Suppl):S15–39.
13. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology. 2002;2:565–73.
14. Hirota M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: severity assessment of acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:33–41.
15. Isaji S, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: surgical management. J Hepatobiliary Pancreat Surg. 2006;13:48–55.
16. Kimura Y, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: treatment of gallstone-induced acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:56–60.
17. 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.
18. Sekimoto M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:10–24.
19. Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, et al. JPN Guidelines for the management of acute pancreatitis: cutting-edge information. J Hepatobiliary Pancreat Surg. 2006;13:2–6.
20. Takeda K, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: medical management of acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:42–7.
21. Blum T, Maisonneuve P, Lowenfels AB, Lankisch PG. Fatal outcome in acute pancreatitis: its occurrence and early prediction. Pancreatology. 2001;1:237–41.
22. Mutinga M, Rosenbluth A, Tenner SM, Odze RR, Sica GT, Banks PA. Does mortality occur early or late in acute pancreatitis? Int J Pancreatol. 2000;28:91–5.
23. Jakobs R, Adamek MU, von Bubnoff AC, Riemann JF. Buprenorphine or procaine for pain relief in acute pancreatitis. A prospective randomized study. Scand J Gastroenterol. 2000;35:1319–23.
24. Kahl S, Zimmermann S, Pross M, Schulz HU, Schmidt U, Malfertheiner P. Procaine hydrochloride fails to relieve pain in patients with acute pancreatitis. Digestion. 2004;69:5–9.
25. Field BE, Hepner GW, Shabot MM, Schwartz AA, State D, Worthen N, et al. Nasogastric suction in alcoholic pancreatitis. Dig Dis Sci. 1979;24:339–44.
26. Fuller RK, Loveland JP, Frankel MH. An evaluation of the efficacy of nasogastric suction treatment in alcoholic pancreatitis. Am J Gastroenterol. 1981;75:349–53.

27. Goff JS, Feinberg LE, Brugge WR. A randomized trial comparing cimetidine to nasogastric suction in acute pancreatitis. Dig Dis Sci. 1982;27:1085–8.
28. Levant JA, Secrist DM, Resin H, Sturdevant RA, Guth PH. Nasogastric suction in the treatment of alcoholic pancreatitis. A controlled study. JAMA. 1974;229:51–2.
29. Loiudice TA, Lang J, Mehta H, Banta L. Treatment of acute alcoholic pancreatitis: the roles of cimetidine and nasogastric suction. Am J Gastroenterol. 1984;79:553–8.
30. Naeije R, Salingret E, Clumeck N, De Troyer A, Devis G. Is nasogastric suction necessary in acute pancreatitis? Br Med J. 1978;2:659–60.
31. Navarro S, Ros E, Aused R, Garcia Puges M, Pique JM, Vilar Bonet J. Comparison of fasting, nasogastric suction and cimetidine in the treatment of acute pancreatitis. Digestion. 1984;30:224–30.
32. Sarr MG, Sanfey H, Cameron JL. Prospective, randomized trial of nasogastric suction in patients with acute pancreatitis. Surgery. 1986;100:500–4.
33. Broe PJ, Zinner MJ, Cameron JL. A clinical trial of cimetidine in acute pancreatitis. Surg Gynecol Obstet. 1982;154:13–6.
34. Meshkinpour H, Molinari MD, Gardner L, Berk JE, Hoehler FK. Cimetidine in the treatment of acute alcoholic pancreatitis. A randomized, double-blind study. Gastroenterology. 1979;77:687–90.
35. Morimoto T, Noguchi Y, Sakai T, Shimbo T, Fukui T. Acute pancreatitis and the role of histamine-2 receptor antagonists: a meta-analysis of randomized controlled trials of cimetidine. Eur J Gastroenterol Hepatol. 2002;14:679–86.
36. Sillero C, Perez-Mateo M, Vazquez N, Martin A. Controlled trial of cimetidine in acute pancreatitis. Eur J Clin Pharmacol. 1981;21:17–21.
37. Bassi C, Larvin M, Villatoro E. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2003;CD002941.
38. Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2006;CD002941.
39. Bai Y, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2008;103:104–10.
40. de Vries AC, Besselink MG, Buskens E, Ridwan BU, Schipper M, van Erpecum KJ, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology. 2007;7:531–8.
41. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet. 1993;176:480–3.
42. Schwarz M, Isenmann R, Meyer H, Beger HG. [Antibiotic use in necrotizing pancreatitis. Results of a controlled study]. Dtsch Med Wochenschr. 1997;122:356–61.
43. Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis—a single-center randomized study. J Gastrointest Surg. 2001;5:113–8. (discussion 118–20).
44. Rokke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LO, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. Scand J Gastroenterol. 2007;42:771–6.
45. Manes G, Rabitti PG, Menchise A, Riccio E, Balzano A, Uomo G. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. Pancreas. 2003;27:e79–83.
46. Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. Am J Gastroenterol. 2006;101:1348–53.
47. De Waele JJ, Vogelaers D, Blot S, Colardyn F. Fungal infections in patients with severe acute pancreatitis and the use of prophylactic therapy. Clin Infect Dis. 2003;37:208–13.
48. He YM, Lv XS, Ai ZL, Liu ZS, Qian Q, Sun Q, et al. Prevention and therapy of fungal infection in severe acute pancreatitis: a prospective clinical study. World J Gastroenterol. 2003;9:2619–21.
49. Shanmugam N, Isenmann R, Barkin JS, Beger HG. Pancreatic fungal infection. Pancreas. 2003;27:133–8.
50. Eggimann P, Jamdar S, Siriwardena AK. Pro/con debate: antifungal prophylaxis is important to prevent fungal infection in patients with acute necrotizing pancreatitis receiving broad-spectrum antibiotics. Crit Care. 2006;10:229.
51. Andriulli A, Leandro G, Clemente R, Festa V, Caruso N, Annese V, et al. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. Aliment Pharmacol Ther. 1998;12:237–45.
52. Seta T, Noguchi Y, Shimada T, Shikata S, Fukui T. Treatment of acute pancreatitis with protease inhibitors: a meta-analysis. Eur J Gastroenterol Hepatol. 2004;16:1287–93.
53. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. Am J Gastroenterol. 1994;89:1863–6.
54. Liu CL, Fan ST, Lo CM, Tso WK, Wong Y, Poon RT, et al. Clinico-biochemical prediction of biliary cause of acute pancreatitis in the era of endoscopic ultrasonography. Aliment Pharmacol Ther. 2005;22:423–31.
55. Wang SS, Lin XZ, Tsai YT, Lee SD, Pan HB, Chou YH, 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.
56. Renner IG, Savage WT, 3rd, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. Dig Dis Sci. 1985;30:1005–18.
57. Lankisch PG, Burchard-Reckert S, Petersen M, Lehnick D, Schirren CA, Kohler H, et al. Morbidity and mortality in 602 patients with acute pancreatitis seen between the years 1980–1994. Z Gastroenterol. 1996;34:371–7.
58. Beger HG, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology. 1986;91:433–8.
59. Oda S, Hirasawa H, Shiga H, Matsuda K, Nakamura M, Watanabe E, et al. Management of intra-abdominal hypertension in patients with severe acute pancreatitis with continuous hemodiafiltration using a polymethyl methacrylate membrane hemofilter. Ther Apher Dial. 2005;9:355–61.
60. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. Br Med J. 2004;328:1407.
61. Al-Omran M, Groof A, Wilke D. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2003;CD002837.
62. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg. 1997;84:1665–9.
63. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg. 2006;23:336–44. (discussion 344–5).
64. Larvin M, Chalmers AG, McMahon MJ. Dynamic contrast enhanced computed tomography: a precise technique for

identifying and localising pancreatic necrosis. Br Med J. 1990;300:1425–8.
65. Takeda K, Matsuno S, Sunamura M, Kakugawa Y. Continuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. Am J Surg. 1996;171:394–8.
66. Hayashi J, Kawarada Y, Isaji S, Yokoi H, Higashiguchi T. Therapeutic effects of continuous intraarterial antibiotic infusion in preventing pancreatic infection in experimental acute necrotizing pancreatitis. Pancreas. 1996;13:184–92.
67. Takeda K, Yamauchi J, Shibuya K, Sunamura M, Mikami Y, Matsuno S. Benefit of continuous regional arterial infusion of protease inhibitor and antibiotic in the management of acute necrotizing pancreatitis. Pancreatology. 2001;1:668–73.
68. Mikami Y, Takeda K, Matsuda K, Qiu-Feng H, Fukuyama S, Egawa S, et al. Rat experimental model of continuous regional arterial infusion of protease inhibitor and its effects on severe acute pancreatitis. Pancreas. 2005;30:248–53.
69. Rau B, Pralle U, Mayer JM, Beger HG. Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis. Br J Surg. 1998;85:179–84.
70. McFadden DW, Reber HA. Indications for surgery in severe acute pancreatitis. Int J Pancreatol. 1994;15:83–90.
71. Runzi M, Niebel W, Goebell H, Gerken G, Layer P. Severe acute pancreatitis: nonsurgical treatment of infected necroses. Pancreas. 2005;30:195–9.
72. Sivasankar A, Kannan DG, Ravichandran P, Jeswanth S, Balachandar TG, Surendran R. Outcome of severe acute pancreatitis: is there a role for conservative management of infected pancreatic necrosis? Hepatobiliary Pancreat Dis Int. 2006;5:599–604.
73. Lee JK, Kwak KK, Park JK, Yoon WJ, Lee SH, Ryu JK, et al. The efficacy of nonsurgical treatment of infected pancreatic necrosis. Pancreas. 2007;34:399–404.
74. Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007;142:1194–201.
75. Nathens AB, Curtis JR, Beale RJ, Cook DJ, Moreno RP, Romand JA, et al. Management of the critically ill patient with severe acute pancreatitis. Crit Care Med. 2004;32:2524–36.
76. Rodriguez JR, Razo AO, Targarona J, Thayer SP, Rattner DW, Warshaw AL, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg. 2008;247:294–9.
77. vanSonnenberg E, Wittich GR, Chon KS, D'Agostino HB, Casola G, Easter D, et al. Percutaneous radiologic drainage of pancreatic abscesses. Am J Roentgenol. 1997;168:979–84.
78. Baril NB, Ralls PW, Wren SM, Selby RR, Radin R, Parekh D, et al. Does an infected peripancreatic fluid collection or abscess mandate operation? Ann Surg. 2000;231:361–7.
79. Yeo CJ, Bastidas JA, Lynch-Nyhan A, Fishman EK, Zinner MJ, Cameron JL. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet. 1990;170:411–7.
80. Vitas GJ, Sarr MG. Selected management of pancreatic pseudocysts: operative versus expectant management. Surgery. 1992;111:123–30.
81. Sharma VK, Howden CW. Metaanalysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. Am J Gastroenterol. 1999;94:3211–4.
82. Heinrich S, Schafer M, Rousson V, Clavien PA. Evidence-based treatment of acute pancreatitis: a look at established paradigms. Ann Surg. 2006;243:154–68.
83. Ayub K, Imada R, Slavin J. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. Cochrane Database Syst Rev 2004;CD003630.
84. Kaw M, Al-Antably Y, Kaw P. Management of gallstone pancreatitis: cholecystectomy or ERCP and endoscopic sphincterotomy. Gastrointest Endosc. 2002;56:61–5.
85. Gislason H, Vetrhus M, Horn A, Hoem D, Sondenaa K, Soreide O, et al. Endoscopic sphincterotomy in acute gallstone pancreatitis: a prospective study of the late outcome. Eur J Surg. 2001;167:204–8.
86. Vazquez-Lglesias JL, Gonzalez-Conde B, Lopez-Roses L, Estevez-Prieto E, Alonso-Aguirre P, Lancho A, et al. Endoscopic sphincterotomy for prevention of the recurrence of acute biliary pancreatitis in patients with gallbladder in situ: long-term follow-up of 88 patients. Surg Endosc. 2004;18:1442–6.

J Hepatobiliary Pancreat Sci (2010) 17:87–89
DOI 10.1007/s00534-009-0219-y

Pancreatitis bundles

Toshihiko Mayumi · Tadahiro Takada · Koichi Hirata · Masahiro Yoshida · Miho Sekimoto · Masahiko Hirota · Yasutoshi Kimura · Kazunori Takeda · Hodaka Amano · Keita Wada · Toshifumi Gabata · Shinjyu Arata · Morihisa Hirota · Masamichi Yokoe · Seiki Kiriyama · Satoru Shikata · Kunihiro Shirai · Takeo Nakayama · Kuni Ohtomo · Masao Tanaka · Tooru Shimosegawa

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

Abstract Clinical indicators set forth in the guidelines have been found to contribute to the improvement in compliance with the guidelines. On the other hand, it has been shown that clinical indicators are more effective when individual indicators are presented in the form of a bundle than when they are given separately. Accordingly, in the JPN Guidelines 2010 for management of acute pancreatitis, those indicators that are judged to be important on the basis of a recommendation classification of "A or B" are presented as a pancreatitis bundle. Each item includes assessment of severity after a diagnosis of pancreatitis has been made, differentiation of pathogenesis, management of gallstone-induced pancreatitis, a sufficient dose of fluid replacement and monitoring, pain control, prophylactic administration of wide-spectrum antibiotics and cholecystectomy following resolution of pancreatic symptoms caused by cholecystolithiasis. Hereafter, the efficacy of these indicators and the significance of their achievement should be examined carefully. Then, the assessment of the

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.

T. Mayumi (✉)
Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8560, Japan
e-mail: mtoshi@med.nagoya-u.ac.jp

T. Takada · H. Amano · K. Wada
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

K. Hirata · Y. Kimura
Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University Graduate School of Medicine, Sapporo, Japan

M. Yoshida
Department of Hemodialysis and Surgery, Clinical Research Center, Kaken Hospital, International University of Health and Welfare, Chiba, Japan

M. Sekimoto
Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan

Masahiko Hirota
Department of Surgery, Kumamoto Regional Medical Center, Kumamoto, Japan

K. Takeda
Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai, Japan

T. Gabata
Department of Radiology, Graduate School of Medical Science, Kanazawa University, Ishikawa, Japan

S. Arata
Critical Care and Emergency Center, Yokohama City University Medical Center, Yokohama, Japan

Morihisa Hirota · T. Shimosegawa
Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

M. Yokoe
General Internal Medicine, Japanese Red Cross Society Nagoya Daini Hospital, Nagoya, Japan

S. Kiriyama
Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

compliance rate with the guidelines as well as the assessment of the guidelines and pancreatitis itself should become possible.

Keywords Pancreatitis bundle · Pancreatitis · Guidelines · Clinical indicators

What are clinical indicators and bundles?

To begin with, the guidelines are made so that they are publicized widely, used in many medical situations and eventually contribute to the improvement in the prognosis of patients. The purpose never lies in just making the guidelines themselves. To achieve that purpose, efforts are made on the basis of evidence to prepare guidelines of high quality that can be used in clinical situations. At the same time, a variety of new ideas are adopted so that they are publicized, known and used widely. These ideas include; (1) Description presented in the form of clinical questions encountered in clinical situations, (2) Flow charts and algorithms attached to each guideline, (3) Brochures and handouts prepared and distributed that are portable and able to be always carried, (4) Easy access to the homepage any time. One of them is a clinical indicator. It has been found that once indicators have been implemented in the guidelines, the compliance rate with the guidelines increases. Also, in the assessment of items, groups such as the AGREE Collaboration (Appraisal of guidelines for research & evaluation) used for appraising the guidelines, there is an item that confirms if clinical indicators have been implemented or not [1].

Efficacy of the bundle

It is thought that when relevant and desirable care related to each other as a bundle, such as sepsis bundle [2–4], ventilator bundle [5, 6] or central line bundle [7] has been delivered, the improvement in the prognosis of patients is more remarkable than when individual intervention has been delivered separately. Good prognosis is also reported in cases in which a bundle has been achieved, but this may show that those cases which have achieved a bundle are in such good condition as to enable achievement of a bundle. However, the improvement in the prognosis in patients achieved through education concerning bundles demonstrates that implementation of bundles and education concerning them have been useful [4, 8].

Controversial points and harmful effects of bundles

There are many problems to be solved for dissemination and implementation of bundles. One of them involves the diffusion of and thorough compliance with bundles. As in the case of the guidelines, even if useful items have been implemented, the prognosis in patients is not improved without the common knowledge of bundles among providers of medical care [8]. Furthermore, it is not possible to put bundles into practice without sufficient manpower and equipment [9].

Manpower and equipment should be improved, if possible. If improvement is impossible, an alternative treatment should be provided or patients should be transferred to a medical facility where the contents of bundles can be put into practice. So that bundles may be disseminated, a big campaign such as a "surviving sepsis campaign" should be started up and made known widely through homepages and journals. It is also possible to distribute handouts or memoranda that are portable any time and in which items of bundles are described. It will also be useful to request checking of the contents of sepsis bundles and to urge the implementation of bundles on the occasion of case registry such as a "sepsis registry". Case registry and education are also important to encourage compliance with bundles.

There is also a concern that bundles are used not for the purpose of improving the prognosis in patients and increasing efficiency, but for limiting the contents of medical care to keep health care costs down. Furthermore, failure to carry out the contents of bundles should not lead to lawsuit.

Pancreatitis bundles

So that the compliance rate with the guidelines may be increased and that patient prognosis may be improved, the present guidelines have implemented the following clinical indications (pancreatitis bundle). The content of every bundle is classified into Recommendation "A or B" and

S. Shikata · T. Nakayama
Department of Health Informatics,
Kyoto University School of Public Health,
Kyoto, Japan

K. Shirai
Department of Advanced Critical Care Center,
Gifu University Hospital, Gifu, Japan

K. Ohtomo
Department of Radiology, University of Tokyo, Tokyo, Japan

M. Tanaka
Department of Surgery and Oncology,
Graduate School of Medical Sciences, Kyushu University,
Fukuoka, Japan