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## Current approaches and questions yet to be resolved for the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis

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### Abstract

Prophylaxis is important for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), which is the most common and serious complication of ERCP. Although the current guidelines include independent patient- and procedure-related risk factors for PEP and available PEP prophylactic measures, the synergistic effect of these risk factors on PEP should also be considered, given that patients often harbor multiple risk factors. Furthermore, a combination of prophylactic measures is often selected in clinical practice. However, established methods estimating the synergistic effect of independent risk factors on PEP incidence are lacking, and evidence on the impact of combining prophylactic measures on PEP should be discussed. Selection of appropriate candidate patients for ERCP is also important to reduce the incidence of PEP associated with unnecessary ERCP. ERCP indications in patients with asymptomatic common bile duct stones (CBDs) and in those with suspected CBDs with no imaging-based evidence of stones are controversial. Further studies are warranted to predict the synergistic effect of independent risk factors on PEP, determine the best prophylactic PEP measures, and identify appropriate candidates for ERCP in patients with asymptomatic CBDs and those with suspected CBDs.

**Key Words:** Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Prophylaxis; Guidelines

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**Core Tip:** To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP should be discussed. Furthermore, ERCP indications in patients with asymptomatic common bile duct stones (CBDs) and patients with suspected CBDs without evidence of stones by imaging are controversial. Further studies are warranted to estimate the synergistic effect of independent risk factors on PEP and to determine the best prophylactic measures as well as the appropriate candidates for ERCP among patients with asymptomatic CBDs and those with suspected CBDs.

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## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential therapeutic procedure for patients with biliopancreatic disorders. However, it is associated with high risks of procedure-related complications. Post-ERCP pancreatitis (PEP) is the most frequent complication, with an approximate rate of 3%-10% [1,2]. A meta-analysis of 108 randomized controlled trials revealed that the incidence of PEP was high at 14.7% [95% confidence interval (CI) 11.8%-17.7%] in high-risk patients, with one or more patient- and/or procedure-related risk factors for PEP [2]. Although most PEP cases are mild or moderate, severe PEP, which is potentially lethal, occurs in approximately 10% of the cases [1]. Therefore, it is important to reduce the incidence of PEP.

Recent guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend prophylactic methods for reducing the incidence of PEP [3,4]. These guidelines encompass patient- and procedure-related risk factors associated with PEP and strategies for reducing the incidence of PEP, including patient selection, pharmacologic prophylaxis, and ERCP technique modifications. This opinion review discusses the current approaches used in PEP prevention and the questions yet to be resolved for the prophylaxis of PEP to further reduce the incidence of PEP.

## RISK FACTORS FOR PEP

Table 1 summarizes the independent risk factors for PEP included in the ESGE and ASGE guidelines for ERCP-related adverse events [3,4]. Specifically, the ESGE guideline categorizes independent PEP risk factors into definitive and likely risk factors, and patients with at least one definitive or two likely patient- or procedure-related risk factors are defined as those at a high risk for PEP [3].

Patients often harbor multiple risk factors for PEP; therefore, the potential synergistic effect of independent risk factors for PEP should be considered. A prospective multicenter study revealed the escalation of PEP risk in patients with multiple risk factors for PEP. The odds ratios in female gender alone, female gender plus normal serum bilirubin, and female gender plus normal serum bilirubin plus difficult cannulation were 2.5, 4.8 and 16.2, respectively [5]. Although scoring systems may be useful for estimating this synergistic effect [6-10], no established scoring system exists due to the limited number of studies. Furthermore, estimating the risk for PEP before ERCP is important for advanced counseling of patients on the specific risk for PEP. A recent study suggesting a disease-based PEP risk stratification approach for choledocholithiasis reported that the incidence rates of PEP were 13.7%, 7.3%, and 1.8% in patients with asymptomatic common bile duct stones (CBDs), obstructive jaundice without cholangitis, and acute cholangitis, respectively [11]. Disease-based risk stratification may be a useful method for easily estimating the average risk for PEP before ERCP in patients with biliary and pancreatic diseases as the synergistic effect of the independent risk factors for PEP may differ among the wide range of diseases requiring ERCP. Furthermore, a study demonstrated that a large pancreatic volume was associated with high risk and increased severity of PEP [12]. Pancreatic volume based on pre-ERCP images may also be useful for predicting the risk for PEP prior to ERCP.

In summary, although several independent risk factors for PEP have been identified [3,4,13], further studies are warranted to establish the methods for estimating the synergistic effect of independent risk factors for PEP. If possible, advanced prediction of PEP before ERCP is desirable to properly counsel patients on the specific risk for PEP and to perform aggressive prophylaxis prior to ERCP based on the

**Table 1 Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis in the European Society of Gastrointestinal Endoscopy and American Society for Gastrointestinal Endoscopy guidelines**

ESGE guideline	ASGE guideline
<b>Patient-related definitive risk factors</b>	<b>Patient-related risk factors</b>
Suspected sphincter of Oddi dysfunction	Suspected sphincter of Oddi dysfunction
Female sex	Female sex
Previous pancreatitis	Previous recurrent pancreatitis
Previous post-ERCP pancreatitis	Previous post-ERCP pancreatitis
<b>Procedure-related definitive risk factors</b>	Younger age
Difficult cannulation	Absence of chronic pancreatitis
More than one pancreatic guidewire passage	Normal serum bilirubin
Pancreatic injection	<b>Procedure-related risk factors</b>
<b>Patient-related likely risk factors</b>	Difficult cannulation (> 10 min)
Younger age	Repeated pancreatic guidewire cannulation
Nondilated extrahepatic bile duct	Pancreatic injection
Absence of chronic pancreatitis	Endoscopic papillary large-balloon dilation of a native papilla
Normal serum bilirubin	
End-stage renal failure	
<b>Procedure-related likely risk factors</b>	
Precut sphincterotomy	
Pancreatic sphincterotomy	
Papillary balloon dilation	
Unsuccessful clearance of bile duct stones	
Intraductal ultrasound	

ASGE: American Society for Gastrointestinal Endoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy.

specific PEP risk of the patient.

## PATIENT SELECTION

Selection of appropriate candidates for ERCP is important to reduce the incidence of PEP associated with unnecessary ERCP. Patients with biliary and pancreatic diseases requiring drainage, such as malignant biliary and pancreatic strictures and symptomatic choledocholithiasis with imaging-based evidence of CBDs, are strong candidates for ERCP. However, determining ERCP candidates may be difficult in patients with asymptomatic CBDs and suspected choledocholithiasis with no imaging-based evidence of stones.

The ASGE and ESGE guidelines for the evaluation and management of choledocholithiasis recommend strategies for selecting ERCP candidates in patients with suspected CBDs based on stratification into low-, intermediate-, and high-PEP-risk groups[14,15]. The criteria and treatment strategy for each risk group are presented in Table 2. In these guidelines, proceeding with ERCP is recommended in high-risk patients regardless of the imaging-based evidence of CBDs. However, the high-diagnostic ability of imaging modalities, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), has been recently described. Two meta-analyses reported that the sensitivity and specificity of EUS were 95%-97% and 87%-93%, and that the sensitivity and specificity of MRCP were 90%-97% and 92%-96%, respectively[16,17]. The rate of detecting even small CBDs was high with EUS[16]. However, a systematic review and meta-analysis revealed that the mean sensitivity and specificity for the diagnosis of CBDs were 23% (range, 18%-32%) and 89% (range, 70%-100%), respectively, when acute cholangitis was used to predict the presence of CBDs in patients with suspected CBDs[18]. Furthermore, one study reported that the sensitivity and specificity for the

**Table 2 Recommended strategies for suspected common bile duct stones in patients with symptomatic cholelithiasis based on the ESGE and ASGE guidelines**

ESGE guideline			ASGE guideline	
Likelihood	Predictors	Recommended strategy	Predictors	Recommended strategy
Low	Normal liver function tests and no CBD dilation at US	Proceed to cholecystectomy	No predictors	Cholecystectomy with/without laparoscopic cholangiography (IOC) or intraoperative US
Intermediate	Abnormal liver function tests and/or dilated CBD on US	Perform EUS/MRCP	Abnormal liver function tests or age > 55 years or dilated CBD on US/cross-sectional imaging	Perform EUS/MRCP, laparoscopic IOC, or intraoperative US
High	CBDs identified at US or features of cholangitis	Proceed to ERCP	CBDs identified at US/cross-sectional imaging or features of cholangitis or dilated CBD with total bilirubin > 4 mg/dL on US/cross-sectional imaging	Proceed to ERCP

ASGE: American Society for Gastrointestinal Endoscopy; CBD: Common bile duct; CBDs: Common bile duct stones; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy; EUS: Endoscopic ultrasonography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasonography.

diagnosis of CBDs were 19% and 96%, respectively, using the high-risk criteria of a total bilirubin level of above 4 mg/dL plus the presence of a dilated common bile duct (CBD) (> 6 mm in patients without cholecystectomy and > 8 mm in those with prior cholecystectomy)[19]. Therefore, high-risk criteria for diagnosis of CBDs based on the clinical diagnosis, such as cholangitis features and dilated CBD with a total bilirubin level > 4 mg/dL without evidence of stones remains controversial. Patients with suspected CBDs who exhibit imaging-based evidence of CBDs are strong candidates for ERCP. However, it remains questionable whether ERCP is indicated in high-risk patients with no imaging-based evidence of stones, except for those with severe cholangitis requiring emergent biliary drainage.

Several studies have demonstrated that the incidence of PEP is significantly higher in patients with asymptomatic CBDs, defined as the absence of abdominal symptoms and abnormal liver function tests, than in those with symptomatic CBDs (12.5%-20.8% *vs* 3.7%-6.9%)[20-23], although only one study reported that the risk for PEP following ERCP performed by experienced endoscopists was comparable between patients with asymptomatic and symptomatic CBDs[24]. Due to the absence of cholestasis, patients with asymptomatic CBDs have normal total bilirubin levels and nondilated CBD, and can confound the assessment of patient-related risk factors for PEP[21]. Furthermore, floppy major duodenal papilla due to low bile duct pressure often results in difficult biliary cannulation in asymptomatic patients[21]. Therefore, the risk of PEP might be higher in patients with asymptomatic CBDs, who are susceptible to the synergistic effect of the independent risk factors for PEP, than in those with symptomatic CBDs.

Studies investigating the natural history of asymptomatic CBDs have demonstrated that the cumulative incidence rate of biliary complications ranges from 0% to 29% during a median follow-up period of 30 days to 4.8 years[25-29]. Although available guidelines recommend endoscopic stone removal even in asymptomatic patients[14,15,30,31], prospective studies comparing the long-term outcomes between endoscopic treatment and the wait-and-see strategy for patients with asymptomatic CBDs are warranted to determine whether routine endoscopic stone removal of asymptomatic CBDs is justified or not.

A recent study reported that the risk for PEP was lower in ERCP for choledocholithiasis with acute cholangitis than in ERCP for choledocholithiasis without acute cholangitis[32]. Although ESGE guideline for the endoscopic management of CBDS recommends elective ERCP for mild cholangitis, performing ERCP before improving cholangitis may be better in the view point of reducing the risk of PEP.

## MODIFICATIONS IN ERCP TECHNIQUE AND PHARMACOLOGICAL PROPHYLAXIS TO REDUCE THE INCIDENCE AND SEVERITY OF PEP

### PEP prophylaxis during ERCP

Recommendations for post-ERCP pancreatitis prophylaxis in ASGE and ESGE guidelines are presented in Table 3.



**Table 3 Recommendations for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis in American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy guidelines**

ASGE guideline	ESGE guideline
<b>PEP prophylaxis during ERCP</b>	<b>PEP prophylaxis during ERCP</b>
Pancreatic duct stenting in high-risk patients (high quality of evidence)	Pancreatic duct stenting in high-risk patients (strong recommendation, moderate quality of evidence)
Early precut sphincterotomy for difficult cannulation (moderate quality of evidence)	
<b>Pharmacologic methods for PEP prophylaxis</b>	<b>Pharmacologic methods for PEP prophylaxis</b>
Rectal NSAIDs in high-risk patients without contraindication (moderate quality of evidence)	Routine rectal NSAIDs of 100 mg of diclofenac or indomethacin immediately before in all patients without contraindication (strong recommendation, moderate quality of evidence)
Rectal indomethacin in average-risk patients without contraindication (moderate quality of evidence)	Hydration with lactated ringers in patients with contraindication to NSAIDs without at risk of fluid overload and without prophylactic pancreatic stenting (strong recommendation, moderate quality of evidence)
Hydration with lactated ringers (very-low quality of evidence)	Not suggested for the routine combination of rectal NSAIDs with other prophylactic measures (weak recommendation, low quality of evidence)
	Not recommended for protease inhibitors and epinephrine onto the papilla (strong recommendation, moderate quality of evidence)
	Somatostatin and octreotide (no recommendation)

ERCP: Endoscopic retrograde cholangiopancreatography; ASGE: American Society for Gastrointestinal Endoscopy; ESGE: European Society of Gastrointestinal Endoscopy; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Prophylactic pancreatic stent placement is a well-known effective method for PEP prophylaxis. Several meta-analyses have indicated that prophylactic pancreatic stent is associated with the decreased overall incidence of PEP (odds ratio, 0.22-0.39) and decreased incidence of severe PEP[33-38]. However, evidence for the benefit of salvage pancreatic stenting in patients with PEP is lacking. Two studies demonstrated that salvage pancreatic stenting might be useful for the rapid resolution of PEP and halting progression to severe PEP[39,40]. The ESGE guidelines recommend against the use of salvage pancreatic stenting in patients with PEP due to the limited evidence; however, this approach has been recommended in select patients, such as those with PEP accompanied by severe abdominal pain and those with more than 10-fold increase in serum amylase levels[3].

Pancreatic injection is a procedure-related definitive risk factor for PEP[3]. The use of low-osmolality contrast media, which might be less harmful for the epithelium of pancreatic duct compared with high-osmolality contrast media[41], may be a possible approach to prevent PEP. However, studies evaluating the efficacy of low-osmolality contrast medium for PEP prevention have reported contradictory findings [41-44].

Difficult biliary cannulation is another definitive risk factor for PEP[3,4]. Although the definition of difficult cannulation varies among the previous studies, the ESGE guidelines for papillary cannulation and sphincterotomy technique in ERCP define difficult cannulation as cases fulfilling one or more of several criteria, such as more than five contacts with the major duodenal papilla during the cannulation attempt, cannulation attempt lasting more than 5 min after the visualization of the papilla, and more than one unintended cannulation or opacification of the pancreatic duct[45]. In cases with difficult biliary cannulation, pancreatic guidewire-assisted cannulation and precut sphincterotomy are used as well-known rescue techniques. Several studies have demonstrated the safety and efficacy of early precut sphincterotomy in reducing the risk of PEP. A recent systematic review and network meta-analysis revealed that early precut sphincterotomy was associated with increased successful biliary cannulation and reduced incidence of PEP compared with the standard cannulation technique and pancreatic guidewire-assisted cannulation[46]. Furthermore, a retrospective study demonstrated that the second ERCP after the failure of initial biliary cannulation following precut sphincterotomy should be performed at least 4 days after the first ERCP[47]. However, a few studies investigated the efficacy and safety of the early use of double-guidewire technique. A randomized controlled trial revealed that the early use of double-guidewire technique increased the rate of successful biliary cannulation and that the incidence of PEP was similar between the double-guidewire technique and the repeated use of single-guidewire technique[48]. Another randomized controlled trial demonstrated that the early use of double-guidewire technique did not facilitate successful biliary cannulation and did not reduce the incidence of PEP[49]. Further studies are warranted to evaluate the efficacy and safety of early use of pancreatic guidewire-assisted cannulation. Furthermore, the optimal timing for the rescue cannulation technique is unclear, although one study suggested that attempting biliary cannulation for 5 min might be a valid cutoff for the implementation of the rescue technique[50].

### Pharmacologic methods for PEP prophylaxis

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are consistently recommended as pharmacologic prophylaxis for PEP in the current guidelines[3,4]. Rectal diclofenac and indomethacin are considered to have a similar beneficial effect for the prophylaxis of PEP, and the rectal NSAID dose of 100 mg is recommended in the ASGE and ESGE guidelines[3,4]. However, the rectal NSAID dose of 100 mg may be too high for elderly patients or those with low body weight, especially among Asian populations. A randomized controlled trial revealed that the incidence of PEP was significantly lower in patients who were administered 25-50-mg rectal NSAIDs than in those who were not administered rectal NSAIDs [3.9% (2/51) *vs* 18.9% (10/53)][51]. However, several retrospective and prospective studies demonstrated that low-dose rectal NSAIDs were not useful for reducing the risk for PEP[52-54]. Further studies are warranted to determine the optimal rectal NSAID dose in elderly patients and in those with low body weight. Studies investigating the combination of rectal NSAIDs with other prophylactic approaches for PEP found no difference in the PEP incidence between rectal NSAIDs alone and rectal NSAIDs in combination with prophylactic pancreatic stenting[55-57]. However, a recent study demonstrated that the combined approach of rectal NSAIDs and prophylactic pancreatic stenting was useful for preventing PEP in patients undergoing ERCP using the double-guidewire technique[58].

Aggressive hydration is recognized as a useful method for PEP prophylaxis[3]. Recent meta-analyses revealed that aggressive hydration with the lactated Ringer's solution of 35-45 mL/kg administered during 8-10 h contributed to reduce the incidence of PEP with odds ratios of 0.29-0.47[59-61]. Furthermore, aggressive hydration was associated with the decreased moderate to severe PEP with the odds ratio of 0.16[59], and there were no differences in fluid overload-related complications[60,61]. While several studies reported that rectal NSAIDs plus hydration was an effective combination for the prevention of PEP[37,62-65], others reported no benefit with this approach[66,67]. A recent network meta-analysis of 24 randomized controlled trials demonstrated that a combination of rectal indomethacin and aggressive hydration is the best conservative approach for prophylaxis of PEP with preventive efficacy 70%-99% higher than that of single prophylaxis[64]. In recent years, with the increasing implementation of prophylactic measures for PEP, the combination of various approaches is often selected in clinical practice[68]. Further studies are warranted to solve the dilemma of combining specific approaches for PEP prophylaxis.

## CONCLUSION

Estimation of the PEP risk based on patient- and procedure-related risk factors, patient selection for ERCP, and technical and pharmacological prophylaxis for PEP are important aspects to be considered to reduce the incidence of PEP following ERCP. Although several independent patient- and procedure-related risk factors for PEP have been identified, methods for estimating the synergistic effect of these risk factors on PEP incidence should be established in future studies. Regarding patient selection, whether routine ERCP in cases of asymptomatic CBDs and highly suspected CBDs without imaging-based evidence of stones is warranted should be discussed. Furthermore, although independent prophylactic measures such as rectal NSAIDs and prophylactic pancreatic stenting have been implemented, further studies are warranted to determine the best prophylactic measures for PEP, including the combination of independent prophylactic measures.

## FOOTNOTES

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