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Guidelines

Clinical Practice Guidelines for post-ERCP pancreatitis 2023

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The Clinical Practice Guidelines for post-ERCP pancreatitis (PEP) 2023 provide updated recommendations for the prevention, diagnosis, and management of PEP. Endoscopic retrograde cholangiopancreatography (ERCP), a valuable procedure for diagnosing and treating pancreatobiliary diseases, can result in PEP as the most common adverse event. Since the first guidelines were published in 2015, advances in techniques and new research findings have necessitated this revision. The guidelines developed using the GRADE methodology target adult patients undergoing ERCP. They offer a comprehensive framework for clinicians to minimize the risk of PEP. For high-risk patients, endoscopic ultrasound before ERCP is recommended to avoid unnecessary procedures. The guidelines also discuss procedural and patient-related risk factors for PEP, highlighting that operator experience does not significantly affect PEP rates if performed under the supervision of skilled endoscopists. The diagnostic criteria include monitoring serum pancreatic enzyme levels postprocedure, and early computed tomography is advised in suspected cases. For treatment, the guidelines recommend following acute pancreatitis protocols. Key preventive measures include the use of temporary pancreatic duct stents and rectal nonsteroidal anti-inflammatory drugs, both of which are supported by strong evidence for reducing the incidence of PEP. Overall, these guidelines aim to enhance clinical outcomes by reducing PEP incidence and improving its management through evidence-based practices.

Key words: clinical practice guideline, endoscopic retrograde cholangiopancreatography, nonsteroidal anti-inflammatory drugs, post-ERCP pancreatitis, temporary pancreatic duct stent

INTRODUCTION

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) has become an essential procedure for the diagnosis and treatment of pancreatobiliary diseases. Post-ERCP pancreatitis (PEP) is the most frequent adverse event following ERCP and requires an early diagnosis and effective management. When severe, it can be life-threatening, making prevention crucial in clinical practice. To diagnose PEP early and provide appropriate treatment, as well as to include prophylactic measures, the Japan Pancreas Society created the first edition of the "Clinical Practice Guidelines for PEP" in 2015.[1]

Eight years have passed since the first edition was published, and new findings have been reported in the treatment of PEP, including advances in ERCP techniques and research on PEP prevention. Therefore, the need to publish a revised edition (2nd edition) led to the creation of this edition.

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METHODS

Guideline purpose

THE MAIN AIM of this guideline (2nd edition) is to offer practical guidance to clinicians performing ERCP in Japan, ensure a proper diagnosis and treatment, clarify the mechanisms and risk factors of PEP, and implement preventive measures to reduce its incidence and improve outcomes. Furthermore, it is essential for patients and their families to understand their condition and treatment in order to foster shared decision-making between medical staff and patients, thereby ensuring better healthcare outcomes.

Target population

These guidelines target adult patients who may undergo ERCP for various diseases or conditions. The dosage recommendations apply only to adults, and pediatric cases were not considered.

Development of the guideline

The guideline was developed following the "Minds Guideline Development Manual 2020 version 3.0," and the structure and recommendation strength were determined accordingly.

1. Scope Creation: The guideline committee reviewed the epidemiological data on PEP, ERCP techniques, and the diagnosis, treatment, and prevention of PEP. The committee decided to follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[2]
2. Creation of Clinical Questions (CQs) and Literature Review: The key clinical issues for ERCP and PEP were framed as CQs using the Patients, Interventions, Comparisons, Outcomes format. The revised edition introduces background questions (BQs) and future research questions (FRQs). BQs provide essential background knowledge for understanding CQs but do not offer recommendations. These cover widely accepted concepts in clinical practice. FRQs highlight areas that require further research, indicating future challenges where high-quality studies are still lacking. Comprehensive literature reviews were conducted using databases such as PubMed and Cochrane for English literature and NPO Japan Medical Abstracts Society. The search terms included "post-ERCP pancreatitis," with searches extending until September 2022. Relevant studies outside the search period or in unlisted databases were manually added.
3. Systematic Review Process: The review assessed both the benefits and harms associated with each CQ. The selected studies were evaluated for bias risk and nondirectness (i.e. how closely the study's conditions matched real clinical practice). Evidence from randomized controlled trials (RCTs) and observational studies was synthesized into a "body of evidence" and rated according to the GRADE approach, with the evidence quality rated on a four-point scale (high, moderate, low, and very low). If a treatment was not covered by insurance, it was noted in the text.
4. Determination of Recommendation Strength: Recommendations were drafted based on the evidence quality, balance between benefits and harms, patient values, and cost considerations. The strength of each recommendation was determined through voting by the guideline committee following the GRADE method and the nominal group technique. The voting decisions required at least 80% agreement. The recommendation strength was categorized as either "strong recommendation," "weak recommendation," or "no recommendation."

RESULTS

ADDITIONAL COMMENTS AND references for BQs and FRQs other than Q1-1 are provided in Appendix S1. The recommendations in these guidelines have been determined based on the clinical background, medical insurance system, and framework in Japan. In applying to different medical systems in other countries, decisions should be made in accordance with the situation in each country.

Indication of ERCP

Q1-1 Should the risks and benefits of ERCP be considered for indications? (BQ)

Indications for ERCP should be decided while considering the benefits and risks.

Comment. ERCP is crucial in diagnosing and treating pancreaticobiliary diseases, providing definitive diagnoses, and aiding in treatment decisions through procedures such as drainage, stenting, and stone removal (Table 1). However, it carries risks, including PEP, hemorrhaging, and perforation.[3–6] Advances in imaging modalities or diagnostic techniques, such as endoscopic ultrasound (EUS)-guided fine-needle aspiration, offer alternatives with higher diagnostic accuracy, especially for pancreatic tumors.[7–10] Endoscopic nasopancreatic drainage tube placement shows promise for making an early pancreatic

Table 1 Indications for endoscopic retrograde cholangiopancreatography

	Biliary	Pancreas
Diagnostic indication	Bile duct stone Biopsy or cytology for bile duct stricture Diagnosis for tumor extension of bile duct cancer Evaluation for gallbladder lesion Diagnosis for ampullary tumor Evaluation of bile duct using cholangioscopy	Diagnosis for pancreatic duct stricture Diagnosis for pancreatic cancer, IPMN, chronic pancreatitis, pancreatic stone, and AIP Evaluation of pancreatic duct using pancreatoscopy
Therapeutic indication	Removal of bile duct stone Biliary drainage/ stenting Gallbladder drainage Papillectomy Treatment for bile duct injury	Removal of pancreatic stone Treatment for benign pancreatic duct stricture Pancreatic drainage/ stenting Treatment for pancreas fistula Treatment for pancreas pseudocyst

AIP, autoimmune pancreatitis; IPMN, intraductal papillary mucinous neoplasm.

cancer diagnosis but lacks strong evidence.[11,12] In cases of chronic pancreatitis, ERCP is mainly used for therapeutic purposes, such as stenting and stone removal, while magnetic resonance cholangiopancreatography (MRCP) and EUS-guided fine-needle-aspiration are preferred for making a diagnosis.[13–15] Biliary drainage, particularly for obstructive jaundice, can be performed by ERCP or EUS-guided biliary drainage, depending on the case.[16–20]

Q1-2 Is it useful to perform MRCP before diagnostic ERCP in the examination of pancreaticobiliary diseases? (CQ)

MRCP is useful for assessing pancreaticobiliary diseases and is proposed to be performed prior to diagnostic ERCP in facilities where available (weak recommendation, evidence quality: low).

Comment. MRCP is a potential alternative to diagnostic ERCP. In a meta-analysis, MRCP showed high sensitivity and specificity for the identification of bile duct stricture.[21] In an RCT on benign bile duct obstruction, there were no significant differences between the two groups. However, it was reported that diagnostic ERCP could be avoided in half of the cases in the MRCP group.[22] In pancreatic diseases, a comparison of ERCP and MRCP was performed for the diagnosis of chronic pancreatitis and showed that MRCP had good diagnostic performance.[23] In a prospective study comparing the diagnostic performance of MRCP and ERCP in clinically suspected pancreatic cancer, no significant difference was noted between the two groups.[24] In autoimmune pancreatitis, MRCP can avoid unnecessary diagnostic ERCP.[25]

However, for the diagnosis of carcinoma in situ, which is almost impossible to achieve by imaging alone, the usefulness and necessity of ERCP for the purpose of pathological search could not be replaced by MRCP, and the usefulness and necessity of ERCP was deemed acceptable.[11,12]

Q1-3 Can EUS help avoid unnecessary ERCP in patients suspected of having gallstone cholangitis or pancreatitis? (CQ)

In cases where common bile duct stones cannot be identified through other imaging modalities, it is recommended to perform EUS before ERCP in facilities where EUS is available (weak recommendation, evidence quality: moderate).

Comment. The diagnosis of the presence of common bile duct stones is crucial because avoiding unnecessary ERCP can help reduce the risk of PEP. EUS is considered superior to other modalities in detecting common bile duct stones.[26–29] We conducted a meta-analysis to assess the rate of ERCP avoidance and the incidence of PEP in patients with an intermediate risk (American Society for Gastrointestinal Endoscopy guidelines[30]) of common bile duct stones. A literature search yielded a total of 230 studies, and 4 RCTs were included in the meta-analysis.[31–34] The results showed that performing EUS before ERCP was able to reduce unnecessary ERCPs by 59.1%. In addition, the incidence of PEP was significantly lower in the EUS-first group than ERCP-first group (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.15–0.99; $P = 0.045$) (Fig. S1). For patients suspected of having common bile duct stones that cannot be identified using other imaging modalities, EUS should be performed before ERCP.

Pathogenesis of PEP

Q2-1 What is the pathogenesis of post-ERCP pancreatitis? (BQ)

The pathogenesis of PEP remains unclear, but biological and chemical factors such as increased intraductal pressure, hyperosmolality of contrast media, and reflux of duodenal contents into the pancreatic duct have been assumed (Fig. 1).

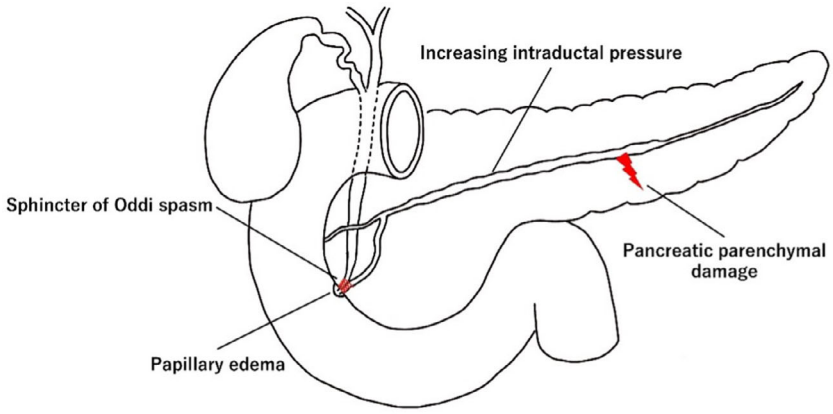

Figure 1 The mechanism of postendoscopic retrograde cholangiopancreatography pancreatitis.

Risk factors of PEP

Q3-1 Do facility factors influence the incidence of PEP? (BQ)

Facility factors do not influence the incidence of PEP in facilities with sufficiently experienced physicians.

Q3-2 Does the experience of the operator influence the incidence of PEP? (BQ)

Operator experience has little impact on the incidence of PEP if ERCP is performed under the supervision of a physician with sufficient experience.

Q3-3 What are the patient-related risk factors for PEP? (BQ)

Suspicion of sphincter of Oddi dysfunction, and female sex, history of pancreatitis, history of PEP, and branch-type intraductal papillary mucinous neoplasm (IPMN), being a young adult, a normal serum bilirubin level, nonchronic pancreatitis, and a long papillary orifice should be noted as patient-related risk factors for PEP.

Q3-4 What are the procedural risk factors for PEP? (BQ)

Procedural risk factors for PEP include the following: precut sphincterotomy, pancreatic duct cannulation, the double-guidewire (GW) technique, more than five cannulation attempts, cannulation time over 10 min, papillary balloon dilation, incomplete bile duct stone extraction, and the placement of large-caliber biliary stents (more than 10F plastic stents [PS] or metal stents [MS]; Table S1).

Q3-5 Is a scoring system for risk factors of PEP useful in predicting its occurrence? (FRQ)

The prediction of PEP using a scoring system may be useful (Table S2).

Informed consent for PEP

Q4-1 What is the incidence rate of PEP? (BQ)

The incidence of PEP is reported to be between 3.5% and 10%, with a severe pancreatitis rate of 0.4%–0.5% and a mortality rate from pancreatitis of 0.02%–0.7%.

Q4-2 What information should be conveyed regarding PEP during informed consent? (BQ)

The symptoms, frequency, and potential for severe, life-threatening outcomes of PEP should be communicated.

Early diagnosis of PEP

Q5-1 What are the symptoms that suggest PEP? (BQ)

The characteristic symptom is the onset or worsening of abdominal pain. Other symptoms include vomiting, a fever, and back pain.

Q5-2 What are the diagnostic criteria for PEP? (BQ)

Post-ERCP pancreatitis is diagnosed according to the diagnostic criteria in Japanese clinical practice guidelines of acute pancreatitis.

Q5-3 Is measuring postprocedure serum pancreatic enzymes on the same day as ERCP useful for predicting PEP? (CQ)

Measuring serum amylase or lipase levels 2–4 h after ERCP is useful for predicting PEP (weak recommendation, evidence quality: low).

Comment. Studies have reported on predicting PEP based on the results of measuring serum pancreatic enzyme levels several hours after ERCP. The results of the meta-analysis of diagnostic test accuracy studies on the prediction of developing PEP using serum amylase or lipase levels measured 2–4 h after ERCP were as follows: a pooled sensitivity of 63.6% (95% CI 53.8–72.4) and pooled specificity of 94.4% (95% CI 91.4–96.4] for the serum amylase cut-off value at 5 times the upper limit of normal and a pooled sensitivity of 85.8% (95% CI 61.9–95.7]) and pooled specificity of 85.3% (95% CI 81.9–88.1] for the serum lipase cut-off value at 3 times the upper limit of normal.[35] Measuring serum amylase or lipase levels 2–4 h after ERCP provides an opportunity to estimate the risk of developing PEP. It is important to understand that there are limitations to diagnostic accuracy.

Q5-4 Does early computed tomography improve the diagnostic yield of PEP in suspicious patients? (BQ)

Early computed tomography is useful in cases suspected of having PEP.

Assessing the severity of PEP

Q6-1 How should the severity of PEP be assessed? (BQ)

At the time of the diagnosis, within 24 h, and between 24 and 48 h, the severity should be repeatedly assessed using the Japanese prognostic factor score revised in 2008.

Treatment of PEP

Q7-1. What is the recommended management for patients with PEP? (BQ)

It is strongly recommended that patients with PEP be managed in accordance with the most recent acute pancreatitis guidelines (Fig. 2).

Q7-2 Is the endoscopic pancreatic drainage after PEP effective? (FRQ)

The usefulness of pancreatic duct drainage for PEP is unclear.

Q7-3 Is urgent stent removal effective in patients with PEP after biliary stent placement? (FRQ)

In patients with PEP who are suspected of having impaired pancreatic juice outflow due to biliary stent placement, stent removal may be beneficial.

Prevention of PEP

Q8-1 Is temporary pancreatic duct stent placement useful for preventing PEP? (CQ)

Temporary pancreatic duct stent placement is proposed for the prevention of PEP in patients at high risk of PEP (weak recommendation; evidence quality: high).

Comment. Repeated pancreatography can increase intraductal and pancreatic tissue pressure, leading to pancreatic juice stasis due to papillary edema, which is a key factor in PEP.[36] This stasis thickens the pancreatic juice, worsens outflow obstruction, and reduces intestinal secretion. As a result, cholecystokinin production increases, further stimulating pancreatic juice secretion, exacerbating stasis, activating trypsin within acinar cells, and triggering pancreatitis. Papillary edema peaks at 24–72 h; temporarily relieving ductal pressure through stenting may prevent PEP.

Meta-analyses of 13 RCTs[37–49] showed that temporary pancreatic duct stent placement significantly reduced the incidence of PEP (OR 0.31, 95% CI 0.21–0.47) and its severity (OR 0.24, 95% CI 0.11–0.54) (Fig. S2). Although adverse events such as ductal injury are possible, their incidence is low (0.6%). In Japan, pancreatic duct stenting for PEP prevention is not covered by insurance and should be considered only in high-risk cases. Therefore, patient-related and procedure-related risk factors should be carefully evaluated. For high-risk groups, please refer to the patient-related risk factors and procedure-related risk factors described in the previous sections ([Q3-03], [Q3-04]). There are no established clear criteria for the indication of temporary pancreatic duct stent placement in the prevention of PEP. However, in cases with patient-related risk factors, where procedural risk factors such as biliary cannulation using the pancreatic GW

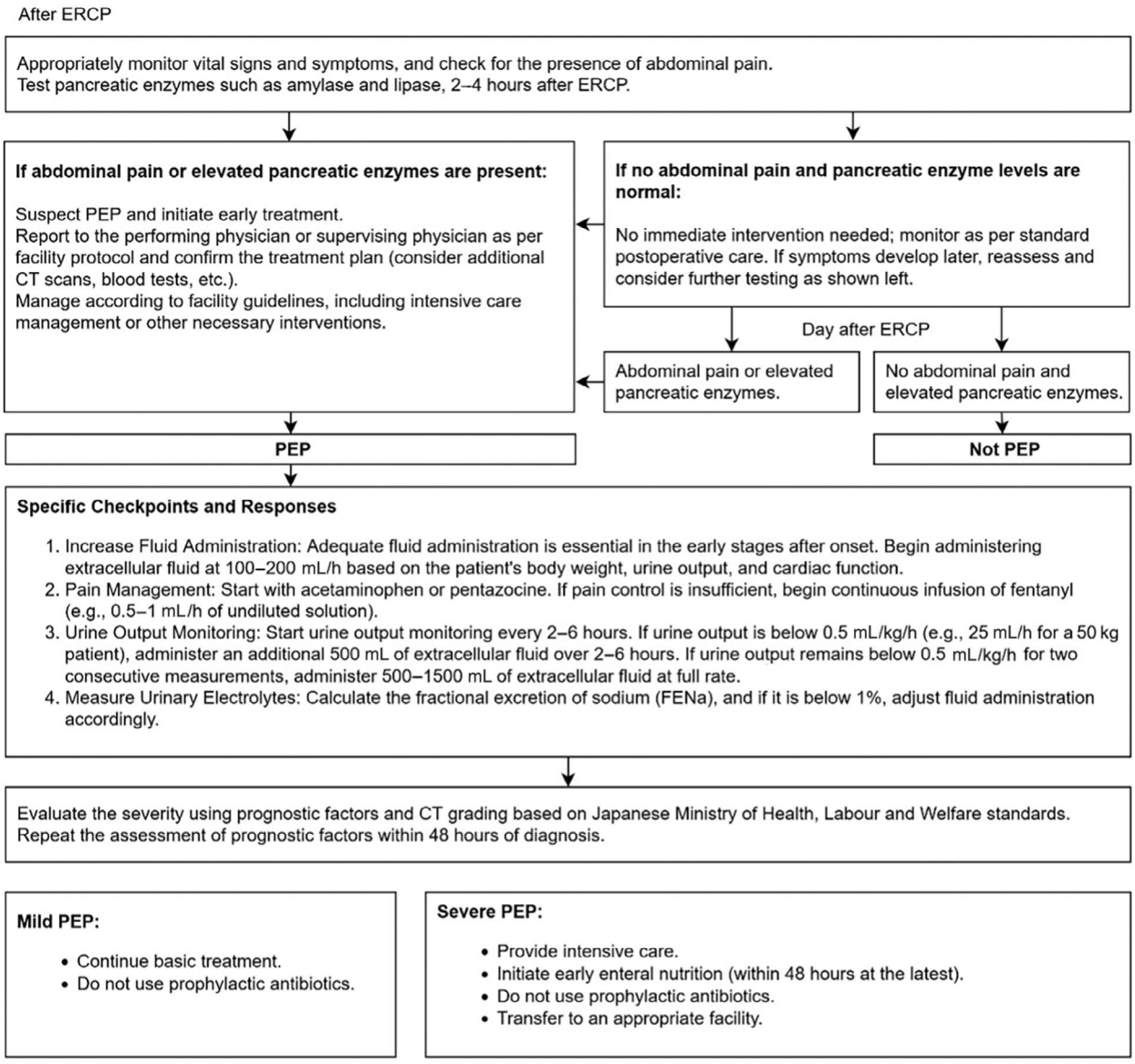

Figure 2 Flowchart for cases of suspected post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). CT, computed tomography.

technique, repeated pancreatography, or endoscopic papillectomy are also present, stent placement is considered a suitable option. However, it has been reported that if pancreatic duct stent placement is attempted but unsuccessful in cases where the GW has not entered the pancreatic duct following biliary intervention, the risk of PEP may actually increase, and caution is required.[50] Moreover, attention is needed to avoid stent obstruction, especially in IPMN cases. Therefore, the indication for temporary pancreatic duct stent placement must take into full consideration the cost and risks, including removal, the skill of the operator, the characteristics of each facility, and the individual condition of the patient. It should not be determined based solely on a single risk factor but should be considered for high-risk groups based on a comprehensive risk assessment that includes the confirmed risks after the procedure.

In the majority of RCTs, a 5F temporary pancreatic duct stent, 3 cm long, and straight with an unflanged inner end, is used. Spontaneous dislodgement stents, which fall out

within a few days, are preferred because of their reduced cost and patient burden.[43] but depending on the case, a 4F pancreatic duct stent, an indwelling pancreatic duct stent with flanges on both ends, and a nasopancreatic duct tube are also used. The choice of stent type to be placed should consider the patient's condition, pancreatic duct anatomy, and future treatment plans.

Q8-2 Does wire-guided cannulation (WGC) prevent PEP? (CQ)

Wire-guided cannulation for biliary cannulation may reduce the incidence of PEP, and it is suggested to be performed at the discretion of the endoscopist or institution (weak recommendation, evidence quality: moderate).

Comment. Our own meta-analysis of six RCTs[51–56] examining the incidence of PEP and the biliary cannulation success rate between the WGC and contrast methods suggested that the WGC method may reduce the incidence of PEP compared to the contrast method, and the biliary cannulation success rate was equivalent between the two (Fig. S3). Our own meta-analysis of three domestic RCTs[51–53] did not find a lower PEP incidence or higher biliary cannulation success rate with the WGC method than with the contrast method (Fig. S4), but our own meta-analysis of three overseas RCTs[54–56] found a significantly lower PEP incidence and a significantly higher biliary cannulation success rate with the WGC method than with the contrast method (Fig. S5). The WGC method for biliary cannulation thus has the potential to reduce the incidence of PEP and should be considered at the discretion of endoscopists or institutions.

Q8-3 Does early pancreatic duct GW/double-GW technique for difficult biliary cannulation affect the incidence of PEP? (CQ)

Statement. Early double-GW technique does not affect the incidence of PEP (no recommendation, evidence quality: moderate).

Comment. Our own meta-analysis of four RCTs[57–60] examining the incidence of PEP and the biliary cannulation success rate in the early double-GW technique showed that the early double-GW technique for difficult biliary cannulation did not significantly increase the incidence of PEP, nor did it significantly increase the biliary cannulation success rate (Fig. S6). The early double-GW technique is unlikely to affect the incidence of PEP or the biliary cannulation success rate.

Q8-4 Does early precut sphincterotomy for difficult biliary cannulation reduce the incidence of PEP? (CQ)

Statement. Early precut sphincterotomy may reduce the incidence of PEP and is recommended for difficult biliary cannulation. However, it should be performed by experienced endoscopists or specialized institutions (weak recommendation; evidence quality: moderate).

Comment. Our own meta-analysis of eight RCTs[61–68] examining the incidence of PEP and the biliary cannulation success rate in early precut sphincterotomy for therapeutic ERCP or difficult biliary cannulation showed that early precut sphincterotomy significantly reduced the incidence of PEP and significantly increased the biliary cannulation success rates compared with controls (Fig. S7). However, precut sphincterotomy is a highly skilled procedure that carries a risk of bleeding and perforation. Therefore, early precut sphincterotomy should be performed by experienced endoscopists or specialized institutions for difficult cases of biliary cannulation.

Q8-5 Conversion to other drainage methods in difficult biliary canulation cases reduce the incidence of PEP? How should we choose? (FRQ)

The incidence of PEP may be high in patients with difficult bile duct canulation, so early conversion to other drainage methods can be considered. However, the timing of such conversion and the choice of treatment methods require further study.

Q8-6 Does performing endoscopic sphincterotomy (EST) when placing a biliary PS reduce the incidence of PEP? (CQ)

Although performing EST when placing a biliary PS carries the risk of post-EST bleeding, it may reduce the incidence of PEP. In addition, it is recommended when using large-diameter stents (conditional weak recommendation; evidence quality: low).

Comment. We performed a meta-analysis of four RCTs examining the efficacy of EST when placing a biliary PS for the prevention of PEP.[69–72] The results showed that it might reduce the incidence of PEP (OR 0.40, 95% CI 0.13–1.21) (Fig. S8). However, although EST is associated with a risk of post-EST bleeding (OR 5.98, 95% CI 1.54–23.2), it is

Table 2 Questionnaire survey conducted by the guideline committee about performing endoscopic sphincterotomy (EST) when placing a biliary plastic stent (PS)

	Yes	No
EST should be performed when placing a 7F biliary PS	3 (27%)	8 (73%)
EST should be performed when placing a 10F biliary PS	11 (100%)	0 (0%)

thought to be outweighed by a reduction in the incidence of PEP (Fig. S9).[73] Furthermore, a questionnaire survey conducted by the guideline committee found that only 27% (3/11) of the facilities performed EST when placing a 7F PS, whereas 100% (11/11) of the facilities performed EST when placing a 10F PS (Table 2). Based on these considerations, the expert opinion is that EST is not necessarily required when placing a 7F PS to prevent PEP; however, EST is recommended for 10F PS.

Q8-7 Does performing EST when placing a biliary MS reduce the incidence of PEP? (CQ)

Although performing EST when placing a biliary MS carries a risk of post-EST bleeding, it has the potential to reduce the incidence of PEP and is therefore recommended (weak recommendation; evidence quality: low).

Comment. We performed a meta-analysis of three RCTs examining the efficacy of EST when placing an MS for the prevention of PEP.[74–76] The results showed that it may reduce the incidence of PEP (OR 0.58, 95% CI 0.16–2.06) (Fig. S9a). In contrast, although EST is associated with a risk of post-EST bleeding (OR 4.3, 95% CI 0.64–28.7), it is thought to be outweighed by the benefit of a reduced incidence of PEP (Fig. S9b). In the unlikely event that post-EST bleeding occurs, it is often possible to stop the bleeding by placing an MS.[73] Furthermore, a questionnaire survey conducted by the guideline committee found that regardless of whether an MS was covered or uncovered, 100% (11/11) of the facilities performed EST when placing an MS (Table 3). Based on these considerations, the expert opinion is that EST is recommended for placing an MS to prevent PEP.

Table 3 Questionnaire survey conducted by the guideline committee about performing endoscopic sphincterotomy (EST) when placing a biliary metal stent (MS)

	Yes	No
EST should be performed when placing covered MS	11 (100%)	0 (0%)
EST should be performed when placing uncovered MS	11 (100%)	0 (0%)

Q8-8 What points should assistants be careful of to prevent PEP? (BQ)

In ERCP-related procedures, assistants who perform tasks such as GW manipulation and contrast media injection must have a thorough understanding of the procedure and perform it with care, keeping in mind the risk of PEP.

Q8-9 What is the best way to insert a GW into the pancreatic duct to prevent PEP? (BQ)

When performing ERCP, avoid inserting the GW into the pancreatic duct as much as possible, and be careful not to insert it into the branch pancreatic duct during intrapancreatic manipulation. A thin-diameter angle-type GW may reduce the risk of PEP.

Q8-10 From the perspective of PEP, what method is recommended for dilating the papilla's orifice to remove common bile duct stones? (BQ)

Based on the incidence of PEP, EST and endoscopic papillary large balloon dilation are recommended.

Q8-11 Is protease inhibitor useful in preventing the development of PEP? (CQ)

The administration of gabexate mesylate and ulinastatin is not recommended in preventing PEP (strong recommendation; evidence quality: moderate).

Nafamostat mesylate potentially has efficacy in preventing PEP; however, no definitive recommendation can be offered due to a lack of high-quality evidence (no recommendation; evidence quality: moderate).

Comment. In our own meta-analysis of five RCTs,[77–81] the administration of gabexate mesylate was not effective in decreasing the incidence rate of PEP (OR 0.61, 95% CI 0.31–1.19) (Fig. S10a). With respect to the administration of ulinastatin for the prevention of PEP, our meta-analysis of two RCTs[82,83] did not confirm its positive effect on PEP prevention (Fig. S10b). Nafamostat mesylate, a more potent protease inhibitor with a longer half-life than other protease inhibitors, had a preventive effect on PEP in our own systematic review and meta-analysis of four RCTs (OR 0.45, 95% CI 0.26–0.76)[84–87] (Fig. S10c). However, during the administration of nafamostat mesylate to prevent PEP, some

issues need to be further examined, such as the timing of administration, inhibitive effect of PEP severity, and cost-effectiveness. Therefore, it is difficult to offer a definitive recommendation regarding whether or not nafamostat mesylate should be administered to prevent PEP.

Q8-12 Is rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) useful in preventing the development of PEP? (CQ)

If the patient is at risk of PEP, rectal administration of NSAIDs (indomethacin or diclofenac) before or after ERCP is suggested (weak recommendation; evidence quality: high).

Comment. Our meta-analysis of 13 RCTs[88–100] examining the effect of rectal administration of NSAIDs on the prevention of PEP revealed that rectally administered NSAIDs significantly reduced the incidence of PEP, including moderate and severe pancreatitis (Fig. S11). Since only two cases (0.1%) of adverse events (acute kidney injury) occurred in 2089 patients in the NSAIDs group across the 13 RCTs, if the drug is used with attention to the contraindications, it is a safe and inexpensive drug for a single rectal administration and is highly useful in the prevention of PEP. In the subgroup analysis in our meta-analysis, both indomethacin and diclofenac significantly suppressed PEP (Fig. S12). Regarding the timing of administration, both pre-ERCP and post-ERCP administration significantly suppressed PEP, suggesting that either timing is acceptable (Fig. S13).

Most RCTs have been conducted with a single dose of 100 mg. However, in Japan, only 50 mg formulations are available, and medical insurance coverage is limited to 50 mg. The effectiveness of low-dose NSAIDs for prevention of PEP has not been sufficiently verified, and there are some cautious opinions in Japan regarding their effectiveness. There are cases where NSAIDs are contraindicated, and despite high levels of evidence, the guideline committee, after careful consideration, concluded with "weak recommendation."

Q8-13 Do nonrectal NSAIDs prevent PEP? (CQ)

Nonrectal administration of NSAIDs is not recommended as it has a low efficacy in preventing PEP (weak recommendation; evidence quality: moderate).

Comment. Numerous studies have reported the efficacy of NSAIDs in preventing PEP, with rectal administration being the most used route.[101] This route avoids liver metabolism, ensuring higher bioavailability and faster action than oral intake.[102] Despite patient discomfort and burden on medical staff, rectal administration offers advantages, such as bypassing digestive fluids and immediate absorption. Other routes of administration, such as oral, intramuscular, and intravenous, have been studied. Meta-analyses of intramuscular NSAID injections showed a slight reduction in pancreatitis risk, but this was not significant (Fig. S14).[103–106] Oral administration failed to show any benefit, likely because of slow absorption and inactivation by gastric acid.[107] Although intravenous administration offers rapid absorption, no effective NSAID formulations exist for this route. Overall, rectal administration remains the most effective and recommended method for preventing PEP, as no other route has proven effective. Further research is required to evaluate alternative methods.

Q8-14 Are somatostatin and octreotide useful in preventing the development of PEP? (CQ)

The administration of somatostatin and octreotide is not recommended in preventing PEP (strong recommendation; evidence quality: moderate).

Comment. Somatostatin suppresses the pancreatic exocrine function, potentially preventing PEP. The prophylactic effect of somatostatin on PEP varies according to meta-analyses.[108,109] With respect to octreotide, a somatostatin analog with a longer half-life, a meta-analysis of 15 RCTs revealed no beneficial effect in the prevention of PEP; however, when limited to large-scale RCTs, octreotide could statistically prevent PEP (OR 0.50, 95% CI 0.32–0.79).[110] In our meta-analysis of eight RCTs assessing the efficacy of somatostatin or octreotide,[79,80,111–117] the medication had no preventive effect in the incidence of PEP (OR 0.58, 95% CI 0.32–1.05) (Fig. S15a), but the occurrence of moderate and severe PEP according to Cotton's severity classification was significantly suppressed (OR 0.40, 95% CI 0.20–0.81) (Fig. S15b). As the results of meta-analyses are conflicting, the current revised guidelines do not recommend the administration of somatostatin or octreotide for the prevention of PEP.

Q8-15 Does administration of nitrate prevent PEP? (FRQ)

Sublingual nitrate could be useful for preventing the development of PEP. Further studies examining the effect of preventing PEP are needed (evidence quality: moderate).

Q8-16 Does peri-ERCP aggressive hydration prevent PEP? (FRQ)

Peri-ERCP aggressive hydration may be useful in preventing PEP; however, further studies are needed (evidence quality: moderate).

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Appendix S1 Supplementary results and references of background questions (BQs) and future research questions (FRQs).

Figure S1 Results of our own meta-analysis of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) rates in patients with intermediate risk of common bile duct stones: ERCP-first vs. endoscopic ultrasound (EUS)-first approaches.

Figure S2 Results of our own meta-analysis of temporary pancreatic duct stenting. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) (mild to severe). (b) Incidence of PEP (moderate to severe).

Figure S3 Results of our own meta-analysis of six randomized controlled trials (RCTs) examining the wire-guided cannulation (WGC) method. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (b) Biliary cannulation success rate.

Figure S4 Results of our own meta-analysis of three domestic randomized controlled trials (RCTs) examining the wire-guided cannulation (WGC) method. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (b) Biliary cannulation success rate.

Figure S5 Results of our own meta-analysis of three overseas randomized controlled trials (RCTs) examining the wire-guided cannulation (WGC) method. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (b) Biliary cannulation success rate.

Figure S6 Results of our own meta-analysis of four randomized controlled trials (RCTs) examining the early

double-guidewire technique. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (b) Biliary cannulation success rate.

Figure S7 Results of our own meta-analysis of eight randomized controlled trials (RCTs) examining early precut sphincterotomy. (a) Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (b) Biliary cannulation success rate.

Figure S8 Results of our own meta-analysis of randomized controlled trials (RCTs) examining the efficacy of performing endoscopic sphincterotomy (EST) when placing a biliary plastic stent (PS) for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Incidence of PEP. (b) Incidence of post-EST bleeding.

Figure S9 Results of our own meta-analysis of randomized controlled trials (RCTs) examining the efficacy of performing endoscopic sphincterotomy (EST) when placing a biliary metal stent (MS) for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Incidence of PEP. (b) Incidence of post-EST bleeding.

Figure S10 Results of our own meta-analysis of randomized controlled trials (RCTs) assessing the preventive effect of protease inhibitors on post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Gabexate mesylate. (b) Ulinastatin. (c) Nafamostat mesylate.

Figure S11 Results of our own meta-analysis of randomized controlled trials (RCTs) comparing rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Incidence of PEP. (b) Incidence of moderate or severe PEP.

Figure S12 Results of our own meta-analysis of randomized controlled trials (RCTs) comparing rectal administration of indometacin or diclofenac and placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Incidence of PEP by indometacin. (b) Incidence of PEP by diclofenac.

Figure S13 Results of our own meta-analysis of randomized controlled trials (RCTs) comparing rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) before or after endoscopic retrograde cholangiopancreatography (ERCP) and placebo for post-ERCP pancreatitis (PEP). (a) Incidence of PEP (administration of NSAIDs before ERCP). (b) Incidence of PEP (administration of NSAIDs after ERCP).

Figure S14 Results of our own meta-analysis of randomized controlled trials (RCTs) comparing intramuscular nonsteroidal anti-inflammatory drug (NSAID) injections and placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP).

Figure S15 Results of our own meta-analysis of randomized controlled trials (RCTs) assessing the preventive effect of somatostatin and octreotide on post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). (a) Incidence of PEP. (b) Incidence of moderate and severe PEP.

Table S1 Procedural risk factors from prospective studies.

Table S2 Risk factors used in the scoring system.