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Review Article

# Endoscopic retrograde cholangiopancreatography complications: Techniques to reduce risk and management strategies

Paul R. Tarnasky,* Prashant Kedia

A B S T R A C T

Adverse events after endoscopic retrograde cholangiopancreatography (ERCP) are not uncommon and can be associated with tragic outcomes. Bleeding, perforation, and post-ERCP pancreatitis are the most common complications. Some events are unavoidable; others are associated with well described risk factors so that they can be either anticipated and/or measures can be taken for prevention or at least risk reduction. This review will focus on the more common complications after ERCP, their risk factors, and potential strategies for risk reduction. Additionally, recommendations for management of ERCP complications will be presented.



Keywords: Cholangiopancreatography, endoscopic retrograde; Hemorrhage; Intestinal perforation; Pancreatitis

## Introduction

Complications after endoscopic retrograde cholangiopancreatography (ERCP) are unfortunately not uncommon as up to 10% of cases are associated with adverse events. Bleeding or perforation occurs in only about 1% of ERCP procedures, but post-ERCP pancreatitis is observed in about 5% of cases. Complications after ERCP are considered to be 20-fold more common overall and there is a 4-fold increase in the severity of complications as compared to standard endoscopic procedures.[1] Most concerning is that ERCP has a high likelihood for very serious sequelae including fatal outcomes in about 0.33%–1% of cases.[1–6] There is also a considerable medicolegal risk associated with ERCP complications.[7] A combination of complications, e.g., pancreatitis, perforation, and/or cardiopulmonary events can be devastating. Complications are more common after procedures involving very advanced ERCP techniques (10%) when compared to less complex (2%) cases.[8]

The severity grading for common post-ERCP complications including pancreatitis, bleeding, perforation, infection (cholangitis, cholecystitis, cellulitis), stent-related, and cardiopulmonary events are well defined.[2,9] It is important to note that any unwanted event within 48 hours of ERCP is technically an adverse event, even if not related to the ERCP. For the purpose of this review, the practical definition of a complication implies that the adverse event is directly related to the procedure.

The purpose of this review is four fold: (1) to define the most common ERCP complications; (2) review the associated risk factors; (3) suggest strategies for reducing the risk; and (4) review management recommendations when complications occur.

## Post-ERCP Pancreatitis

A consensus definition and severity grading of post-ERCP pancreatitis (PEP) has remained the standard.[2] Diagnosis of PEP is usually not difficult. An important distinction is that PEP comprises clinical pancreatitis that is above baseline as defined by: steady midepigastric abdominal pain that is new or increased after ERCP, accompanied by a three-fold increase in serum pancreatic enzymes more than 24 hours after ERCP, and requires unplanned hospitalization. Severity is defined as: mild for length of stay 1–3 days; moderate if hospitalized for 4–10 days; and severe if requires hospitalization > 10 days, need for percutaneous or surgical therapy, develops fluid collection or necrosis, and/or contributes to death. The revised Atlanta classification specifies that patients with local complications (i.e., peripancreatic fluid collections or necrosis) and/or transient organ failure are categorized as having moderately severe pancreatitis.[10]

There is wide disparity but the most accurate overall risk of

*Methodist Dallas Medical Center, Methodist Digestive Institute, Dallas, TX, USA*
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* Corresponding author. Methodist Dallas Medical Center, Methodist Digestive Institute, Graduate Medical Education, 5th floor, 1441 N. Beckley Ave., Dallas, TX 75203, USA.
*E-mail address:* paultarnasky@mhd.com (P.R. Tarnasky).

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PEP from prospective studies ranges from 3%–10%.[1,4,5,11–16] A survey of prospective studies in 2007 reported that about 10% of PEP cases were graded as severe and the overall mortality of PEP was 3%.[1]

### *Risk factors*

Risk for PEP is influenced by specific scenarios that can be attributed to both patient and procedure-related variables[17] but physician factors also play a role. Factors associated with an increased risk for ERCP are found in Table 1.[18,19] It is important to recognize that a cumulative effect is expected when more than one risk factor is present. For example, the risk of PEP can be > 40% in a young female with suspected SOD and a difficult cannulation.[13] Multivariate analysis of another study suggested that the PEP risk was nearly 30% when multiple risk factors were present.[20]

*Patient factors*

Patient-related risk factors for PEP are either discernable before ERCP or discovered at the time of ERCP. Patients with only biliary indications including stones and distal biliary strictures, or those with either chronic calcific pancreatitis or pancreatic cancer are low-risk for PEP. Fortunately, we can identify most of the high-risk patients before deciding why ERCP might be indicated to guide who should undergo ERCP as well as who should perform the procedure.

Young age and female gender are reported to be independent risk factors for PEP. In our opinion, the risk of PEP is not increased in a young female with a biliary etiology e.g., bile duct stone, assuming no other risk factors come into play (see below).

**Table 1 Factors Associated with an Increased Risk for Post-ERCP Pancreatitis**

| |
|---|
| Patient |
| Age < 50 yr |
| Female |
| Suspected sphincter of Oddi dysfunction |
| Prior acute pancreatitis |
| Sclerosing cholangitis |
| Anatomical factors |
| Papillary stenosis |
| Non-patent minor papilla |
| Long common channel |
| Choledochocele |
| Hilar biliary strictures |
| Procedural |
| Increased cannulation attempts |
| Inadvertent pancreatography |
| Repeated pancreatic guidewire cannulations |
| Access (precut) sphincterotomy |
| Minor papilla therapy |
| Ampullectomy |
| Balloon sweeps (e.g., removal of stones) with inadequate sphincterotomy |
| Balloon sphincter dilation without prior sphincterotomy |
| Transpapillary covered metal biliary stent placement without prior sphincterotomy for benign biliary strictures (not chronic pancreatitis) |

ERCP, endoscopic retrograde cholangiopancreatography.

The greatest risk for PEP exists in patients with unexplained upper abdominal pain and prior acute pancreatitis. Without prophylactic measures, the risk of PEP in patients with suspected SOD is at least 20%. An increased risk for PEP associated with papillary stenosis and suspected sphincter of Oddi dysfunction contributes to the complexity of caring for patients with post-cholecystectomy pain.[21] The risk for PEP in patients with a history of unexplained acute pancreatitis perhaps related to SOD or pancreas divisum can approach 30%. Not surprisingly, prior PEP is also considered a risk factor for PEP.[12,13,20,22] Patients with primary sclerosing cholangitis (PSC) are at higher risk for PEP[23]; this is perhaps due to sclerosis of the papilla leading difficult cannulation and/or impaired pancreatic drainage.

Other patient factors include anatomical findings and those that are discovered during ERCP. Anatomy conditions associated with PEP risk include those that increase cannulation difficulty (e.g., periampullary diverticulum, Billroth II) and adequacy of pancreatic ductal drainage. Patency of the minor papilla in patients without pancreas divisum is associated with a lower risk of PEP.[24] Patients with a long common channel are subject to inadvertent pancreatography even with only biliary cannulation (Fig. 1). Impaired pancreatic ductal drainage can also occur due to the combination of anatomy and procedure details. For example, bile duct stenting in patients with hilar strictures might impair pancreatic ductal drainage due to a fulcrum effect; biliary sphincterotomy may prevent stent-induced compression of the pancreatic orifice in this setting.[25] Impaired pancreatic drainage more commonly occurs as a result of papillary trauma/edema associated with difficult cannulation, repeated cannulation attempts, and/or inadvertent pancreatography (see below).

*Physician factors*

Interpreting studies regarding the potential effect of physician (operator and/or center) are complex, in part because adequate case volume is required and high-volume centers typically treat higher risk patients.[9,26] Specific physician-related risk factors largely pertain to expertise. Defined components of expertise include skill, knowledge, and judgment, all of which are variably influenced by experience. Endoscopic skill can be the greatest

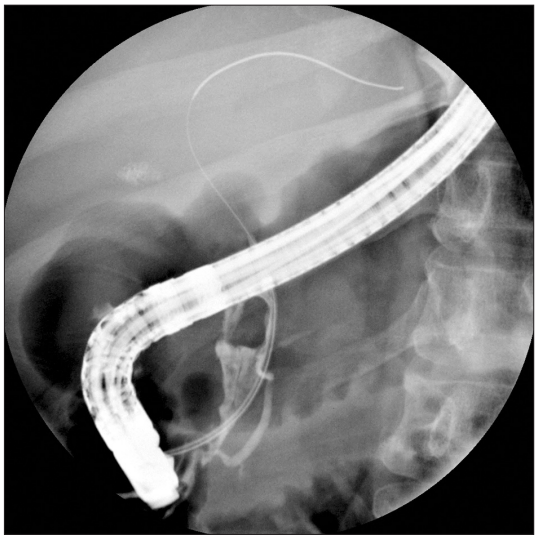

**Fig. 1.** An endoscopic retrograde cholangiopancreatography (ERCP) was performed to treat choledocholithiasis and complicated by post-ERCP pancreatitis. An inadvertent pancreatogram was obtained despite injection only after deep cannulation of bile duct.

obstacle and may not be attainable and/or available. Knowledge and judgment, theoretically, is more likely to be acquired with increased experience. The risk of PEP increases when ERCP is performed by physicians with less experience[27,28] while the risk is decreased when ERCP is performed at referral centers.[22] Some of the procedure factors (see below) are considered attributable to techniques associated with less operator expertise.[9] It has been recommended that advanced techniques (e.g., precut sphincterotomy) should only be performed by skilled endoscopists as defined by those who achieve biliary cannulation in > 80% of cases using standard methods.[29]

Restraint and recognizing the need for caution are advisable with the goal toward avoiding unnecessary and/or high-risk ERCP. Restraint may be appropriate during evaluation of the potential procedure indications and patient risk factors (see below). During ERCP, caution is valuable to guide the physician regarding cannulation techniques, duration of cannulation attempts, and decisions regarding therapy options.

Lastly, the physician's role in informed consent is of paramount importance for any ERCP procedure but particularly with regards to PEP.[30] Information regarding risk provided to the patient, and family if appropriate, should be unambiguous and specific for the particular procedure indication and the physician performing that procedure. Discussion on risk should be individualized to the scenario at hand; it is not appropriate to simply quote the overall risk of PEP (e.g., 3%–10%).

*Procedure factors*

Technical factors associated with an increased PEP risk are mostly related to cannulation and access techniques. There is no question that "difficult cannulation" is associated with an increased incidence of PEP (> 10%).[31] The Freeman difficulty of cannulation score (1 = easy: ≤ 5 attempts; 2 = moderately difficult: 6–15 attempts; 3 = difficult: > 15 attempts) has correlated with the risk of PEP.[11,13,32] Subjective and objective variables contribute to the challenge in defining a difficult cannulation. Both physician skill and patient conditions are relevant regarding "difficult" cannulation, and importantly, these variables are related to outcomes.[26,33] Definition of a cannulation attempt is also subjective and the specific numbers of cannulations to define a difficult cannulation vary by studies. From a large prospective multicenter study, the risk of PEP was significantly increased even with only > 1 cannulation attempt.[22] Testoni et al[34] reported that ≥ 10 cannulations was associated with higher PEP (10.7%) compared to < 10 attempts (2.1%). Number of pancreatic injections and the extent to which the pancreatic duct is filled is associated with PEP.[11,13,32,35,36] When pancreatography is completely avoided, PEP should be very uncommon (< 3%).[13,37,38] Reasonable definitions for difficult cannulation range from cannulation attempts for > 5–10 minutes, > 5–15 cannulation attempts, and/or > 1–5 inadvertent pancreatic duct manipulations.[11,29,31]

In situations where biliary cannulation is difficult and repeated pancreatic cannulation occurs, some experts advocate a double guidewire technique (DGWT) to increase success.[39–42] There are, however, reports of increased PEP with DGWT[43,44] and the risk is considerably higher (20%–30%) when pancreatic stents are not placed for prophylaxis (see below). A Japanese multicenter study reported that the risk of PEP (11%–32%) with the DGWT was directly correlated with the number of inadvertent pancreatic duct guidewire cannulations (GWCs).[45] Authors of a systemic analysis concluded that the DGWT is not superior to alternative methods of cannulation.[46] It is recommended that prophylactic pancreatic stents are placed in cases where a DGWT is employed because of repeated inadvertent pancreatic duct cannulations.[47]

Precut (access) sphincterotomy in association with difficult cannulation was identified in early studies to be associated with PEP.[48] The risk of precut, however, might not be attributed to the technique itself but more related to prolonged cannulation attempts before the precut.[47] For example, precut sphincterotomy when performed after prolonged cannulation attempts is associated with a high PEP (14%–19%) rate.[34,49] There are a number of precut techniques practiced and utilization ranges from rarely to as high as 50%.[50,51] The choices between different precut strategies and methods (transpancreatic, fistulotomy, needle-knife) are largely based on operator preference. The transpancreatic precut (TPP) technique has been associated with an increased risk (> 10%) of PEP.[52,53] With increased experience of the operator, Goff[54] reported no PEP after TPP, performed without an indwelling pancreatic duct guidewire and with only "nominal" pancreatography. Risk of PEP after TPP was low (5.6%) in one study in which the pancreatic duct was not injected with contrast.[55] Zang et al[56] reported that both guidewire assisted TPP and needle-knife sphincterotomy (NKS) were associated with relatively low PEP (7%) in otherwise low-risk patients. Halttunen et al[23] reported a low risk of PEP after TPP overall (9%) but the risk was excessive (25%) in patients with PSC. Pancreatic stenting is recommended after attempted TPP when performed over a guidewire.[29]

Papillary trauma from even standard techniques that might impair pancreatic ductal drainage is also associated with an increased risk of PEP. Repeated balloon sweeps and/or removal of large stones/fragments from the bile duct without adequate sphincterotomy has potential to cause papillary trauma. Balloon dilation of the biliary sphincter without prior sphincterotomy has also been associated with PEP.[57,58] It is recommended that balloon sphincter dilation should only be considered as an alternative to sphincterotomy in certain situations e.g., coagulopathy and Billroth II.[47,59] Large balloon dilation after biliary sphincterotomy to facilitate removal of large stones does not appear to increase the risk of PEP.[60]

Placement of fully covered self-expanding metal stents (FCSEMS) in the bile duct may also impair pancreatic ductal drainage, particularly in cases without a biliary sphincterotomy. Usually, sphincterotomy has been done previously or is performed at the time of metal stent placement. However, even with a prior biliary sphincterotomy, the risk of PEP is increased (10%–18%) when FCSEMS are placed for benign biliary strictures.[61] One retrospective study reported very high PEP (50%) after placement of FCSEMS without biliary sphincterotomy for treatment of anastomotic strictures in liver transplant patients.[62] From a systematic review in which the incidence of biliary sphincterotomy was not reported, patients with benign biliary strictures due to chronic pancreatitis had a moderate risk for PEP (13%) after FCSEMS, but this is not different when compared to multiple plastic stenting.[63] A recent prospective randomized controlled trial (PRCT) comparing FCSEMS to multiple plastic stents for benign biliary strictures reported a low PEP (5%); more than 90% of the patients underwent or had prior biliary sphincterotomy at time of randomization.[64] There does not appear to be an increased risk of PEP in patients with malignant biliary obstruction treated with FCSEMS even without biliary sphincterotomy.[65] This may be relevant; however, only in patients with pancreatic cancer who are known to be at low risk for PEP.

Other technical factors as potential contributors to risk including sphincter of Oddi manometry (with aspirating port), type of contrast agent, and mode of electrothermal energy for sphincterotomy are no longer considered to be causal.[18,31]

### *Strategies to reduce post-ERCP pancreatitis*

Fortunately, there are strategies to reduce both the risk and severity PEP (Table 2). Conceptually, the concept of risk reduction is most relevant for high-risk patients. However, application of the following principles may be appropriate for all patients, particularly when physicians with less expertise are performing ERCP.

*Restraint*

Avoiding ERCP is obvious but often ignored concept which is the only way to prevent PEP. The most important message is "ERCP is most dangerous for those who need it least".[66] Diagnostic ERCP should be very rare, e.g., when needed to diagnose subtle PSC or when required to pursue other diagnostic techniques such as cholangioscopy, pancreatoscopy and/or tissue sampling. The likelihood for choledocholithiasis and ERCP expertise are important variables related to utilization of ERCP in the peri-cholecystectomy setting.[67] Intraoperative cholangiography is recommended for patients having an intermediate likelihood of choledocholithiasis and may help avoid unnecessary ERCP. One should practice restraint when asked to consider ERCP for the common scenario of "rule out bile duct stone" in patients with unexplained abdominal pain. Noninvasive imaging such as MRCP should be utilized for diagnostic purposes when possible to potentially avoid an unnecessary ERCP.

*Procedure techniques*

Methods associated with expeditious cannulation and that avoid pancreatography result in a lower risk for PEP. Cannulation technique and decisions regarding duration of cannulation attempts are most important.

Wire-guided cannulation (WGC) with a hydrophilic-tip wire is now recommended as the preferred biliary cannulation technique.[29] Systemic analyses suggest that WGC is more successful and associated with less PEP when compared to catheter and contrast injection.[68–71] The risk of PEP is similar for both cannulation techniques when pancreatic stenting is allowed, however the protective effect of WGC is negated when trainees are involved.[70]

There are two methods of WGC.[72] With a pure GWC technique, the tip of the guidewire (advanced several mm from the catheter tip) is inserted directly into the papilla before trying to achieve deep cannulation. A guidewire-assisted cannulation (GAC) involves inserting the catheter tip into the papilla first and then trying to achieve deep cannulation by manipulating the guidewire. Who controls the guidewire during WGC is an important variable. Operator control of guidewire manipulations, including during cannulation, became possible with the advent of short-wire systems.[73] Operator-controlled WGC allows maximum tactile sense and optimizes timing of guidewire manipulations. There has been very little data,[74] despite being a widely practiced technique, until recently. Buxbaum et al[75] reported a PRCT in which operator-controlled WGC was associated with significantly less PEP (2.8%) when compared to when an assistant manipulated the guidewire (9.3%).

Inadvertent pancreatography is decreased with WGC but unintentional pancreatic duct GWC is common. Importantly, there is not an increased risk of PEP after inadvertent pancreatic duct WGC if the depth of insertion is limited and when performed carefully with limited force to avoid side-branch perforation. A PRCT comparing WGC to contrast injection techniques reported PEP rates of 0% and 19% after inadvertent pancreatic duct WGC or contrast injection, respectively.[76] A meta-analysis comparing WGC to contrast injection techniques reported that while the incidence of inadvertent pancreatic duct manipulation (guidewire or contrast) was similar (30% and 33%, respectively), the risk of PEP was significantly lower with WGC (1.1% vs 9.5%).[69] Another meta-analysis reported a similar reduction in PEP (1.7% vs 8.7%) favoring WGC in setting of inadvertent pancreatic manipulation.[70]

Any potential for risk associated with inadvertent pancreatic GWCs is perhaps related to the WGC technique. A retrospective study of WGC for biliary indications reported that inadvertent pancreatic GWC (median of 3 insertions in 55% of cases) was associated with an increased risk of PEP (13%).[77] However, a GAC method was used and the operator did not control guidewire manipulations.

Some experts advocate placement of a pancreatic stent, a concept similar to DGWT to straighten the distal duct but with the added advantage of augmenting drainage, as a safe method to facilitate biliary cannulation in cases of difficult cannulation.[78,79] The risk of PEP (5%) was acceptable with this method while the need for precut sphincterotomy may be increased (> 25%).[80]

Needle knife fistulotomy (NKF), whereby the cut is initiated away from the papillary/pancreatic orifice, is perhaps a safer precut method with regard to PEP.[47] A PRCT comparing NKF to NKS reported no cases of PEP after NKF compared to only 7.6% for NKS but one fatality occurred.[81] In a retrospective analysis of patients in which > 80% had pancreatography but only 10% underwent pancreatic stenting, risk of PEP was low (3%) after NKF compared to either NKS or TPP that was associated with a high risk for PEP (> 20%).[82] Jin et al[83] recently reported no cases of PEP when NKF was utilized as a primary access technique before any standard cannulation methods in patients with bile duct stones. However, the risk of NKF is likely higher in patients with small diameter bile ducts.[84] A lower risk of PEP with fistulotomy should also be weighed against the possibility of lower initial success and final success if/when repeat ERCP is attempted.[85] Risk of NKS is quite low when pancreatic stenting is employed (see below).

Many studies have suggested that early precut sphincterotomy is associated with a low risk for PEP.[51,86–91] Meta-analyses support early precut when compared to ongoing cannulation attempts.[92–94] Definition of "early" and the precut technique are other variables. Lee et al[95] reported results using a sequential approach that involved "early" precut. When biliary cannulation was difficult (> 5 attempts and/or for > 5 minutes), then either a NKF was performed or a DGWT was used when > 3 pancreatic GWCs were done. A NKS over a pancreatic stent was done if the above approach failed. The incidence of PEP was similar for NKF (10%), DGWT (12%), or the NKS (8%) techniques.

**Table 2 Strategies to Reduce Post-ERCP Pancreatitis**

| |
|---|
| Avoid unnecessary ERCP |
| Limit cannulation attempts |
| Avoid inadvertent pancreatography |
| Prophylactic pancreatic stenting |
| Rectal NSAIDs |

ERCP, endoscopic retrograde cholangiopancreatography; NSAIDs, nonsteroidal anti-inflammatory drugs.

### *Post-ERCP prophylaxis*

Successful early strategies for PEP prophylaxis utilized pancreatic duct stenting and focused on only high-risk patients. The administration of rectal nonsteroidal anti-inflammatory drugs (RNSAIDs) was initially suggested as effective pharmacologic

prophylaxis in average-risk patients. There are some data to support post-ERCP prophylaxis for all patients; this strategy may perhaps control and/or compensate for additional risk attributed to physician and/or unanticipated procedure related factors. Thus, evaluation of any PEP prophylaxis needs to consider all variables, e.g., cannulation technique, inadvertent pancreatography, and operator expertise. Pancreatic stent design and the specifics related to RNSAID administration are additional important variables. Finally, baseline risks need to be considered when assessing for any potential benefit of PEP prophylaxis. Among over 13,000 patients that participated as controls in over 100 PRCT, the PEP risk in untreated patients overall was nearly 10% and almost 15% for high-risk patients.[96] Our suggested PEP prophylaxis strategies are found in Table 3.

*Prophylactic pancreatic duct stenting*

Impaired pancreatic duct drainage, most likely as a result of papillary manipulation during cannulation, is thought to be the principal pathophysiologic mechanism for PEP. Among patients with suspected SOD, only those with pancreatic SOD were found to be at higher risk for PEP.[97] Thus, augmenting drainage (Fig. 2) is the rationale for prophylactic pancreatic duct stenting (PPS). Analyses of prospective trials have suggested benefit from PPS.[98–101] The number needed to treat to prevent one case of PEP is less than 10. More importantly, the risk of severe PEP is virtually abolished with PPS.[18] The risk of PEP is reduced from about 20% to 5% in high-risk patients after PPS; this was observed most commonly using short 5 F stents with proximal flaps to prevent early spontaneous migration. Some studies have reported that short 5 F stents without proximal flaps effectively prevent PEP but the risk of PEP in controls was high (12%–15%).[102–105] In those studies, however, the subjects were mostly average-risk patients. Das et al[106] conducted a cost-effectiveness analysis comparing no PPS, PPS in only high-risk patients, and PPS in all patients. The strategy of PPS in high-risk patients was overall most cost effective and even more so as the cohort's patient age decreased. As discussed earlier, PPS significantly reduces PEP in patients undergoing precut sphincterotomy.[107,108] The risk of PEP in SOD patients with difficult cannulation was very high (43%) in patients not treated with PPS versus no PEP in patients treated with NKS over a pancreatic stent.[109]

Several significant potential problems with PPS need consideration.[110] First, premature spontaneous migration of pancreatic stents may result in failure to prevent PEP. Second, endoscopic removal of stents is required for PPS with proximal flaps, may also be needed occasionally for stents without proximal flaps and pancreatitis can occur in association with stent extraction. Third, stent malfunction due to occlusion, fracture, proximal migration, and/or stent-induced ductal injury as possible. Finally and most concerning, about 5%–20% of attempted PPS fails and there can be substantial risk of PEP (35%–67%) associated with failed stent placement.[101,111–114] From a meta-analysis, the risk of PEP after failed PPS placement was 19%.[101] Attempted but failed PPS stent placement is considered to have worse consequences in high-risk patients when compared to those not treated with pancreatic stents.[111] It is also possible that subtle technical details during placement may affect the success of PPS. For example, PEP can range from 2%[24] to 11%[115] after pancreatic sphincter of Oddi manometry, biliary sphincterotomy and PPS.

The ideal prophylactic pancreatic stent has the following characteristics: easy to place, does not cause ductal damage, effectively reduces PEP, and migrates spontaneously within one to several days. As above, most of the prospective PPS efficacy data is derived from studies using short 5 F stents with internal flaps (IF) that later require endoscopic removal. Short stents without IF rarely require endoscopic removal but they may migrate too soon.[114] Small caliber 3 F stents without IF frequently migrate spontaneously and seldom need removal but require small caliber (< 0.035 in diameter) guidewires. Some experts prefer the use of smaller caliber (0.018 in diameter) guidewires for placing PPS[111] but there may be an increased risk for ductal perforation.[116] Nevertheless, a meta-analysis concluded that 3 F stents are less effective for prevention of PEP compared to 5 F stents.[117] Preliminary data on 4 F stents for PPS (Fig. 3) that can be placed over a standard 0.035 in diameter guidewire are favorable; PEP was observed in 16 of 308 high-risk patients (5.2%) and the spontaneous migration rate was 86%.[118]

**Table 3 Suggested Post–ERCP Prophylaxis Strategies**

1. Not required for average-risk patients when ERCP is performed by expert operator and undergo only skillful biliary cannulation +/– intervention(s)
2. Place pancreatic stent for the following:
   a. Difficult cannulation defined by repeated cannulation attempts, repeated inadvertent pancreatography and/or pancreatic duct guidewire cannulations
   b. Cannulation requiring double guidewire technique
   c. Precut using needle-knife technique initiated at papillary orifice after difficult cannulation (not required for precut over an impacted stone)
   d. High-risk patients including suspected sphincter of Oddi dysfunction and/or prior acute pancreatitis that undergo pancreatic duct cannulation +/– intervention(s)
3. Consider rectal nonsteroidal anti-inflammatory administration:
   a. After ERCP in average-risk patient with inadvertent pancreatography
   b. After ERCP in high-risk patient with failed prophylactic pancreatic stent placement
   c. Before every ERCP procedure performed by operators with less expertise

ERCP, endoscopic retrograde cholangiopancreatography.

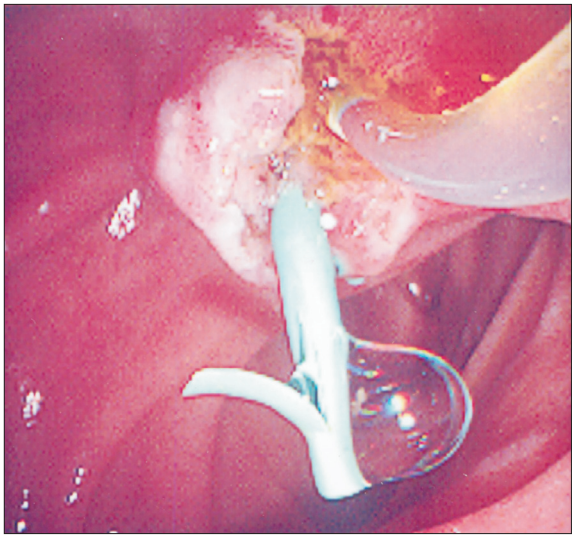

**Fig. 2.** There is obvious drainage of pancreatic fluid via short 5 F pancreatic stent after a precut sphincterotomy.

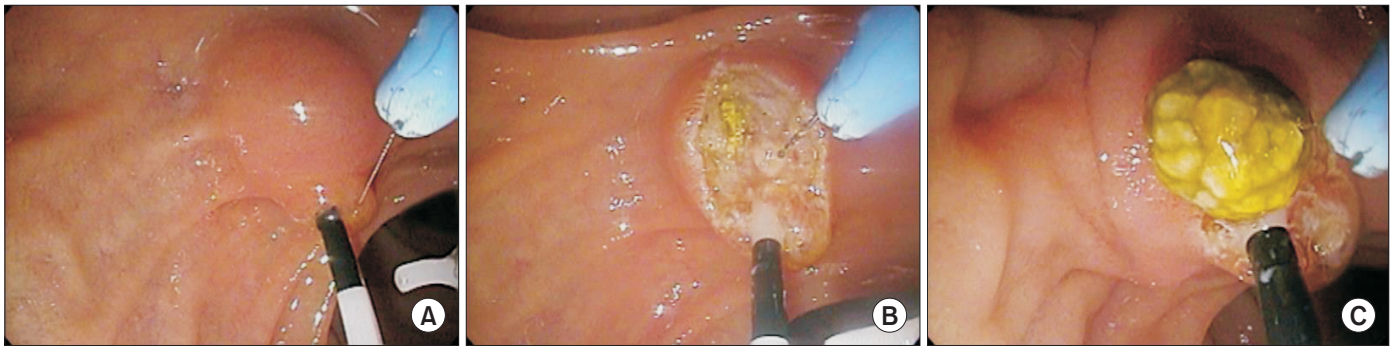


**Fig. 3.** (A) A 4 F single pigtail prophylactic pancreatic stent was placed before a needle-knife precut sphincterotomy. There was evidence of an impacted bile duct stone (B) that was expelled from the duct (C) after completion of the sphincterotomy.

*Pharmacologic prophylaxis*

A number of medications have been deemed as possibly effective for PEP prophylaxis, but now only RNSAID are considered as having the best evidence.[47] It is thought that indomethacin is the most potent inhibitor of phospholipase A2 and may interrupt the inflammatory cascade that is responsible for injury in acute pancreatitis.[119] In a strict sense then, NSAIDs may not prevent initiation of acute pancreatitis but instead might mitigate the ongoing damage.

A number of meta-analyses have suggested that RNSAID protect against PEP.[120–127] Validity of these conclusions could be questioned however, due to some findings which was difficult to explain or discordant to each other.[128]

Several of the early PRCT reported that RNSAID (diclofenac) significantly reduced PEP in average-risk patients. However the PEP rates for placebo controls (10%–20%) were higher than should be expected.[129–131] For comparison purposes, a PRCT concluding that neither somatostatin or gabexate was better than placebo in average-risk patients reported that the overall incidence of PEP was 5.6%.[32] Another PRCT in average-risk patients reported a nonsignificant trend in favor of rectal indomethacin (given before ERCP) for protection of PEP (3% vs 7%). There was, however, a significant protective effect among patients with inadvertent pancreatography (2% vs 19%).[132] Khoshbaten et al[133] reported that RNSAIDs significantly reduced PEP (26%–4%) in a study where pancreatography was the criterion for entry.

A recent PRCT by Levenick et al[38] reported that RNSAIDs did not protect against PEP in consecutive patients undergoing ERCP, the majority of which were average-risk patients. The overall rates for PEP after placebo (4.9%) were similar to that after RNSAID (7.2%). Pancreatic stents were placed in only 16% of cases overall and the risk of PEP in patients treated with pancreatic stents in the placebo group was calculated to be 11%. Surprisingly, it appeared that 22% of the patients undergoing pancreatic stenting treated with NSAIDs developed PEP. A recent meta-analysis suggested that RNSAIDs do not protect against PEP in average-risk patients.[134]

The landmark multicenter study Elmunzer et al[135] studied high-risk patients of which > 80% also received PPS. The protective effect was limited to one center but overall, rectal indomethacin after ERCP significantly reduced PEP in high-risk patients (9%) compared to placebo (19%). A post-hoc analysis of the data suggested that RNSAIDs were better than PPS.[136] However the risk of PEP in patients with PPS alone was excessive (16%). Another post-hoc analysis of data from the same study (including only two of the centers) suggested that RNSAIDs decrease PEP from 35% to 5% in patients with failed PPS.[113] This has been criticized due to assumptions made regarding attempted and failed PPS as well as a very high failed PPS rate (19%) from one institution.[137] Results from a network meta-analysis suggested that RNSAIDs alone were superior when indirectly compared to PPS alone for prevention of PEP.[138] Current recommendations suggest that RNSAID should not replace the need for PPS in high-risk patients[139] but direct comparison studies are warranted.

A recent retrospective study of over 4,000 patients compared outcomes in patients from an early cohort to a latter group that received post-ERCP indomethacin.[140] Among some high-risk patients (< 20% of total), the latter cohort (that received RNSAID) experienced significantly less PEP (4.5%) compared to the earlier cohort (8%). The incidence of pancreatic stenting in the high-risk patients was not disclosed but significantly more patients in the RNSAID group were treated with pancreatic stents (5% vs 3.8%) overall. The PEP rate after RNSAID was also significantly less in low-risk patients. For example, PEP in the latter cohort of patients with pancreatic cancer that received RNSAID was acceptable (2.3%) compared to what is higher than expected (7.5%) in the earlier cohort. The potential protective effect on an evolution of techniques (e.g., WGC) during the study was not controlled for. A recent PRCT concluded that universal pre-ERCP RNSAID was superior to selective administration of RNSAID post-ERCP in only high-risk patients but the number needed to treat (NNT) was high = 25.[141] Overall, mostly average-risk patients were studied; a minority (23% overall) became high-risk due to difficult cannulation +/– need for precut. Overall, there was a statistically significant reduction of PEP for pre-ERCP RNSAID (4%) compared to the risk-stratified approach of post-ERCP RNSAID (8%) in which only the high-risk patients were treated. In the average-risk subjects, pre-ERCP RNSAID PEP was what one might expect without any prophylaxis (3%) but it was even higher than expected (6%) without RNSAID (in the risk stratified group). In the high-risk patients, PEP after post-ERCP RNSAID was again what one might expect without any prophylaxis (12%). However, pre-ERCP RNSAID resulted in a reasonably low PEP (6%), even after high-risk procedures. The obvious dilemma is that pre-ERCP RNSAID may protect against PEP in high-risk patients but the high-risk designation is only determined post-ERCP. Thus, some experts administer RNSAID in all patients at the time of cannulation.[142]

*Risk reduction summary*

As noted above, risk factors can affect others. For example, ERCP performed by a highly skilled physician is more likely to result in successful cannulation utilizing careful WGC techniques,

early precut strategy, and/or successful PPS when needed. An ERCP performed by a physician with limited expertise might not be indicated, be marred by excessive cannulation attempts, unintentional pancreatic duct manipulations, and/or failed technical success that might include PPS.

### *Management*

The diagnosis of PEP (as defined above) should be suspected when patients have significant upper abdominal pain within a period of hours after ERCP. Mild pain immediately after ERCP is usually related to distention but when pain is severe a perforation (see below) should be considered. Management of PEP is not different from that as for pancreatitis of any etiology. Aggressive fluid resuscitation, early enteral feeding, and judicious use of antibiotics and imaging are the mainstay of management recommendations.[139] There are some data to suggest that early (within 24 hours of original ERCP) endoscopic therapy might be beneficial. Biliary sphincterotomy[25] (if not already done) or pancreatic stent insertion/exchange[143–145] as a rescue strategy has been reported to hasten improvement in selected cases of PEP but further studies are needed.

## Bleeding

The majority of ERCP-related bleeding is secondary to performance of sphincterotomy, which has become the foundation of therapeutic ERCP. Occasionally bleeding can be caused by mechanical trauma to the ampulla or fresh sphincterotomy site during balloon extraction of large or jagged stones. Rarely will manipulation or dilation of intraductal malignancies or strictures result in significant hemobilia or hemosuccus pancreaticus during ERCP.

Determining the true incidence of post-sphincterotomy bleeding is challenging because not all bleeding is clinically significant and/or considered an adverse event. The Cotton consensus criteria stratify bleeding into three categories of mild, moderate and severe.[2] Mild bleeding exhibits melena or hematemesis with a less than 3 g drop in hemoglobin without the need for transfusion. Moderate bleeding requires less than 4 units of blood transfusion and no angiographic or surgical intervention. Severe bleeding requires more than 5 units of blood transfusion or angiographic/surgical intervention. Overall rates of post-sphincterotomy bleeding are estimated at 1.34% in a meta-analysis of over 16,000 patients.[1] The majority of bleeding events were moderate in nature based on the Cotton consensus classification. However the criteria for what was considered reportable event was not consistent across all studies.[4,11]

What further complicates the picture is that rates of insignificant or 'trickle' bleeding range up to 30%–69% after sphincterotomy.[146,147] Also, the threshold for clinical significance varies including criteria such as duration (# of minutes) of ongoing blood loss, need for blood transfusion, hospitalization, and secondary therapeutic intervention (endoscopic, angiographic, etc.).[146,148,149] It seems reasonable to consider the minimum threshold for reporting immediate post-sphincterotomy bleeding as an adverse event if there is the need to intervene in any fashion to address bleeding other than intra-procedure observation. This includes immediate endoscopic therapy, which is not included in the Cotton classification. For example, if post sphincterotomy bleeding at index ERCP requires epinephrine injection and bipolar electrocautery or metal stent placement to manage, but does not cause overt melena or hemoglobin drop due to successful endoscopic intervention, it should still be reported as a minor immediate adverse event as it changed management of the patient. A revised table of ERCP-related bleeding classification to include both immediate and delayed bleeding may be clinically useful (Table 4).

More severe bleeding defined as melena, hematemesis, at least a 2 g drop in hemoglobin, and need for blood transfusion and possibly secondary intervention (angiography, surgery) occur in 0.1%–2% of cases in prospective studies.[5,6,11,14,22] The risk of mortality secondary to severe bleeding is quite low at 0.3%.[2,150] While most post-sphincterotomy bleeding is seen immediately during the procedure, it may present as late as 10–14 days after ERCP.

### *Risk reduction*

It is imperative for endoscopists performing sphincterotomy to understand the risk factors that predispose to bleeding. These risk factors may be patient, physician, or procedure-related. The identification of risk factors varies between studies due to the heterogeneity of study populations/comorbidity, underlying pancreaticobiliary pathology, along with operator techniques and equipment.

Low physician case volume has been shown to be a risk factor for bleeding in multiple prospective studies in multivariate analysis.[6,11] Also evidence of intra-procedural bleeding, anticoagulation therapy prior to or within 3 days after the procedure, and cholangitis appear to be significant risk factors in multivariate analysis (Table 5).[11] A plethora of other elements have been shown in either univariate or multivariate analysis as potential risk factors to consider including: precut sphincterotomy, zipper cut, pure cutting current, hemodialysis, cirrhosis, ampullary stone, stone extraction, and papillary stenosis.[5,6,11,22,48,147,151] NSAIDs or aspirin use do not appear to increase the risk of bleeding, however the effect of newer antiplatelet and antithrombotic agents has been less well-studied.[11]

The type of energy application during sphincterotomy is also important to consider. Newer electrical generators that can alternate the current of energy may be safer than previous generators,

**Table 4 ERCP-Related Bleeding: Stratification of Severity**

| Early | | Ongoing/delayed | | |
|---|---|---|---|---|
| Self-limited | Immediate | Mild | Moderate | Severe |
| 'Trickle' bleeding that stops/slows spontaneously during the ERCP and requires no intervention | Intraprocedural bleeding that does not stop after 2–3 minutes of observation and requires some form of endoscopic therapy to achieve hemostasis | Melena or hematemesis with a less than 3 g drop in hemoglobin, without need for transfusion | Melena or hematemesis with less than 4 units of blood transfusion and no angiographic or surgical intervention | Melena or hematemesis requiring more than 5 units of blood transfusion or angiographic/surgical intervention |

ERCP, endoscopic retrograde cholangiopancreatography.

**Table 5 Risk Factors for ERCP-Related Bleeding**

| Likely | Possible | Unlikely |
|---|---|---|
| Low endoscopists case volume | Precut sphincterotomy | NSAIDs |
| Intraprocedural bleeding | Pure cutting current | Aspirin |
| Anticoagulation prior to procedure | Hemodialysis/cirrhosis | |
| Resumption of anticoagulation within 3 days of procedure | Ampullary stone/stone extraction | |
| Cholangitis | Papillary stenosis | |

ERCP, endoscopic retrograde cholangiopancreatography; NSAIDs, nonsteroidal anti-inflammatory drugs.

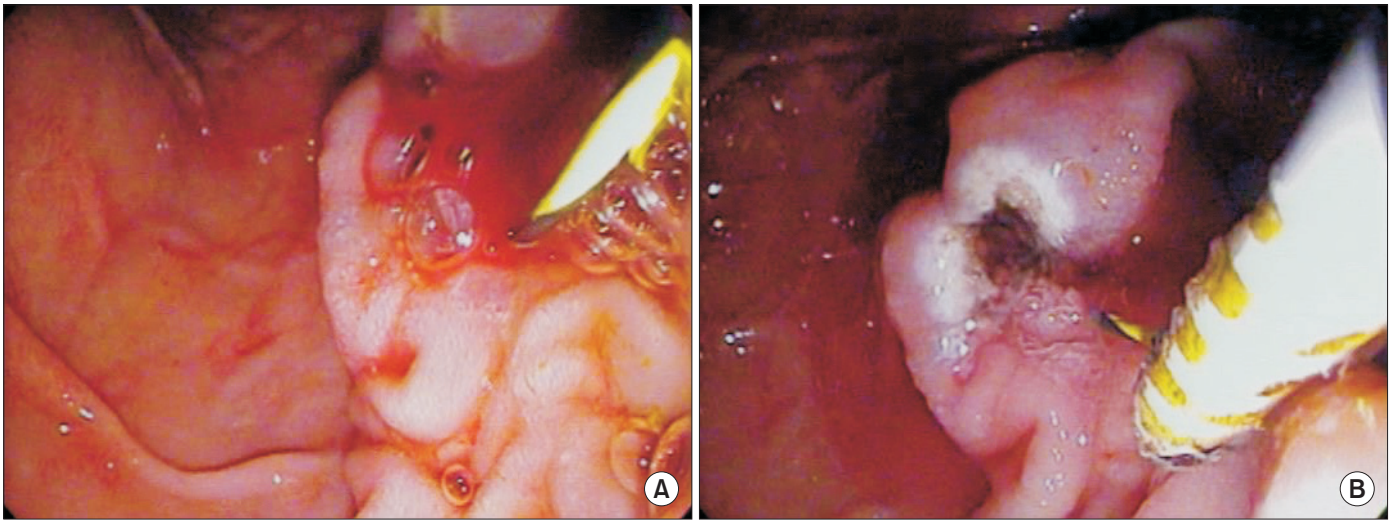


**Fig. 4.** Oozing of bright red blood is observed after sphincterotomy (A) that is controlled with multipolar electrocautery (B).

which deliver pure cutting currents. This alternation of energy current between cut and coagulation has been shown to reduce the risk of an uncontrolled rapid extension of sphincterotomy incision, also known as the 'zipper cut'.[2,152,153] A small PRCT showed that feedback-controlled generators with alternating currents significantly reduced the rates of immediate bleeding after sphincterotomy.[153]

Addressing factors that can be adjusted by the endoscopist both prior to and during the procedure is a prudent approach. All coagulopathy should be reversed if possible. A reasonable threshold prior to sphincterotomy are platelets ≥ 50 K and INR ≤ 1.5. Any irreversible antithrombotic agent should be held if possible for the appropriate amount of time based on their half-life, which is usually around 2–7 days depending on the agent.[154] Also, holding anticoagulation for at least 3 days after sphincterotomy if medically safe may also reduce bleeding. If coagulopathy cannot be reversed at the time of procedure then avoiding sphincterotomy altogether may be a reasonable option. Alternatives to performing sphincterotomy to achieve biliary drainage may be placing a plastic bile duct stent or using balloon dilation to expand the ampullary orifice for stone extraction. Endoscopic papillary balloon dilation has been shown in a meta-analysis of over 1,700 patients to have a lower risk of bleeding compared to sphincterotomy but also there is significant increase in risk of pancreatitis (see above).[155] Nevertheless, endoscopic papillary balloon dilation is considered an accepted alternative to sphincterotomy in patients with coagulopathy based on recommendations from international consensus guidelines.[156] Less experienced or low-volume endoscopists may consider referring patients that are high-risk for bleeding to larger/tertiary centers if that option is available to them and it is medically appropriate. Employing newer-generation alternating current electrical generators that can maintain a constant voltage is recommended. Finally meticulous control and direction of the cutting wire and endoscope during sphincterotomy is crucial. Generally the force of the wire in the direction of the cut should be provided by gentle torque of the scope with the right hand, rather than use of the elevator or extreme bowing of the sphincterotome.

### *Management*

Fortunately the vast majority of significant post-sphincterotomy bleeding can be successfully managed endoscopically. Bleeding of potential relevance is one that does not stop or significantly slow by the end of the procedure despite observation for at least several minutes (Fig. 4). Usually the flow rate of insignificant or 'trickle' bleeds will decrease or cease with intermittent irrigation and/or simple observation. Retrospective case series show that topical spray irrigation of epinephrine solution may control bleeding in > 93% of these cases.[147] However in reality the need for any intervention in these types of 'trickle' bleeds is likely unnecessary as they are generally self-limited.

If bleeding does not stop spontaneously, injection and/or cautery therapies should be considered; decisions related as to which techniques are used first are often operator dependent. Dilute epinephrine using a 1:10,000 dilution of epinephrine in 1 mL aliquots is injected into the submucosa usually at the upper edges and apex of the sphincterotomy. It is important that techni-

cians assisting the endoscopist extend and retract the needle from the catheter tip when the elevator in the down position. After the needle is extended then it is okay to use the elevator to visualize the tip and direct it to the site of therapy. Retracting the needle tip with the elevator in an up position may damage the device catheter and limit subsequent ability to control needle advancement. Hemostasis with epinephrine injection alone is reported to be very successful at > 96%–100%.[156,157] A small randomized controlled trial showed that there may be some benefit to prophylactic epinephrine injection prior to cannulation, however the study was conducted with low-experienced endoscopists with higher than average rates of bleeding and pancreatitis.[158]

Other hemostasis modalities include thermal energy (such as bipolar electrocautery, heater probe, and argon plasma coagulation), placement of clips, balloon papillary dilation, and metal biliary stent placement. The outcomes regarding these methods are less well studied and reported. Small case series have shown clinical success rates of 89%–100% using thermal energy for achieving hemostasis with low rates of adverse events.[159,160] There is a theoretical concern that thermal energy may cause acute pancreatitis if the pancreatic duct orifice is involved and becomes edematous and/or injured. However, with controlled delivery of energy toward the apex of the sphincterotomy and away from the pancreatic orifice, this adverse event can usually be avoided.

Few case reports and case series have reported on the utility of placing hemoclips in cases of refractory bleeding.[161–163] Hemoclips are technically difficult to place, as they are generally not designed to be deployed through a side-viewing endoscope with an elevator mechanism. Raising of the elevator mechanism across the device shaft can often damage or prematurely fire the deployment system. Misfire with using hemoclips is significant and can be frustrating and futile in an acute situation. In a small case series of six patients with post-sphincterotomy bleeding treated with hemoclips, the misfire rate in a single procedure was as high as three.[163] Care must also be taken during clip deployment to not occlude the biliary orifice in efforts to seal off the source of bleeding.

Tamponade of the ampulla/sphincterotomy site with an inflatable balloon or FCSEMS in the bile duct has also been reported in small numbers with successful outcomes.[164–167] Placing FCSEMS is technically easy and frequently very effective (Fig. 5) to control bleeding. However, due to the cost of the device itself and the need for the second endoscopy for removal, they should not be used as primary therapy but more as a salvage hemostasis technique when epinephrine or other methods fail. Nevertheless, if FCSEMS placement can prevent delayed bleeding or the need for secondary interventions such and angiographic embolization or surgery, then their cost may be justified. Other considerations of the stent related adverse events such as migration and post-ERCP pancreatitis may also complicate the risk-benefit profile for this technique and further studies are needed.

In rare cases when bleeding cannot be controlled endoscopically, salvage hemostasis options include angiographic embolization and surgery. Generally in brisk post-sphincterotomy bleeds, angiography will reveal extravasation of contrast in the anterior or posterior pancreaticoduodenal arcade and less commonly a branch of the hepatic or gastroduodenal artery.[168] Retrospective studies show a technical success rate of 97%–100% with a clinical success rate of 83%–91% for embolization of control of bleeding.[156] Finally, surgery would exist as a last alternative for uncontrollable life-threatening bleed, although its use has decreased in the past two decades.[169]

## Perforation

Perhaps the most dreaded and devastating adverse event of ERCP is perforation. A variety of mechanisms can induce perforation during ERCP including duodenoscope related trauma, sphincterotomy, and intraductal guidewire manipulation. Multiple case series have shown the overall risk of perforation during ERCP to be < 1% with a mortality range of 7.8%–9.9%.[1,14,22,48,170–172]

The accepted classification scheme for ERCP-related perforations proposed by Stapfer et al[173] is logically based on location and mechanism of injury. Type 1 perforations are characterized by luminal perforations, which most often occur in the duodenum. These types of perforations are due to shearing force or angle-related trauma to the bowel wall by the shaft or tip of the endoscope. These occur most often in cases of scope advancement where the shaft of the endoscope exerts too much force on the wall of the duodenum or a periampullary diverticulum. Type 1 perforations may also during uncontrolled forceful retraction of the duodenoscope such as during extraction of a difficult stone. Type 1 perforations generally cause intraperitoneal leakage of bowel contents and contrast. Type 2 perforations are defined as 'perivaterian' or periampullary perforations caused by overextension of a sphincterotomy beyond the intraduodenal portion of the ampulla, thus causing a retroperitoneal leak. Type 3 perforations are intraductal (either biliary or pancreatic) punctures via inadvertent over-advancement of guidewires or other tools (i.e., stents, baskets). And finally, Type 4 perforations are described as small

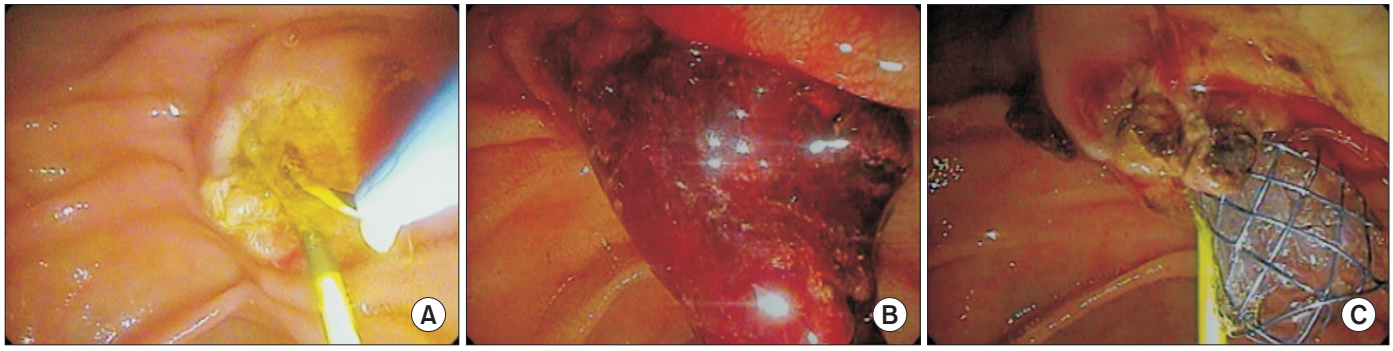


**Fig. 5.** (A) An uneventful access precut sphincterotomy was performed over a prophylactic pancreatic stent in a liver transplant patient with an anastomotic stricture. (B) The patient developed recurrent jaundice, a decrease in hemoglobin, and was diagnosed with stent dysfunction due to a large clot from a sphincterotomy bleed. (C) The clot was removed, electrocautery was applied, then a fully coated metal biliary stent was placed to ensure hemostasis.

**Table 6 Perforation Types and Characteristics**

| | Type 1 | Type 2 | Type 3 | Type 4 |
|---|---|---|---|---|
| Location | Luminal, lateral wall of duodenum | Periampullary | Intraductal (biliary or pancreatic) | Retroperitoneal air |
| Mechanism | Shearing force or angle-related trauma from the endoscope | Overextension of sphincterotomy beyond intraduodenal portion | Over advancement of wires/tools inside ductal structures | Insufflation, sphincterotomy-related |
| Relative percentage | 25 | 46 | 22 | |
| Management | Surgical > endoscopic | Endoscopic > surgical | Endoscopic | None |

amounts of retroperitoneal air alone and are considered clinically insignificant. Small studies have shown rates of asymptomatic, clinically insignificant retroperitoneal air (Type 4) after sphincterotomy to be as high as 29%.[174] In a systemic review of over 142,000 patients having undergone ERCP, Type 1 accounted for 25% of perforations, 46% were Type 2, and 22% were Type 3 (Table 6).[175]

### *Risk reduction*

Predicting risk for the prevention of perforation is challenging. Risk factors for perforation are less well defined partly due to the various mechanisms of injury and rarity of the event. Circumstances that have been shown to potentially increase the overall risk of perforation include older age, longer duration of procedure, sphincter of Oddi dysfunction, dilated bile duct, and performance of a sphincterotomy. Other possible risk factors include altered enteral anatomy (i.e., Billroth II, Roux-en-Y bypass) or application of precut sphincterotomy.[146,170] In a multiple large series of Billroth II patients at tertiary centers, the rate of perforation during ERCP was 1.8%, which is higher than the reported average of < 1%.[176,177] However, smaller case series report perforation rates as high as 18%, which may reflect closer to the experience of community ERCP endoscopists.[178] Post-Whipple (pancreaticoduodenectomy) anatomy does not appear to significantly increase the risk of perforation during ERCP.[179]

It is important to consider that various risk factors may predispose to each type of perforation. Type 1 perforations may be more likely in Billroth II anatomy and older patients due to fixed position, immobility and fragility of the bowel wall. Having a very clear conversation regarding the informed consent about risks prior to the procedure cannot be overemphasized in this particular scenario. It is crucial that the patient understand the potential risk for perforation and emergent surgery prior to undergoing an ERCP in altered anatomy. For Billroth II anatomy, it can be useful to start the procedure with a standard upper endoscope to identify and mark the entrance of the pancreaticobiliary limb prior to advancing a side-viewing duodenoscope. Low-volume endoscopists should consider referring Billroth II anatomy patients to tertiary care centers.

Type 2 perforations may be more common in sphincter of Oddi and precut sphincterotomy due to difficult cannulation and access techniques. Prevention of type 2 perforations is predicated on performing a deliberate and controlled sphincterotomy. Multiple factors contribute to ability of an endoscopist to consistently perform an effective but safe sphincterotomy, namely experience and case volume. However there are some tips that may help with decreasing risk. Minimizing the length of cutting wire in contact with the ampulla and using stepwise incisions can help control and direct the delivery of energy.[146] Also the force and direction of the cut should be directed by the endoscopist's right hand on the shaft of the endoscope creating counter-clockwise torque, as opposed to lifting the elevator or bowing the sphincterotome. Finally, using newer generation electrical generators with alternating currents can reduce the incidence of zipper cuts.[152,153]

Risk factors specifically for Type 3 perforations are not well described. They likely occur due to a wire handler's either lack of understanding or concentration on the position of the wire/tool within the pancreaticobiliary intraductal anatomy. Physical properties of the guidewire and who controls the guidewire are also important variables. It is crucial for the person handling the wire (endoscopist or technician/nurse) to have a strong understanding of the general pathway of the bile and pancreatic ducts to help avoid aberrant wire cannulation and perforation. In the setting of highly-trained technicians assisting with long-wire advancement, small studies have not shown any significant difference in rates of perforation.[73,180] In endoscopy units where technicians are not as highly trained or experienced, short-wire systems may confer an advantage. Aside from keeping careful track of the wire position using both fluoroscopic and endoscopic vision, avoiding advancing wire/tools through resistance or strictures without fluoroscopic view may also mitigate the risk of Type 3 perforations.

A final aspect regarding overall risk reduction strategy for perforation is the use of carbon dioxide ($CO_2$) insufflation. Conventionally, endoscopy units have used standard air insufflation for all endoscopic procedures, but in recent years there has been a shift to utilizing $CO_2$ insufflation due to its potential physical and physiologic advantages. Unlike air, $CO_2$ is lighter and rapidly reabsorbed by the body and does not require suctioning or passage through the gastrointestinal system for elimination. Multiple meta-analyses of numerous randomized-controlled trials show that the use of $CO_2$ insufflation reduces the risk of overall adverse events during ERCP.[181,182] The exact effect on perforation risk is unclear. However, $CO_2$ insufflation has consistently been shown to reduce post-ERCP abdominal distension and pain scores.[181–183] Reduction in abdominal distension may be important not only to prevent adverse events but also after a perforation event has occurred to reduce the risk of tension pneumoperitoneum or pneumothorax. An analogy of using $CO_2$ during high risk endoscopic procedures is like wearing a seatbelt when driving a car. While it may not prevent adverse events, it may reduce the consequential damage from those events.

### *Management*

The first and foremost related to the management of ERCP-related perforation is recognition. The overall prognosis of the patient is directly related to the time before recognition of the event to trigger early management decisions. Early or intra-procedural recognition of perforation events improve prognosis and reduce the need for surgical intervention.[184] A multicenter analysis noted that delayed recognition of a perforation more then 6 hours after ERCP was associated with increased length of hospital stay and mortality.[185] The timing to recognition may also dictate the com-

plexity and risk of the surgery, in terms of need for enteral diversion.[186] Generally, Type 1 perforations can be seen endoscopically while Type 2 and 3 perforations are noted fluoroscopically. For a Type 2 perforation, an occlusion cholangiogram with a retrograde injection balloon may reveal contrast extravasation at the level of the ampulla. Also air may be seen in the retroperitoneum on fluoroscopy (Fig. 6). It is imperative for endoscopists to understand how to recognize and diagnose ERCP-related perforations since as many as 44% of perforations are diagnosed after the procedure.[175] Symptoms of abdominal pain, tachycardia, leukocytosis, peritoneal signs, a tympanic abdomen and fever should alert the endoscopists about the possibility for perforation. Differentiating perforation from PEP may be challenging as they can present similarly and they can also coexist. Sometimes severe bowel distension with bacterial translocation after long procedures may also mimic the presentation of perforation. In such cases the most effective test to make a diagnosis is a computed tomography scan of the abdomen with contrast.

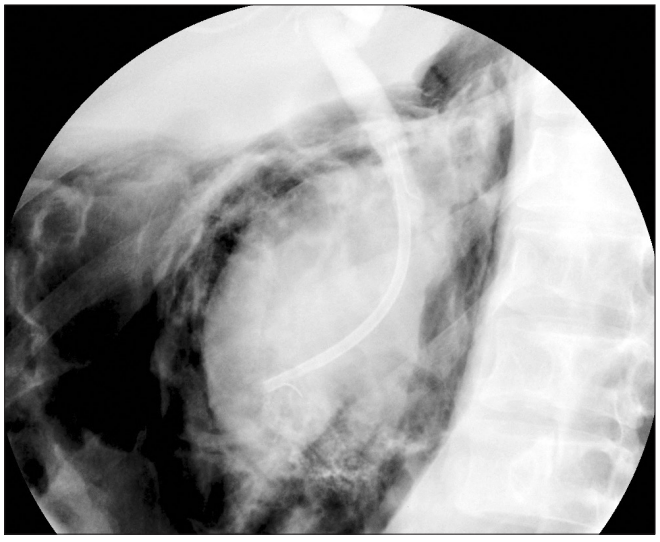

**Fig. 6.** Obvious air is noted following sphincterotomy in the retroperitoneum as seen on fluoroscopy during an endoscopic retrograde cholangiopancreatography.

When perforation has been recognized, the management depends on type, severity, patient condition and local endoscopic/surgical expertise. In cases of early recognition during ERCP, insufflation should be immediately switched to $CO_2$ if available for the reasons mentioned above. Invariably in all Type 1 and 2 perforations, patients should be admitted for observation, made NPO, given IV fluids (IVF) and broad spectrum antibiotics covering gram negative and anaerobic organisms, undergo nasogastric tube (NGT) placement for biliary diversion and have a surgical consultation.

Type 1 perforations commonly require surgical intervention to salvage an optimal clinical outcome unless early endoscopic closure can be successfully achieved. Immediate closure is paramount as Type 1 perforations allow of spillage of bowel contents directly into the peritoneal cavity resulting in peritonitis and sepsis. The types of surgery described to treat Type 1 perforation include surgical repair of the duodenum, abdominal washout, drain placement, with or without duodenal diversion.[186] More recently there have been successful reports of early endoscopic closure of these perforations with a variety of devices including through-the-scope clips (Fig. 7), over-the-scope clips, band ligation and endoloops.[172,187–189] Novel endoscopic suturing devices may be applied in this scenario to close large defects. Although the technical application of endoscopic suturing may be challenging and not readily available in most units, the potential to close large defects with multiple sutures through the endoscope is attractive.[190,191] The rates of successful endoscopic closure for small duodenal perforations (< 13 mm) with clips range from 88%–100%.[188,192] In patients that do undergo successful endoscopic closure, the chance of clinical successful recovery without surgery is > 90%.[172] Conservative management after endoscopic closure includes IVF, bowel rest, antibiotics and NGT placement. Usually within the next 24–48 hours the patient will declare clinically if they require surgical intervention. Ongoing or worsening abdominal pain with peritoneal signs and systemic inflammatory response are indications for surgery.[185] If the patient continually improves clinically, then usually by 3–4 days post procedure a water-soluble upper gastrointestinal series can be performed to confirm lack of extravasation prior to re-initiating a clear liquid diet.

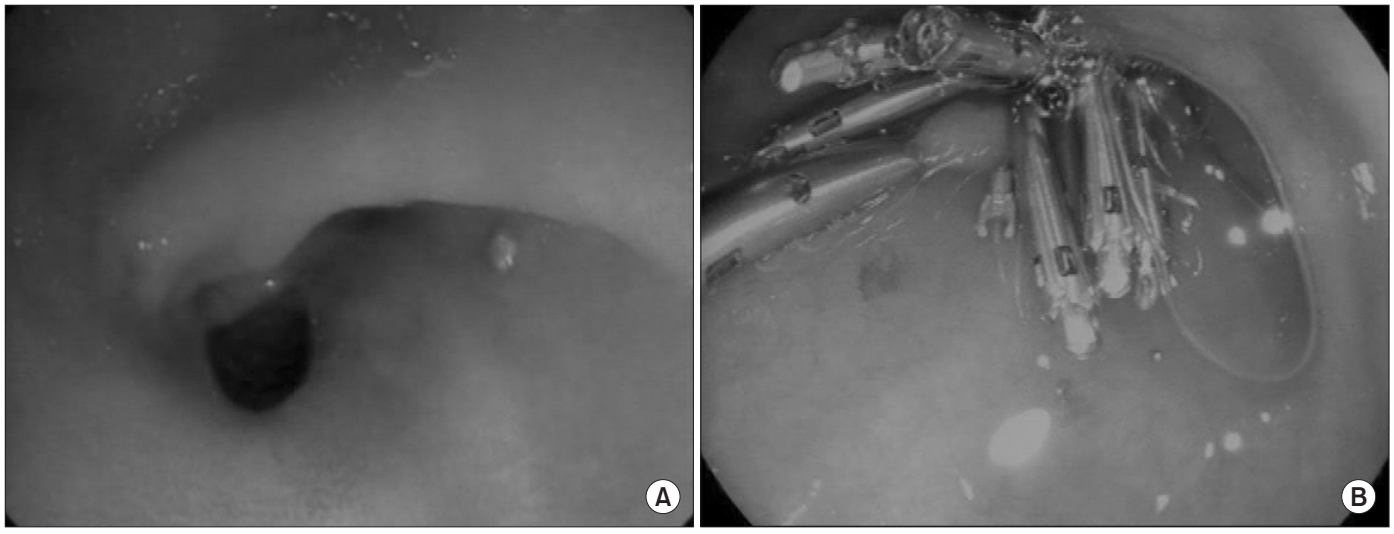


**Fig. 7.** A small (1 cm) Type 1 perforation on duodenal lateral wall (A) is closed with through the scope clips (B).

Type 2 perforations are typically less dire than Type 1 perforations as their leakage is into the retroperitoneal space and can be contained. There are however cases where Type 2 perforations can lead to abscess, peritonitis and mortality. Therefore early recognition and management is paramount. The goal of therapy is to seal the area of leakage and prevent leakage of panceaticobiliary contents extraluminally. This can be accomplished by placement of a FCSEMS directly into the bile duct across the ampulla with a near perfect clinical success rate.[164,193,194] Hemoclip application has also been described but as above-mentioned, is much more technically challenging and can risk ampullary trauma/closure.[195]

Type 3 perforations a relatively straightforward and rarely lead to significant clinical morbidity if recognized and managed during ERCP. The goal of therapy is to redirect the flow of bile or pancreatic fluid away from the site of leak. Sphincterotomy and plastic stent placement can help create a path of least resistance for flow away from an area of ductal perforation. Stent position across the area of perforation intraductally is optimal, but not necessary. Generally Type 3 perforations do not require surgical management. Type 4 perforations are considered clinically insignificant and do not require any intervention.

## Cholangitis/Infection

Our current understanding of post-procedure infection and cholangitis is evolving. Based on the Spaulding classification, ERCP is considered a semi-critical procedure as the duodenoscope engages in mucosal contact but does not directly enter a sterile space.[196] Thus, duodenoscopes require high-level disinfection between procedures to reduce risk of infection transmission. It has been well recognized over the last few decades that ERCP may introduce pathogenic flora into sterile intraductal environments through a variety of mechanisms. Despite the fact that ERCP is a semi-critical procedure, various tools such as wires, stents, balloons, etc. are pushed through a long duodenoscope instrument channel across a complicated elevator mechanism to enter a sterile ductal environment. What is also important to note is that these tools may be advanced into and withdrawn from a sterile bile duct via a non-sterile duodenoscope multiple times during a single procedure. Thus the definition of a semi-critical as opposed to a critical procedure is debatable. The fundamental cause for cholangitis in the biliary system is stasis or inadequate flow and excretion of bile into the duodenum. Any mechanism that contaminates a biliary system or segment and does not achieve adequate biliary drainage potentiates the chances for cholangitis. Examples include injection but inadequate drainage of intrahepatic systems in PSC, failure of stent placement across a biliary stricture, or late biliary stent occlusion. The overall rates of cholangitis or cholecystitis from ERCP have been reported at 1.0%–1.6% with 0.1% mortality.[1,4,14,22]

Transmission of multidrug resistant organisms and carbapenem-resistant enterobacteriae (CRE) via a duodenoscope has been reported in the last few years.[197–201] Colonization and incomplete sterilization of the complex elevator hinge mechanism at the tip of the duodenoscope is the suspected culprit for transmission of these infections.[201] Even more concerning is that multiple recent CRE outbreaks have occurred despite complete compliance with the recommended multisociety duodenoscope reprocessing guidelines.[197,198,200] CRE infections have been associated with poorer prognosis, longer hospital stays and increased mortality, up to 10% in large series.[202] For this reason multiple endoscopic and infection-control societies have issued newer recommendations regarding the handling and reprocessing of duodenoscopes.[203–205]

### *Risk reduction*

Incomplete biliary drainage is the major risk factor for post-ERCP cholangitis. Thus most efforts to prevent post-ERCP cholangitis are directed at achieving successful drainage. Risk factors which may contribute to cholangitis are not well defined, but are linked by their likelihood to complicate biliary drainage. Accepted factors include PSC, low endoscopist experience, rendezvous procedures, cholangioscopy, and proximal complex cholangiocarcinoma-related strictures.[148,206–208] Endoscopists should anticipate complex drainage cases and plan their approach for ERCP. Pre-procedure imaging with MRCP may provide the endoscopist with a 'roadmap' of the biliary system; this helps target the efforts of their injection and instrumentation and thus avoiding unwarranted systems. In cases of challenging strictures where proximal opacification of the biliary system has occurred, various hydrophilic wires, angle-tipped wires, rotating and swinging catheters are available to gain access for drainage. Cautious use of contrast and air injection is always recommended to avoid opacification and contamination of unintended segments. The utility of prophylactic antibiotics universally during ERCP and even in only in cases with incomplete drainage has not been proven.[208,209] However multiple experts with anecdotal experience recommend administering 3–5 days of oral antibiotics with gram-negative coverage for cases of incomplete drainage and one dose during cholangioscopy.[148,149,206,207]

A recent single-center case series of 115 patients with ERCP-related CRE exposure concluded that ERCP with contaminated duodenoscopes, biliary stent placement, diagnosis of cholangiocarcinoma and active inpatient status were risk factors for transmission of CRE infection. Although the risk of a patient contracting a CRE infection from ERCP is still exceedingly low, it is prudent for endoscopy units performing ERCP to develop updated systematic protocols for the reprocessing of duodenoscopes. This may include specific documentation of duodenoscopes associated with individual ERCP procedures, training and credentialing of technicians involved in reprocessing with special attention to cleaning of the elevator mechanism, periodic audits of automated endoscope reprocessing devices, and consideration of a culturing protocol to detect duodenoscope colonization.

One controversial risk factor for ERCP-related cholecystitis is the use of FCSEMS for distal biliary obstruction. The concept is that a FCSEMS may occlude the cystic duct entry into the common bile duct thus inducing iatrogenic cholecystitis. Reported rates of ERCP-related cholecystitis are 1.9%–12% with FCSEMS.[210] However multiple studies have shown that the primary risk for developing cholecystitis after ERCP is tumor involvement of the cystic duct orifice, regardless of whether a covered or uncovered metal stent is used.[211–213] Thus, whether cholecystitis occurs as a result of the stent itself versus the actual tumor biology is unclear. As the literature is not definitive it is not unreasonable for endoscopists to assess the location of the cystic duct orifice during ERCP to choose the appropriate length and size stent whose proximal end will terminate distal to the cystic take off. If the cystic duct orifice is not visible despite occlusion cholangiogram and is likely involved with tumor, then the choice and position of stent may be inconsequential.

### *Management*

In cases of post-ERCP cholangitis, treatment with IVF and antibiotics is the first line therapy. Many patients will respond to conservative therapy alone. In severe or refractory cases, it may

be necessary to consider secondary intervention to achieve improved biliary drainage such as repeat ERCP with stent revision or percutaneous biliary access.

Multiple options for treatment of acute cholecystitis after palliative stent placement exist including percutaneous drain placement or repeat ERCP with stent revision to either uncovered metal or plastic stents.[210,214] Many of these patients are inoperable due to their comorbidity and tumor involvement of the biliary system. More recent reports of ERCP guided transcystic gallbladder drainage has shown to be as effective as percutaneous drainage with lower pain scores and need for repeat procedures.[215,216]

For confirmed CRE infections from a contaminated duodenoscope, the suspected device should be taken out of working circulation and quarantined. The event should be reported to the appropriate public health agencies, Food and Drug and Administration, the device manufacturers, and the persons responsible for infection control for the endoscopy unit. An audit should be considered for recent patient exposures with potential notifications. This event should prompt a procedure review of all duodenoscope reprocessing and culturing protocols. Any breach in the reprocessing protocol may require re-education or remediation of involved staff. Finally, a dedicated protocol agreed upon by physicians, administrators, and infection control specialists should be enacted to clear the endoscope of any residual contamination prior to re-entering it into the work cycle. This protocol has not been standardized by any society as of yet, but can include various processes such as double high-level disinfection, bacterial culture, adenosine triphosphate bioluminescence, and ethylene oxide sterilization.[217] Single high-level disinfection is likely not an acceptable form of reprocessing and confirming eradication of the organism after such an event has occurred.

## Cardiopulmonary

While rare, cardiopulmonary adverse events (CPEs) are a significant cause of morbidity and mortality from ERCP.[146] Cardiopulmonary events range from mild transient hypoxia and hypotension to critical myocardial infarction, pulmonary embolism, respiratory failure, cerebrovascular accidents, cardiac arrest, amongst others. This incidence of CPEs range from 0.9% to 2.3% with a mortality from 0.07%–0.1% of cases.[1,16,22] The rates of CPE are higher for ERCP than general endoscopic procedures due to the complexity of intervention, use of electrocautery, increased length of procedure, often increased underlying morbidity of the patient, and the need for deeper sedation.[218]

### *Risk reduction*

Unfortunately multiple comorbid conditions has been shown to be a preprocedure risk factor for CPEs.[16] This may not be a controllable scenario as many elderly and ill patients require urgent or emergent ERCP for a variety of reasons. For critically ill patients that require non-urgent ERCP, optimizing cardiopulmonary status and obtaining cardiac clearance in appropriate cases prior to the procedure is prudent. Also the type of sedation used for ERCP varies from IV conscious sedation to monitored anesthesia care with propofol and also general anesthesia. There has been a recent shift toward more propofol usage in the last decade for ERCP. Multiple meta-analyses have shown no increased risk of CPEs with propofol usage and possibly shorter recovery times.[218–221] The decision to proceed with general anesthesia should be made by the endoscopists and anesthesia team and be individualized based on patient morbidity and complexity of the underlying procedure. Generally in cases of duodenal/gastric outlet obstruction, gastric stasis, or anticipated long procedure times, general anesthesia with endotracheal intubation may be wise to prevent aspiration. Management of CPEs depends on the nature of the event and may involve multiple specialists depending on the acuity and organs affected.

## Conclusions

Answers to the questions of why, who, and what are instructive when considering ERCP complications. Why the procedure is being done pertains to the indications. Who is the patient and who is performing the procedure reflects on the patient related risk factors and operator expertise. What is discovered and what techniques that are employed during the procedure defines those that are associated with both increased risk as well as risk reduction. Confounding the complexity of ERCP complications is the fact that the three principle variables (patient, physician, and procedures) are interrelated and all have the potential to both increase or decrease risk. It is imperative that endoscopists understand these complex interactions in order to recognize high-risk scenarios before and during ERCP so that prudent decisions are made to both prevent and manage potential complications. To summarize the important principles toward the reduction of ERCP complications, one should consider ERCP to represent Expertise, Restraint, Caution, and Prevention.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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