

JPN Guidelines for the management of acute pancreatitis: treatment of gallstone-induced acute pancreatitis

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Abstract

Gallstones, along with alcohol, are one of the primary etiological factors of acute pancreatitis, and knowledge of the etiology as well as the diagnosis and management of gallstones, is crucial for managing acute pancreatitis. Because of this, evidence regarding the management of gallstone-induced pancreatitis in Japan was collected, and recommendation levels were established by comparing current clinical practices with optimal clinical practices. The JPN Guidelines for managing gallstone-induced acute pancreatitis recommend two procedures: (1) an urgent endoscopic procedure should be performed in patients in whom biliary duct obstruction is suspected and in patients complicated by cholangitis (Recommendation A); and (2) after the attack of gallstone pancreatitis has subsided, a laparoscopic cholecystectomy should be performed during the same hospital stay (Recommendation B).

Key words Gallstone pancreatitis · Emergency endoscopy · Laparoscopic cholecystectomy

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Clinical questions

CQ1. Is an emergency endoscopy approach beneficial in the treatment of gallstone-induced acute pancreatitis?

CQ2. Is one-stage cholecystectomy followed by common bile duct (CBD) clearance safer and more effective than endoscopic procedures?

CQ3. When should laparoscopic cholecystectomy be undertaken in patients with gallstone pancreatitis?

Introduction

Research on the pathophysiology of acute pancreatitis has advanced dramatically during the past 20 years, and, as the number of randomized controlled studies (RCTs) of severe acute pancreatitis has steadily increased, mainly in the United States and Europe, evidence-based management has come to be demanded for acute pancreatitis. In Japan, three institutions — the Japanese Society for Abdominal Emergency Medicine, the Japan Pancreas Society, and the Research Group for Intractable Diseases and Refractory Pancreatic Diseases, which is sponsored by the Japanese Ministry of Health, Labour, and Welfare — collaborated to publish “Evidence-based clinical practice guidelines for acute pancreatitis: proposals.”¹ This article incorporates the latest evidence in relation to gallstone pancreatitis and

presents these guidelines (the JPN Guidelines) for the treatment of gallstone-induced acute pancreatitis, citing the relevant Recommendations.

Management of bile duct stones in gallstone-associated acute pancreatitis

Clinical questions (CQ) 1. Is an emergency endoscopy approach beneficial in the treatment of gallstone-induced acute pancreatitis?

An emergency endoscopy approach is beneficial in patients with acute pancreatitis in whom bile duct obstruction is suspected or there are complications from cholangitis (Recommendation A)

Emergency endoscopic approaches to the management of bile duct stones in gallstone-associated acute pancreatitis include endoscopic sphincterotomy (ES), endoscopic papillary balloon dilation (EPBD), endoscopic nasobiliary drainage (ENBD), and stenting. Those procedures are performed to remove gallstones and to drain the bile duct, which mostly results in relieving the obstruction of the pancreatic duct. The endoscopic approach seems to be most beneficial in those patients with acute pancreatitis suspected of having concomitant gallstones complicated with the occurrence or exacerbation of jaundice, and in patients complicated by cholangitis. The decision whether or not to perform one-stage choledocholithotomy after ES or endoscopic biliary drainage must be based on the pathophysiological condition of the patient and the skill of the physician. It is important to refer any patient who requires an endoscopic approach to an advanced medical unit if the patient meets the criteria for transfer (see page ■■).

Emergency or early endoscopic procedures for acute pancreatitis have been assessed in four randomized controlled trials (RCTs; Level 1b),²⁻⁵ and a metaanalysis of these RCTs has been performed (Level 1a).⁶ The metaanalysis involved a total of 834 patients, comprising 460 patients treated by endoscopic retrograde

cholangiopancreatography (ERCP) followed by ES (ERCP/ES group) and 374 patients treated conservatively (conservative treatment group). The analysis led to the conclusion that the ERCP/ES group had lower incidences of morbidity and mortality (Table 1), but because pancreatitis patients with treated by ERCP or ES alone have never been analyzed, it remains unclear whether ERCP or ES is more useful.

The results of two studies (Level 1b)^{2,3} that published data stratified by severity indicate that ERCP/ES is not very useful in patients with mild pancreatitis (Table 2), and a report expressing a negative opinion in regard to early endoscopic treatment (Level 1b)⁵ excluded patients with jaundice from the analysis, and the percentage of subjects with gallstone pancreatitis was only 19%. It is concluded from these reports that urgent ERCP/ES is useful only in severe gallstone pancreatitis.

However, there are differences in severity assessment, particularly of severe cases, between Japan and Western countries, and no convincing evidence supporting the application of emergency ERCP/ES in patients with severe cases has been established in Japan. It is currently thought that the indications for emergency ERCP/ES should be restricted to patients suspected of having prolonged biliary duct obstruction, as manifested by the occurrence or exacerbation of jaundice, and to patients complicated by cholangitis. Various other techniques besides ERCP/ES are used for biliary drainage and are generally accepted in Japan. A report, entitled "Evaluation of urgent treatment for impacted bile duct stones" (published in 1992 in Japanese), claims that endoscopic nasobiliary drainage (ENBD) is a useful and safe urgent treatment method for impacted bile duct stones, although no high-quality evidence supported by RCTs or metaanalysis has yet emerged to support that report.

In terms of the safety of ERCP/ES in the acute stage of pancreatitis, no difference has been found between the incidence of complications after early intervention (within 48h of onset) and the incidence after delayed intervention (Level 3b),⁷ and it has been reported that ERCP/ES within 24 to 72h after onset is safe (Level

Table 1. Reported morbidity and mortality rates in early ERCP/ES and conservative treatment groups

Author	Morbidity (%)		Mortality (%)	
	ERCP/ES group	Conservative treatment group	ERCP/ES group	Conservative treatment group
Neoptolemos ²	16.9	33.9	1.7	8.1
Fan ³	17.5	28.6	5.2	9.2
Nowak ⁴	16.9	36.3	2.3	12.8
Folsch ⁵	46.0	50.9	11.1	6.3
Pooled data	25.0	38.2	5.2	9.1

(cited from Sharma and Howden⁶, with some modifications)

Table 2. Reported morbidity and mortality rates in early ERCP/ES and conservative treatment groups, stratified according to severity

Author	ERCP/ES group			Conservative treatment group		
	Number of patients	Morbidity (%)	Mortality (%)	Number of patients	Morbidity (%)	Mortality (%)
Mild pancreatitis group						
Neoptolemos ²	34	4	0	34	4	0
Fan ³	56 (34 ^a)	8 (6 ^a)	0	58 (35 ^a)	6 (6 ^a)	0
Pooled data	90	12 (13 ^a)	0	92	10 (11 ^a)	0
Severe pancreatitis group						
Neoptolemos ²	25	6	1	28	17	5
Fan ³	41 (30 ^a)	9 (4 ^a)	5 (1 ^a)	40 (28 ^a)	23 (15 ^a)	9 (5)
Pooled data	66	15 (23 ^a)	6 (9 ^a)	68	40 (59 ^a)	14 (21 ^a)

^aPatients with CBD stones followed-up with ERCP

2b).⁸ Similar results were reported in a retrospective study of a large number of patients (Level 4).⁹ The four RCTs referred to above²⁻⁵ have suggested bleeding as a complication of ERCP/ES, but the bleeding occurred in only a few patients with mild pancreatitis and was never a direct cause of death. Based on the reports from overseas, we cannot conclude that ERCP/ES is highly risky in the acute stage of pancreatitis. According to the results of a third nationwide survey in Japan (in 2000) of accidental complications from gastrointestinal endoscopy (Level 4), the incidence of accidental complications of ERCP performed for examination purposes and of ES done to treat the papilla of Vater was 0.1% and 0.7%, respectively, and the mortality rate was 0.006% and 0.048%, respectively. The issue of whether or not ERCP/ES is indicated should be carefully evaluated and adequate care should be taken to prevent accidental complications. Effective performance obviously requires an advanced medical institution with experienced specialists and a special unit whose staff is capable of carrying out emergency ERCP/ES examinations and dealing with bleeding and other complications.

Surgical approach

CQ2. Is one-stage cholecystectomy followed by common bile duct (CBD) clearance safer and more effective than endoscopic procedures?

Open choledochotomy or sphincterotomy (operative removal of CBD stones is recommended) (Recommendation D)

In Japan, choledocholithotripsy with emergency endoscopic procedures (ES, EPBD) is performed by endoscopists, as well as by many surgeons, and it has become the treatment of first choice for CBD clearance. One-stage cholecystectomy and CBD clearance has not

been demonstrated to be safer and more effective than endoscopic procedures, and it is not recommended in either the JPN Guidelines or the International Association of Pancreatology (IAP) guidelines.¹⁰

CQ3. When should laparoscopic cholecystectomy be undertaken in patients with gallstone pancreatitis?

Laparoscopic cholecystectomy should be considered after recovery from an attack of gallstone pancreatitis and should be performed during the same hospital stay (choledochotomy and CBD clearance are performed as required) (Recommendation B)

Cholelithiasis is one of the major causes of acute pancreatitis, and gallstone-induced acute pancreatitis is an absolute indication for cholecystectomy (and choledochotomy, when necessary). However, there has been no consensus regarding the timing of this surgical intervention. One RCT claims that the earlier surgery is performed after onset, the more beneficial it is, while another RCT has proposed delayed surgery once the inflammatory process has subsided. The latter RCT (Level 1b)¹¹ compared earlier surgery (within 72h of hospital admission) and delayed surgery, and the results suggested that the earlier surgery was more beneficial. Because the results showed no significant difference in the incidence of complications (8.3% vs 10.3%) or the mortality rate (2.8% vs 6.9%), this RCT concluded that surgery on the bile duct system with the aim of removing the cause of the pancreatitis or preventing its progression could be performed safely even in the acute state. According to another RCT (Level 1b),¹² which is often quoted as grounds to justify delayed surgery, patients subjected to early surgery (within 48h of hospitalization) had a significantly higher complication rate (30.1% vs 5.1%) and mortality rate (15.1% vs 2.4%) than those subjected to delayed surgery. This conflicting evidence may be explained by potential differences in the severity of the disease in the patients included in the

Table 3. Prospective cohort studies of laparoscopic cholecystectomy employed for gallstone-associated acute pancreatitis

Author	Number of patients	Timing of surgery (days after onset)	Completion rate (%)	Conversion rate (%)	Operation time (min)	Morbidity (%)	Mortality (%)	CBD exploration ^d
Rhodes et al. ¹⁶	16	10 (4–34) ^a	100	0	50 (30–120)	0	0	15/1
Tate et al. ¹⁷	24	7 (3–24) ^a	87.5	12.5	76 (NA)	8	0	23/0
Ballestra-Lopez et al. ¹⁸	40	3.4/15 ^{b,c}	100	0	86 (45–210) ^a	10	2.5	0/40
Ricci et al. ¹⁹	51	NA	100	0	NA	1.9	0	40/47
Uhl et al. ²⁰	48	10 (4–29) ^a	79	21	80 (30–225) ^a	7.9	0	0/33
Chang et al. ²¹	59	NA	100	0	NA	3.4	0	0/58

NA, not assessed

^aMedian (range)^bMean^cMild/severe disease^dPreoperative ERC/intraoperative cholangiogram

clinical trials. Discussion of the timing of surgery alone, without adequate consideration of the impact of severity, has caused confusion in clinical settings. However, the introduction of emergency ERCP/ES^{2,3} has completely changed the options available for the management of gallstone pancreatitis and has dramatically reduced the need for performing surgery in the acute stage.

There are two options in regard to delayed surgery: (i) surgery during the same hospital stay as that for the initial treatment, and (ii) surgery during re-hospitalization after a sufficient recovery period. Because the rate of recurrence of pancreatitis during the recovery period after discharge is 32% to 61% (Level 3b),^{13–15} patients with mild uncomplicated gallstone pancreatitis should undergo biliary tract exploration and cholecystectomy after the symptoms have been alleviated. Whenever possible, even patients with severe disease should undergo surgery during the same hospital stay as that for the initial treatment.

Laparoscopic cholecystectomy (LC) has been increasingly used to treat gallstone pancreatitis over the past 10 years. According to prospective cohort studies reported to date (Levels 1b–2c),^{16–21} LC was associated with a completion rate of 94.5% (range, 79% to 100%), a complication (morbidity) rate of 5.5% (range, 0% to 10%), and a mortality rate of 0.4% (range, 0% to 2.5%; Table 3), implying that LC resulted in performance equal to or better than that of laparotomy. Based on these results, the use of LC in mild gallstone pancreatitis is feasible and its clinical usefulness has been demonstrated.

The conventional standard surgical intervention for gallstone pancreatitis used to be open cholecystectomy and operative cholangiography, followed by choledochotomy when choledocholithiasis was observed. The

introduction of LC, however, has made several options available for biliary tract exploration and the management of choledocholithiasis. Four typical procedures are:

1. ERCP/ES prior to surgery, and LC after diagnosing and removing CBD stones. In some patients, removal of CBD stones by ERCP/ES after LC.
2. Intraoperative cholangiography (IOC) during LC, and conversion to the open method when CBD stones are present.
3. IOC during LC, and when CBD stones are present, the addition of ES during or followed by LC.
4. LC, and laparoscopic choledochotomy/lithotripsy when CBD stones are discovered by IOC.

Procedure (1) has become increasingly popular in Japan. However, opinions differ concerning the application of ERCP in all patients with gallstone-associated pancreatitis. Some surgeons argue that ERCP should be performed only when choledocholithiasis is suspected on the basis of blood studies and other diagnostic imaging, or when it is diagnosed during IOC (Level 1b–2b).^{21,22} The risk inherent in ERCP should be noted, particularly in patients with acute pancreatitis (Level 2b).²³ It may be possible to substitute IOC for preoperative ERCP as a standard method to confirm those patients who are less likely to have choledocholithiasis, if the surgeons in charge of this procedure have sufficient experience and technique to perform IOC successfully. The choice of which of the above four procedures to opt for when choledocholithiasis is discovered by IOC depends on the skill and technique of the specialist physicians currently at each institution. Collection of more data on the safety, invasiveness, and completion rates associated with each of these procedures is an important task for the future.

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