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# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

## Complications of Endoscopic Retrograde Cholangiopancreatography

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**Up to 1 in 6 patients will experience an unplanned hospitalization after endoscopic retrograde cholangiopancreatography (ERCP), largely for the evaluation and management of adverse events. Therefore, a commitment to the prevention, early recognition, and effective rescue of complications related to ERCP is critical toward improving outcomes. ERCP is most often complicated by acute pancreatitis, bleeding, infection, or perforation, although myriad other adverse events may occur. The prevention of post-ERCP pancreatitis has been the area of greatest interest and progress in the last decade, but the application of evidence-based prophylactic measures remains inconsistent. Innovations in stent, hemostasis, and perforation closure technology now allow effective and efficient endoscopic management of several important non-pancreatitis complications. Overall, our ability to prevent and treat ERCP-related adverse events has improved substantially, amplifying the importance of a high level of suspicion for and a thorough understanding of these events.**

*Keywords:* Adverse Events; Complications; Endoscopic Retrograde Cholangiopancreatography; Pancreatitis; Post-ERCP Pancreatitis.

In the last decade, the field of interventional gastrointestinal (GI) endoscopy has experienced a stunning transformation with ever-expanding indications, capabilities, impact, and risks. For example, a perforation or post-operative leak in the foregut – once considered an absolute contraindication to endoscopy – has now become, at many institutions, a common reason for endoscopic intervention. Similarly, endoscopy now plays a clear complementary and often primary role in the treatment of achalasia, cancer, and obesity, conditions traditionally addressed surgically. Interventional endoscopic ultrasound (EUS) allows for the creation of anastomoses within and outside the GI tract, blurring the distinction between endoscopy and surgery, and often improving the risk-benefit ratio of treating conditions such as pancreatic walled-off necrosis, gastric outlet obstruction, and cholecystitis. However, despite the recent development and dissemination of these game-changing advances, endoscopic retrograde cholangiopancreatography (ERCP) – the quintessential "advanced" endoscopic procedure for decades – remains the most dangerous intervention commonly performed by GI endoscopists. Therefore, a thorough understanding of its adverse events – with an emphasis on prevention, early recognition, and effective rescue – remains a major priority in ERCP practice.

Herein is a comprehensive but concise evidence-based review of ERCP-related complications, focusing on information most relevant to the practicing endoscopist. Where necessary, we have augmented existing evidence with expert insights that may be practically helpful, but for which existing literature remains lacking. This review is divided into 5 sections: (1) important considerations related to iatrogenesis in ERCP; (2) pancreatitis; (3) bleeding; (4) perforation; and (5) infectious complications. Additional considerations for each of these sections as well as content on rare and underappreciated complications (including gas embolism, basket impaction, and stent migration) and special ERCP populations (pediatrics and pregnancy) are included in the Supplementary Material. We do not address sedation-related and cardiopulmonary complications unless they directly relate to the sections above. Nevertheless, a commitment by ERCP practitioners to the prevention, recognition, and management of such complications, often in collaboration with anesthesiology colleagues, is essential.

## Important Considerations Related to Iatrogenesis in ERCP

Iatrogenic complications affect all aspects of medical care and have major implications for patients, caregivers, clinicians, health care organizations, payors, and other stakeholders. Given the potential morbidity and mortality relative to most other endoscopic procedures, these

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*Abbreviations used in this paper:* CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; fcSEMS, fully covered self-expanding metallic stent; GI, gastrointestinal; IVF, intravenous fluids; MRCP, magnetic resonance cholangiopancreatography; NSAIDs, nonsteroidal anti-inflammatory drugs; PEP, post–endoscopic retrograde cholangiopancreatography pancreatitis; PSP, prophylactic stent placement; RCT, randomized controlled trial.

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implications are amplified in the context of ERCP. Indeed, interventional gastroenterologists – who generally perform large numbers of ERCP – experience the highest levels of burnout and stress within our specialty.[1] The second victim syndrome, denoting the emotional trauma experienced by a health care professional as a result of iatrogenesis, may be particularly prevalent and salient after ERCP, as it is in surgical specialties.[2] Most endoscopists – trained as gastroenterologists by way of an internal medicine residency – do not experience the same exposure to adverse events early in their training as compared with surgical counterparts, and thus may be less prepared to cope longitudinally with being a second victim. An improved understanding of the psychological implications of iatrogenesis and effective strategies to mitigate their impact is critical across medical specialties and would be highly valuable to physicians who perform ERCP.[3,4]

In addition to the clinical implications discussed later in this article, the psychological consequences of iatrogenesis on the physician underscore the importance of review articles, quality indicator statements, and guidelines focused on adverse events because a deep understanding of and real-time access to such documents allow the clinician to obtain truly informed consent[5,6] and play an active role in preventing and treating these events, which may be valuable in mitigating the resultant psychological stress. Additionally, it is important for endoscopists to recognize – drawing from the surgical experience – that while adverse event rates may not differ substantially between providers, outcomes vary more so according to promptness of recognition and treatment efficacy. Indeed, high- and low-surgical mortality hospitals have similar overall adverse event rates but high-mortality hospitals are less adept at rescuing patients from complications.[7] Although mortality is thankfully uncommon after ERCP, failure to rescue is likely an important determinant of other untoward outcomes, again highlighting the value of a thorough understanding of, a high level of suspicion for, and a steadfast commitment to addressing adverse events related to ERCP.

Lastly, as with other invasive procedures and operations, a strong volume-outcomes relationship in ERCP exists, with high-volume providers having higher success rates and fewer complications.[8–11] Although this relationship has not been consistently observed for post–endoscopic retrograde cholangiopancreatography pancreatitis (PEP) because high-volume endoscopists and centers take on the highest-risk cases,[12] greater experience and expertise is clearly advantageous in ERCP. On this basis, lower-volume providers are encouraged to participate in coaching programs and other postgraduate pathways to improve skills, have a low threshold to refer complicated and/or high-risk cases to tertiary centers, continually refresh their knowledge base around adverse event mitigation and management, and augment procedural volume with indicated cases if possible. This last suggestion is the most difficult to operationalize and may involve reducing the number of endoscopists who perform ERCP within a practice. Instituting minimum privileging standards and/or centralization of ERCP services have been proposed and implemented internationally,[13] but have not gained traction in the United States and may potentially be counterproductive in certain under-resourced areas. Therefore, in parallel with efforts to standardize credentialing, alternative strategies to improve the performance and outcomes of physicians who perform ERCP, leveraging novel approaches such as report cards[14] (and the platforms necessary to generate them), coaching,[15] intelligent simulator technologies, and augmented reality platforms, may represent the most viable approach to improving the safety of ERCP in the United States.

## Post-ERCP Pancreatitis

Acute pancreatitis is the most common ERCP-associated adverse event and probably the most dreaded. Considerable research has improved this problem for individual cases, but the overall incidence and mortality of PEP continue to increase,[16] presumably due to inconsistent application of prophylactic interventions and the increasing complexity of patients and procedures.[17–19] An intentional approach to minimizing this complication is mandatory in every case (Figure 1).

### *Diagnosis and Incidence*

PEP is most commonly diagnosed using Cotton's consensus criteria, which require: (1) the presence of pancreatic-type abdominal pain; (2) an unplanned hospital stay (or an extension of an ongoing hospitalization) of at least 2 nights; and (3) serum amylase (or lipase) level at least 3 times above the upper limit on the day after the procedure.[20] The revised Atlanta classification criteria, which includes diagnostic imaging (but not length of hospitalization), is more sensitive for PEP,[21,22] but mandates cross-sectional imaging in all patients with postprocedure abdominal pain, which is impractical and overexposes patients to radiation. In clinical practice, some combination of both diagnostic criteria is typically used depending on whether imaging has been obtained, sometimes to evaluate for other concurrent complications. Although both criteria provide a framework for classifying the severity of PEP, the revised Atlanta classification appears to better reflect severity and predict mortality.[23,24]

A recent systematic review of 145 randomized trials found that PEP occurred in 10.2% of patients overall, and in 14.1% of those at high risk.[25] The true incidence in real-world practice varies widely from 1%–15% depending on clinical context, but has been reported to be higher than 40% in particularly high-risk patients without any form of prophylaxis.[26] However, based on existing data and with the use of contemporary mitigation measures, it is reasonable to quote patients a risk of approximately 5% in routine cases and up to 15% in high-risk cases (see Risk Stratification section).[27,28] Approximately 10% of patients with PEP – and therefore $<$1% of all patients who undergo ERCP – will follow a severe course, resulting in prolonged hospitalization, complications that require additional invasive interventions, or death.[27]

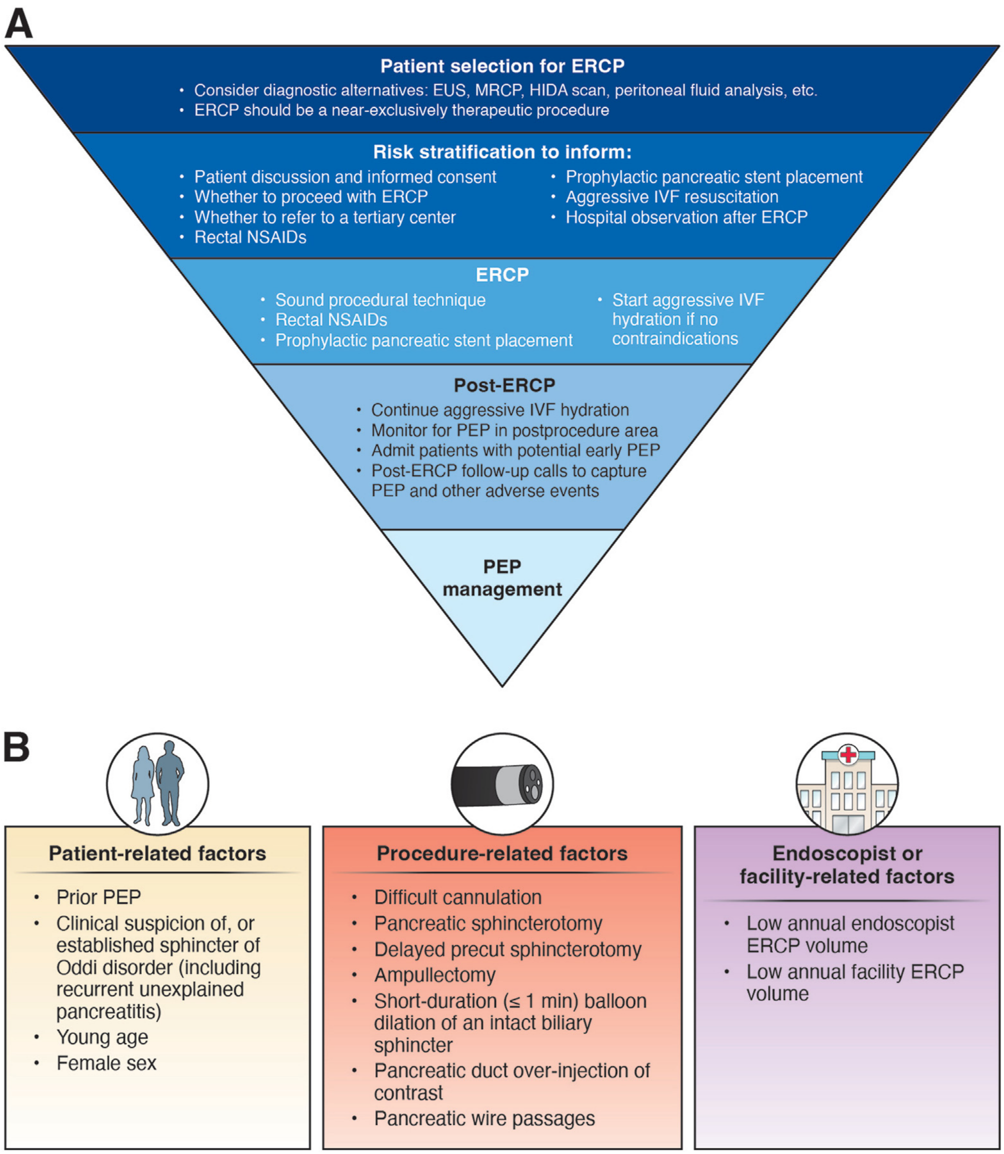


**Figure 1.** (*A*) Framework for the prevention of post-ERCP pancreatitis. (*B*) Risk factors for post-ERCP pancreatitis.

### *Patient Selection*

The single most important intervention to reduce the incidence of PEP is appropriate patient selection. Given the widespread availability of highly accurate but much safer diagnostic alternatives – namely, EUS and magnetic resonance cholangiopancreatography (MRCP) – ERCP should be a near exclusively therapeutic procedure, restricted to those with a high pretest probability of requiring an intervention such as stone extraction or stent placement.[29] In the last decade, these diagnostic alternatives have been most impactful in the evaluation of suspected choledocholithiasis, for which both EUS and MRCP are highly accurate.[30–32] On this basis, patients at intermediate probability of ongoing choledocholithiasis (ie, with a reasonable chance of having spontaneously passed their stone[s], which is believed to occur in >80% of cases) should undergo EUS or MRCP (or intraoperative cholangiography) to confirm the presence of a stone or sludge before incurring the risks of ERCP.[33] For choledocholithiasis, EUS and MRCP can be considered diagnostically equivalent, but some evidence and clinical experience suggest that EUS is more sensitive for particularly small stones,[34] and those impacted at the papilla. When a patient continues to exhibit signs and symptoms of a persistent and/or ball-valving stone (eg, ongoing pain, fluctuating liver tests) despite a negative MRCP, EUS is warranted.

The paradigm of applying less-invasive diagnostic testing to confirm the presence of pathology before ERCP should apply across pancreaticobiliary conditions. EUS, magnetic resonance imaging, and other noninvasive modalities such as radionucleotide-labeled scans and percutaneous drain fluid analysis are very accurate in diagnosing or excluding a multitude of processes such as chronic pancreatitis, malignancy, and leaks, often obviating the need for ERCP.[35–37] Historically, ERCP has inflicted the most harm on those who have needed it the least,[38] and some evidence suggests that purely diagnostic ERCP is still common in clinical practice.[39]

Of course, there are uncommon situations in which diagnostic ERCP is justified and beneficial, such as for the confirmation and mapping of main duct intraductal papillary mucinous neoplasm or perhaps after liver transplantation,[40] but the decision to proceed with ERCP should always involve thoughtful consideration of diagnostic alternatives.

### Risk Stratification

Risk stratification according to patient- and procedure-related predictors of PEP informs decision-making around: (1) proceeding with the ERCP; (2) referral to a tertiary facility for the procedure; (3) placement of a prophylactic pancreatic stent; (4) administration of rectal indomethacin or diclofenac; (5) aggressiveness of intravenous fluid hydration; and (6) observation in the hospital after the procedure. These predictors are listed in Figure 1 and are further discussed in the Supplementary Material.

An important principle of risk stratification is that predictors of PEP appear to be at least additive, and perhaps multiplicative.[41,42] Thus, the presence of multiple risk factors should elicit growing concern and factor into decision-making.

### Pharmacologic Prevention

**Rectal nonsteroidal anti-inflammatory drugs.** On the background of solid preclinical data and a meta-analysis of preliminary trials suggesting benefit,[43] a methodologically rigorous randomized controlled trial (RCT) of patients at high risk for PEP published in 2012 demonstrated a 7.7% absolute risk reduction associated with rectal indomethacin, with a number needed to treat of 13.[41] Subsequently, several additional trials and meta-analyses have consistently demonstrated that rectal indomethacin and diclofenac reduce risk by approximately 50%.[44] There had been controversy around whether rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in all patients or only those at high risk, but the overall evidence now suggests efficacy in all-comers.[45–47] As a result, recent clinical practice guidelines in the United States now recommend rectal NSAID administration in unselected patients (without contraindications) undergoing ERCP, having previously restricted this recommendation to high-risk patients.[48]

The timing of rectal NSAID delivery has also been controversial, and evidence suggests that administration immediately before or after ERCP is efficacious.[49,50] However, a large-scale RCT published in 2016 demonstrated superiority when systematically giving the medication before ERCP.[47] Because real-world procedural flow makes it difficult to reliably predict the time of ERCP, and to reduce the likelihood of missing the putative therapeutic window in the event cannulation is delayed (eg, duodenal stricture requiring dilation) or because of a prolonged case (eg, difficult stone management), many experts administer the drug during ERCP.

There are patients at negligible risk for PEP who do not require prophylaxis, such as those with a pre-existing biliary sphincterotomy undergoing biliary endotherapy or severe chronic calcific pancreatitis who have had prior uneventful ERCPs, for example. To allow flexibility for such patients, as well as for those with contraindications or who are likely to directly incur the skyrocketing cost of rectal indomethacin,[51,52] forthcoming multisociety quality indicators for ERCP will assign a >90% (not 100%) performance target for administration of rectal NSAIDs to patients with an intact papilla.

**Intravenous fluids.** Aggressive fluid hydration, especially using lactated Ringer's solution, is believed to reduce the risk of PEP through microcirculatory and anti-inflammatory mechanisms. RCTs evaluating aggressive intravenous fluids (IVF) alone for the prevention of PEP have consistently demonstrated benefit.[53,54] However, the benefit is not as clear when aggressive IVF is evaluated in addition to other prophylactic interventions, with 1 large-scale methodologically rigorous trial showing no incremental benefit in patients receiving rectal NSAIDs.[55] On this basis, while U.S. guidelines recommend aggressive IVF for unselected patients,[48] European guidelines restrict this recommendation to patients with contraindications to NSAIDs and when a prophylactic stent has not been placed.[56]

The principal challenge to operationalizing an evidence-driven approach to IVF in clinical practice is that all studied regimens have included a prolonged infusion, which is not feasible in North America where the majority of patients are discharged within 2 hours after ERCP. Blinded trials comparing more practical bolus regimens delivered periprocedurally (rather than in a prolonged fashion) in high-risk patients who receive the combination of NSAIDs and a prophylactic stent are sorely needed.

In our practices, we routinely administer a periprocedural bolus (range, 1–3 L) of lactated Ringer's solution to generally healthy, high-risk patients (regardless of other prophylactic interventions) and continue an aggressive rate of infusion (150–250 mL/h) overnight when patients are admitted for suspicion of PEP, recognizing that this approach is not evidence-based and that the traditional enthusiasm for aggressive IVF in acute pancreatitis in general has been tempered.[57] This approach is naturally modified according to the patient's risk for volume overload, and sometimes IVFs have to be avoided altogether. Occasionally, when the risk-benefit ratio of aggressive IVF is truly in question (eg, post-ERCP pain with only a modestly increased risk of PEP in someone with cirrhosis or compensated heart disease), we use a 2-hour (after ERCP) serum lipase assessment to inform the need for ongoing aggressive hydration.[58]

### Procedural Techniques to Mitigate Risk

Several technical strategies in ERCP have been shown to reduce risk, with some relating to the described procedural risk factors. For example, repeated and aggressive contrast injection of the pancreatic duct and short-duration balloon dilation of an intact biliary sphincter should be avoided. In coagulopathic patients who require stone extraction, balloon dilation can be avoided by placing an endobiliary stent and repeating the ERCP with sphincterotomy when coagulation parameters have been corrected. If this is not possible, and balloon dilation is mandatory, a longer duration of dilation (2–5 minutes) appears to result in lower rates of pancreatitis.[59] Papillary balloon dilation after biliary sphincterotomy to facilitate stone extraction does not increase risk.[60]

Although every endoscopist aims to limit the number of cannulation attempts, the potential injury induced by these attempts can be reduced by using the guidewire-assisted cannulation technique. This technique is less traumatic than contrast-facilitated free cannulation as the small diameter and soft tip of the wire is more seamlessly able to negotiate the sphincter zone, subsequently guiding passage of the catheter into the duct. Because the wire does the work, this approach also limits the likelihood of inadvertent pancreatic or intramural papillary injection. Guidewire-assisted cannulation has become the predominant approach in practice, and a recently updated Cochrane meta-analysis affirms that it reduces PEP by approximately 50%.[61] It is important to consider, however, that pancreatic duct injection has been overly vilified of late; occasionally, when the catheter is deeply engaged in the papilla but the wire will not advance, a gentle injection of contrast can provide an anatomic roadmap that ultimately makes cannulation more efficient and atraumatic. The most significant potential consequence of guidewire cannulation is pancreatic duct injury, which can occur when, during intended biliary cannulation, the wire enters the pancreatic duct inadvertently and is forcefully advanced. Thus, cautious wire advancement is critical, and gentle injection of contrast to produce a roadmap is advisable if the wire does not travel seamlessly in its intended direction.

Another important concept related to reducing the number of cannulation attempts is to pivot relatively quickly to an alternative technique when access to the duct proves challenging. This principle is best demonstrated by evidence that early precut sphincterotomy, as opposed to ongoing cannulation attempts, is consistently advantageous in reducing PEP.[62,63] In these trials, patients were typically randomized to early precut sphincterotomy (vs ongoing cannulation attempts) after 5–10 minutes of unsuccessful cannulation or 2–3 inadvertent pancreatic wire passages. Other alternative techniques include double-wire cannulation, wire cannulation alongside a pancreatic stent, transpancreatic septotomy, and needle-knife fistulotomy. Additional discussion related to these techniques is included in the Supplementary Material.

Scenarios that exert excess pressure on the pancreatic orifice during ERCP are also believed to increase the risk of PEP and should be avoided, including short-duration dilation of an intact sphincter (especially without appropriate prophylaxis) and placement of a fully covered metallic stent (or even a large-caliber plastic stent through a small papilla) without prior sphincterotomy.[64,65] Although the evidence to support stent-related PEP is controversial,[56,66] our approach is to perform at least a limited sphincterotomy to create separation away from the pancreatic orifice before stent placement. Last, interventions for hilar strictures, such as sampling and stenting, require using the papilla as a fulcrum, which can exert excess pressure on the pancreatic orifice. Our preference is to perform a sphincterotomy before such interventions to minimize the risk of PEP.

### *Prophylactic Stent Placement*

The goal of prophylactic stent placement (PSP) is to counteract pancreatic orifice edema and obstruction (and consequent intraductal hypertension) that occurs during and immediately after ERCP. RCT data have consistently shown benefit[44,67] and clinical practice guidelines strongly recommend this intervention in high-risk cases.[48,56] However, the overall benefit has remained in question because of the potential disadvantages of PSP and the perception that stent placement is not necessary when rectal NSAIDs are given.[68,69] Indeed, since the widespread diffusion of rectal indomethacin, the use of PSP appears to have decreased significantly,[70,71] with some data suggesting placement in $<$5% of high-risk cases.[17] A recent methodologically rigorous RCT conducted across 20 centers, which addresses some of the limitations of prior trials – the Stent versus Indomethacin trial – affirmed the benefit of PSP in patients at elevated risk.[28] In this trial, the combination of rectal indomethacin plus a prophylactic stent reduced the risk of PEP by $>$30% compared with indomethacin alone and resulted in numerically fewer cases of severe pancreatitis and pancreatitis-related death. PSP is generally indicated in the presence of 1 or more of the predictors of PEP (Figure 1), including inadvertent wire passages into the pancreatic duct.

Because of its technical complexity, its potential to cause the very harm it aims to mitigate, and the associated costs and inconvenience (related to abdominal x-rays to ensure that the temporary stent has spontaneously migrated from the duct and upper endoscopies to remove retained stents), the decision to perform PSP depends on several factors, the most important of which are the patient's risk of post-ERCP pancreatitis and the anticipated level of difficulty in stent placement. For example, PSP is clearly advisable in a high-risk case when pancreatic duct access is already achieved (eg, inadvertent pancreatic wire passage during biliary ERCP). In contrast, the risk-benefit equation is not as clear when the risk of PEP is only modestly elevated and access to the pancreatic duct is anticipated to be difficult. Overall, because of the possible harms, physicians who perform ERCP should avoid overambitious efforts to place a stent, continually assessing the risk-benefit ratio in real-time. Those without experience in PSP should refer anticipated high-risk cases – the patients who are most likely to require PSP – to referral centers.

## ERCP-Related Bleeding

Clinically important bleeding after ERCP complicates 1%–2% of cases and is most commonly the result of endoscopic sphincterotomy (Figure 2).[72–74]

### *Postsphincterotomy Hemorrhage*

Factors associated with postsphincterotomy bleeding include ascending cholangitis, peri-ampullary diverticulum, thrombocytopenia (platelet count $<$50,000), use of

**ERCP-related bleeding**

- **Occurs in 1%—2% of cases (mostly sphincterotomy-related)**
- **Avoidance**
  - Hold anticoagulation according to published guidelines
  - For ascending cholangitis in an anticoagulated patient, place stent for decompression and repeat ERCP for sphincterotomy after correction of coagulation parameters
  - If anticoagulation cannot be held, consider balloon dilation alone (with PEP prevention measures) or limited sphincterotomy with fully covered metallic stent placement
- **Treatment**
  - Endoscopic hemostasis with clips or diathermy
  - For clip placement, straighten duodenoscope and drop elevator before deployment
  - Consider clip placement using gastroscope with clear cap (avoid pancreatic orifice)
  - For diathermy, avoid pancreatic orifice or place a prophylactic pancreatic stent
  - For difficult to control bleeding, place fully covered metallic stent

**Figure 2.** Overview of the avoidance and management of ERCP-related bleeding.

anticoagulation, and hemodialysis.[72,75–77] Cirrhosis is also a risk factor, although portal hypertension and Child-Pugh Class have not been consistently implicated.[78] It is important to recognize, however, that an elevated international normalized ratio in a patient with cirrhosis is as likely to reflect hypercoagulability as it is bleeding diathesis; it does not predict procedure-related bleeding and does not require correction before ERCP with sphincterotomy.

Similarly, aspirin and other NSAIDs at standard doses do not increase the risk of bleeding and do not require cessation.[79,80] Other antiplatelet agents and anticoagulants, however, should be held before ERCP according to current guidelines[81,82] and existing evidence suggests that management of antiplatelet agents in particular is suboptimal before ERCP.[74] The resumption of anticoagulation (including antiplatelet agents) after the procedure is more opaque and not evidence-based, and RCT data in this area would be highly beneficial. If reasonably safe from a cardiovascular perspective, we prefer to hold anticoagulation for 48–72 hours afterwards. When it must be resumed immediately and its future need is not expected to change (eg, mechanical valve in the mitral position), we avoid sphincterotomy altogether by performing a long-duration papillary balloon dilation (with appropriate mitigation measures) or perform the smallest sphincterotomy that achieves the endoscopic objective (eg, small sphincterotomy followed by papillary balloon dilation for stone extraction) while also considering non–evidence-based concurrent prophylactic measures, such as fully covered self-expanding metallic stent (fcSEMS) or empiric placement of clips at the apex of the sphincterotomy. Such patients are observed closely in the hospital.

Postsphincterotomy bleeding usually, but not always, occurs at the apex of the sphincterotomy. Intraprocedural bleeding, while identified as a risk factor for delayed hemorrhage,[72,74] is usually inconsequential and will often stop spontaneously or after basic maneuvers such as direct tamponade with an inflated extraction balloon or injection of 1:10,000 epinephrine solution.[76] Significant intraprocedural bleeding and delayed hemorrhage, the latter of which is much more problematic, require proper endoscopic hemostatic therapy, akin to peptic ulcer bleeding for which epinephrine injection alone is considered suboptimal (Figure 3).

Deployment of through-the-scope clips is effective but challenging and idiosyncratic through a duodenoscope and is further discussed in the Supplementary Material. Thermal therapy using a bipolar hemostasis probe or coagulation grasper is technically more straightforward, but invokes the risks of pancreatic orifice injury and retroperitoneal perforation.[83] Regardless of the technical approach, all efforts should be made to avoid injury to the pancreatic orifice, and, if not possible, to place a prophylactic pancreatic stent. Sphincterotomy-related bleeding can result in accumulation of blood in the bile duct and consequent obstruction/cholangitis; endoscopists should be prepared to also perform an ERCP for decompression if cholestasis accompanies bleeding.

When standard hemostatic approaches are unsuccessful, placement of a fcSEMS has become the primary salvage intervention, as the radial force exerted by the stent compresses the culprit vessel.[84] Disadvantages of fcSEMS include the risk of acute cholecystitis if the cystic takeoff cannot be avoided, the need for another procedure to remove the stent, and the observation that this intervention is not always successful, especially when the duct and associated sphincterotomy are large.[85] Nevertheless, fcSEMS as primary therapy for bleeding is becoming more popular and should certainly be considered for refractory bleeding before transcatheter arterial embolization, which is often successful but associated with important adverse events.[86] Hemostatic powder has been successfully applied in this context,[87] but its role remains uncertain given the concern for pancreaticobiliary ductal occlusion.[88] However, there does appear to be emerging evidence for hemostatic gels.[89,90]

### *Nonsphincterotomy-Related Bleeding*

Other (nonsphincterotomy) bleeding events related to ERCP are uncommon. Hemobilia can occur after therapeutic interventions within the biliary tree such as dilation, biopsy, radiofrequency ablation, or photodynamic therapy.[91–93]

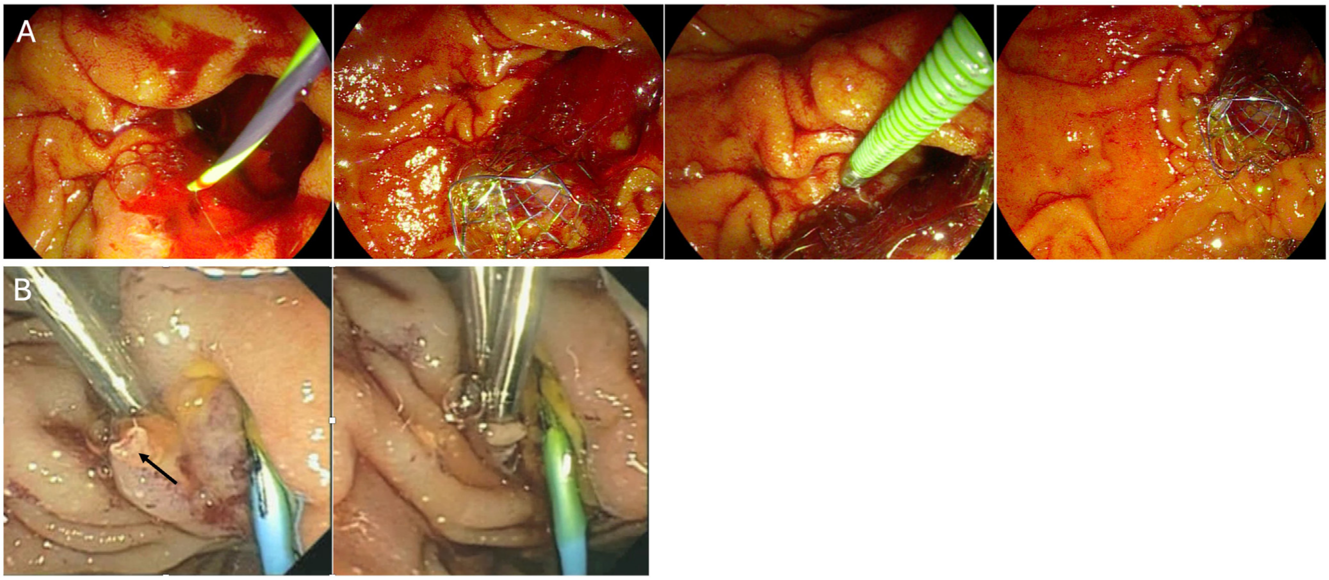

**Figure 3.** (*A*) Postsphincterotomy bleeding with hemostasis achieved using multimodality therapy of fully covered metallic stent placement and epinephrine injection. (*B*) Nonbleeding visible vessel at sphincterotomy site managed using endoscopic placement of a second clip.

Reducing the intensity of diathermy (from 10–7 W) is recommended during radiofrequency ablation of hilar malignancy given the proximity of the hepatic arteries. Subcapsular or parenchymal hepatic hematoma can also occur because of injury to adjacent vessels and occasional pseudoaneurysm formation, usually by the tip of the guidewire or stent.[94–97] Splenic hematoma and rupture have been reported after ERCP secondary to looping of the duodenoscope along the greater curvature of the stomach, leading to traction on the splenic vessels.[94,98,99] A high index of suspicion for these events, usually indicated by hypotension (with possible associated abdominal pain) shortly after ERCP, is critical for prompt resuscitation and expedient hemostasis. Other than hemobilia from a known source in the extrahepatic bile duct, which can be treated with a fcSEMS, these sources of bleeding are typically addressed angiographically. Splenic rupture requires early surgical consultation.

## Perforation Due to ERCP

Perforation during ERCP is rare but potentially devastating (Figure 4). Guidewire penetration into the retroperitoneum or outside the duct is not uncommon and is typically inconsequential. In contrast, frank perforation with extraluminal contamination can result in life-threatening sequela and mandates prompt recognition and management. The incidence is reported to range between 0.08% and 0.6%,[27,56] however, these estimates are likely imprecise due to inconsistent definitions and reporting, and small sample sizes in relevant studies. Patient-related risk factors for perforation include suspected sphincter of Oddi dysfunction, surgically altered foregut anatomy, and presence of strictures proximal to the ampulla, the latter 2 of which increase the risk of a luminal perforation.[56,100] Sphincterotomy – particularly when performed as a redo/extension or when performed in combination with sphincteroplasty – is the action most likely to result in perforation during ERCP (Figure 5).[101] Other procedure-related risk factors include prolonged and challenging biliary cannulation as well as intraductal balloon dilation.[56,100,102]

Perforation avoidance is grounded in sound procedural judgment and technique. The 3 most important principles to minimize risk are: (1) the use of caution when the duodenoscope does not advance seamlessly to the third portion of the duodenum (to avoid luminal perforation); (2) for sphincterotomy (and papillectomy), a clear understanding of the anatomic landmarks that denote the junction of the papilla and duodenal wall, and the recognition that these landmarks are not always visually clearcut (to avoid sphincterotomy-related perforation); and (3) selection of the intended size of a dilating balloon according to the size of the upstream duct (to avoid sphincteroplasty-related papilla or ductal perforation). Routine assessment of the duodenum and fluoroscopic gas pattern at the end of each ERCP is prudent in general but is particularly important when these principles have not been fully satisfied. If there has been significant difficulty advancing the duodenoscope, another look with a gastroscope before completing the case is worthwhile.

Ideally, a perforation would be recognized intraprocedurally, before significant extraluminal contamination. Akin to non-ERCP iatrogenic perforations, real-time endoscopic treatment has become a game-changer, often avoiding untoward sequelae and obviating the need for hospitalization. Retroperitoneal perforations related to biliary sphincterotomy/sphincteroplasty are best managed with placement of fcSEMS, which seals the defect and diverts the flow of bile downstream.[103] Traumatic ductal perforations (leaks) that are detected during ERCP are

**ERCP-related perforation**

- **Occurs in 0.08%—0.6% of ERCPs**
- **Common sites**
  - Duodenum (associated with scope trauma)
  - Retroperitoneum or periampullary (associated with sphincterotomy or balloon dilation)
- **Avoidance**
  - Cautiously advance duodenoscope to papilla
  - Understand anatomic landmarks relevant to sphincterotomy
  - Select size of dilating balloon according to the size of the upstream duct
- **Treatment**
  - Placement of a fully covered metallic stent for periampullary or retroperitoneal perforation
  - Endoscopic defect closure for duodenal perforation (clip, suturing, or luminal stent)
  - Surgical management when endoscopic closure is unsuccessful and/or for concurrent peritonitis or systemic inflammatory response

**Figure 4.** Overview of the avoidance and management of ERCP-related perforation.

treated according to the same principles that apply to bile leaks and pancreatic disruptions in general, that is, to create a path of least resistance for bile or pancreatic juice into the duodenum, typically via stent placement. Luminal perforations can typically be managed by primary closure using through-the-scope or over-the-scope clips or suturing. When a perforation occurs in or around a stricture because of difficulty advancing the duodenoscope, there is usually insufficient working space for primary closure and, depending on anatomy, a fully covered esophageal stent may successfully seal the defect. In this context, care must be taken to avoid jailing off the pancreaticobiliary orifices and to minimize the risk of downstream migration by securing the prosthesis in place.

A dose of antibiotics should be given as soon as a perforation is suspected, but if closure is expedient and robust, no further antimicrobial therapy is needed. No follow-up imaging is required in an asymptomatic patient after successful treatment of a sphincter perforation with fcSEMS, but we would typically confirm closure of a bona fide luminal perforation with an oral contrasted computed tomography (CT) scan immediately after ERCP, even if the patient awakens from sedation without symptoms. If robust closure is not confirmed or the patient is clinically unwell, early surgical consultation for multidisciplinary care is always prudent.

The more problematic scenario is delayed presentation of a perforation, either because it was not recognized during the index procedure or because it developed over time, usually as a result of an evolving muscle injury related to electrosurgical current. Such cases typically present within a few days of ERCP with abdominal pain, possible fever and tachycardia, and sometimes peritonitis and abdominal sepsis.[102,104] Because many of these perforations are retroperitoneal and/or contained, abdominal radiographs are not adequately sensitive, and CT scan is the most appropriate diagnostic modality.

In patients with peritonitis and systemic inflammation, surgical intervention is necessary for washout and drain

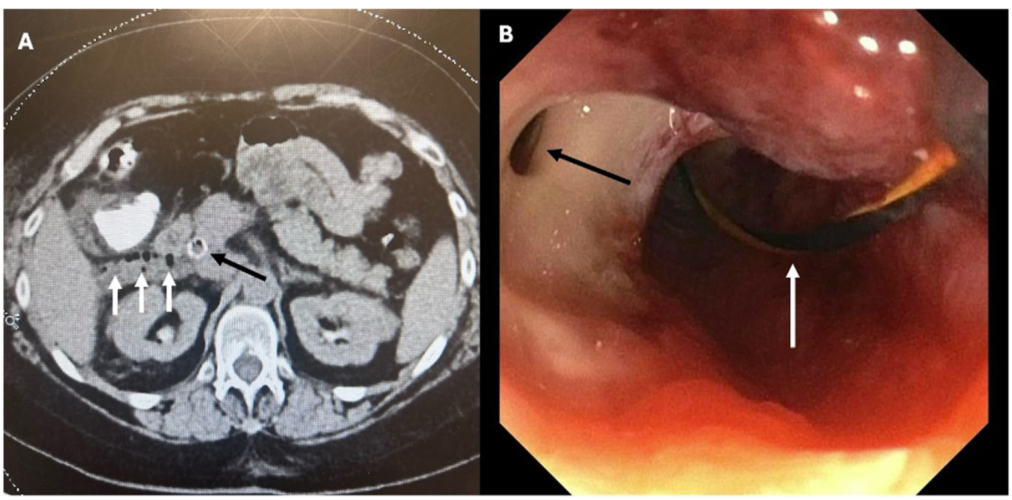


**Figure 5.** (*A*) Retroperitoneal gas and fluid (short white arrows) due to a postsphincterotomy perforation that was treated with placement of a fcSEMS (*black arrow*). (*B*) Persistent defect into the retroperitoneum at the biliary-duodenal junction (*black arrow*) observed after removal of the fully covered stent 4 days later. Retroperitoneal pus was aspirated through this defect before placing a new fully covered stent over a guidewire (*white arrow*).

placement, and to close the defect if possible. These perforations are more likely to be larger, peritoneal, recognized >12 hours postprocedure, and associated with systemic infection. In this situation, the location and size of the perforation determine the surgical approach.[105] Patients with delayed luminal perforation but without significant peritonitis and/or systemic toxicity can be managed endoscopically as described already in this article using clips, suturing, or stents. Given the possible disadvantages of diagnostic endoscopy in this scenario, antecedent oral-contrasted CT scan to confirm that the luminal defect has not spontaneously closed and surgical consultation for multidisciplinary decision-making are important.

In contrast, incidentally detected gas in the retroperitoneum on follow-up imaging after ERCP requires no intervention at all.[106] Symptomatic retroperitoneal perforations that appear to be small and contained and without associated peritonitis may be managed expectantly with bowel rest, antibiotics, and serial imaging to determine resolution or progression.[105,107] However, it has become popular in this situation to repeat ERCP for fcSEMS placement. This approach may expedite clinical improvement, resumption of oral intake, and discharge, but it mandates a future ERCP for stent removal. Perforations that are not amenable to stenting or primary closure but result in a contained extraluminal collection can be successfully managed with transmural drainage (and, if needed, direct endoscopic necrosectomy) akin to the management of pancreatic fluid collections or sleeve leaks.

Last, biliary and pancreatic stents can migrate externally and occasionally penetrate through the contralateral duodenal wall. This phenomenon is almost always detected incidentally at the time of follow-up ERCP or presents as stent occlusion. When this is the case, the stent(s) can simply be removed, and no further action is necessary. However, when the patient is symptomatic and/or extraluminal fluid/gas is present around the defect/stent, then – in addition to antibiotics – expedient stent removal and clip closure of the defect is indicated and effective. Occasionally, a distally migrated stent penetrates in such a fashion as to produce a frank perforation with peritonitis, requiring surgical intervention. Anecdotally, this seems to occur more frequently in immunocompromised patients.

## Infectious Complications of ERCP

ERCP introduces bacteria into the bile duct and/or pancreas (and any connected structure, such as a cyst) through devices and contrast that are inherently contaminated, having passed through the scope that traverses the mouth. This introduction of nonsterile contents is a natural part of the procedure and is generally insignificant. However, any situation in which outflow from the duct is compromised after ERCP can result in stasis, proliferation of the introduced bacteria, and clinically important infection. This phenomenon is almost always the result of undrained contrast, presumably due to the volume of inoculum, but could potentially complicate wire or device access to an occluded duct. Additionally, stents provide a direct conduit into the duct for bacteria, which will become trapped if the prosthesis becomes obstructed or migrates, resulting in delayed infection. Infectious adverse events of ERCP most commonly affect the biliary system, but suppurative infection of the pancreatic duct does occur and should be suspected in patients who have undergone pancreatic endotherapy.

### *Ascending Cholangitis*

Post-ERCP cholangitis is relatively common, occurring in 0.5%–3% of cases.[56] Although it most often occurs within the first few days after ERCP, it can happen up to 14 days after the procedure or beyond, depending on the mechanism(s) at play.[104] The most common scenarios that predispose to inadequate drainage and post-ERCP cholangitis are primary sclerosing cholangitis (in which contrast can stagnate upstream of multifocal strictures), perihilar strictures (for which achieving drainage with stents is more challenging), and residual/missed choledocholithiasis. Additionally, post-ERCP papillary edema, often after sphincterotomy and challenging stone extraction, can result in transient obstruction of the duct, which predisposes to ascending cholangitis. Two situations in which cholangitis and systemic infection are a concern, but sometimes without an obvious obstructive phenomenon, are when cholangioscopy is performed,[108,109] and perhaps during ERCP for liver transplant recipients.[110] Older patients and those who undergo inpatient ERCP are also more commonly affected.[56,110,111]

Prevention of cholangitis involves a procedural commitment to ensuring, to the greatest extent possible, adequate ductal drainage after ERCP (eg, minimizing the likelihood of a missed stone and placing stents into any ductal segment that has been opacified with contrast) as well as the evidence-based use of prophylactic antibiotics. Clinical practice guidelines and quality indicator documents recommend the use of prophylactic antibiotics whenever biliary drainage is suspected to be incomplete after ERCP (including scenarios already listed), and as a single intraprocedural dose in cases that involve cholangioscopy or perhaps liver transplantation.[106,112] We also administer antibiotics any time contrast is introduced into a space that is not adequately drained, such as during transpapillary treatment of a bile leak or pancreatic ascites and when there is intraprocedural concern for a perforation.

The presence of fever and/or leukocytosis in association with evidence of cholestasis should always prompt suspicion of cholangitis and initiation of broad-spectrum antibiotic coverage. Radiographic imaging is often obtained in such patients, but, regardless of findings, repeat ERCP is almost always warranted to achieve source control. Most patients with cholangitis will have a favorable initial response to antibiotics and intravenous fluids, and ERCP does not need to be performed emergently, although urgent decompression is occasionally necessary in patients with progressive hemodynamic compromise. In stable patients, we aim to perform ERCP as soon as logistically feasible (eg, first add-on case of the day), however, clinical practice guidelines recommend the procedure for this indication within 48 hours.[113] In cases of proximal obstruction due to hilar stricture, percutaneous biliary drainage may be necessary to achieve source control if repeat ERCP cannot decompress the biliary sector(s) of interest. The European Society for Gastrointestinal Endoscopy suggests culturing bile at the time of repeat ERCP to inform more tailored antibiotic therapy,[56] however, this practice remains uncommon in the United States.

Although cross-sectional imaging is not necessary for the diagnosis of cholangitis, it should be performed in any patient who does not respond favorably after ERCP to exclude a concurrent source of infection, such as liver abscess or acute cholecystitis.

### *Acute Cholecystitis*

The true incidence of cholecystitis after ERCP has historically been poorly characterized due to inconsistencies in definition and because cholecystitis can coexist with other indications for ERCP (eg, choledocholithiasis or cancer). A recent prospective study that used rigorous outcome definitions and 30-day follow-up demonstrated an incidence of post-ERCP cholecystitis of 0.4% in more than 4400 patients with a gallbladder who underwent ERCP.[114] The incidence was highest after placement of metallic biliary stents, both uncovered and covered (1.3% and 1.5%, respectively).[114]

The symptoms of cholecystitis develop a median of 5 days after ERCP.[114] Some patients can be treated with antibiotics alone, but many will require gallbladder decompression. This can be achieved by removal of the fcSEMS alone (and replacement with plastic stents), but sometimes requires additional endoscopic drainage, percutaneous cholecystostomy tube placement, or cholecystectomy. In reasonably stable patients, unless cholecystectomy is independently indicated, our preference is to decompress the gallbladder endoscopically with transpapillary gallbladder stent placement or EUS-guided transmural drainage. Where experience with these procedures is limited, or if the patient is unstable, percutaneous cholecystostomy tube placement is highly efficient and effective.

### *Duodenoscope-Associated Infections*

In recent years, based on high-profile outbreaks, much attention has been devoted to duodenoscope-transmitted pathogens. Although infection control in endoscopy is nuanced, with multiple interacting potentially causative factors,[115] the common bond is difficulty associated with adequately reprocessing the elevator mechanism. Ultimately, the rate of clinically significant duodenoscope- (or linear echoendoscope–) transmitted infection remains low, being estimated at approximately 0.01%.[116] Nevertheless, the possibility of catastrophic outcomes due to a potentially preventable cause prompted major gastroenterology and endoscopy societies to make this a priority area.[117] As a consequence, several novel duodenoscope designs have emerged with variable capacities for infectious harm reduction and technical performance parameters.[118–123] However, the cost implications of using some of these duodenoscope designs for all-comers appear unfavorable, especially for high-volume centers.[124,125] Thus, other solutions are likely needed to fully eliminate this problem, including designing duodenoscopes capable of withstanding full sterilization rather than reprocessing alone.[126]

## Conclusions

ERCP has and will continue to serve as the primary modality to address many pancreaticobiliary disorders that require anatomic intervention. The patients helped by this procedure far outnumber those harmed, but complications remain a serious problem. The evidence and insights presented in this document will hopefully help clinicians improve ERCP outcomes through a commitment to prevention, recognition, mitigation, and treatment of adverse events related to this salutary but complicated procedure.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.03.009.

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# Supplementary Material

## Additional Considerations for PEP

### Pathophysiology

The pathophysiology of PEP remains poorly understood. The most widely accepted hypothesis is that mechanical (from cannulation) and/or thermal (from sphincterotomy) trauma will cause capillary endothelial injury resulting in papillary edema and obstruction, which impedes outflow of pancreatic juice and increases hydrostatic pressure within the duct. However, prophylactic pancreatic stent placement (which addresses this phenomenon) is not completely protective, suggesting that even brief fluctuations in intraductal pressure can be the culprit and/or additional mechanisms are at play. Other possible etiologic factors include increased hydrostatic pressure from aggressive pancreatic injection, injury from the contrast medium itself (either its low pH or high osmolality), and bacterial contamination of the pancreatic duct by gut flora.[e1] The relative contribution of each of the aforementioned injurious factors remains uncertain and is probably variable, but no single factor appears dominant. Thus, a prophylactic approach involving several complimentary pharmacologic and mechanical measures addressing different mechanisms of injury is currently the mainstay of PEP prevention. Interventions that impact downstream inflammatory targets (eg, zymogen activation or the early inflammatory cascade) or patient predisposition (eg, microbiome) may also prove effective and merit additional research.

### Diagnosis of PEP

In research, the systematic application of the Atlanta classification – which is more sensitive and objective than Cotton's consensus definition – is problematic because of the requirement of routine imaging. Cotton's criteria are thus more practical for clinical studies but are limited by their subjective nature because decisions regarding admission and length of hospitalization are nonrandom and vary according to practice setting and style. This underscores the importance of blinding in randomized trials studying PEP and the need for an accurate biomarker to predict/diagnose PEP for clinical practice and research.

### Patient-Related Risk Factors for PEP

A prior episode of PEP appears to be the strongest predictor of recurrence.[e2] It is important to recognize, however, that endoscopic sphincterotomy separates the biliary and pancreatic orifices, reducing the risk of pancreatic injury during subsequent ERCPs. Thus, patients undergoing repeat biliary therapy in the context of a prior sphincterotomy are protected and typically do not require prophylaxis, even if their index ERCP was complicated by PEP. Female sex, younger age ($<$40 years), clinical suspicion of sphincter of Oddi dysfunction, and history of recurrent pancreatitis have also been consistently identified as independent predictors.[e2–e6] Conversely, chronic pancreatitis, a pancreatic head mass, and older age are thought to be protective secondary to the associated pancreatic fibrosis, atrophy, and decline in exocrine function.[e7]

Patients with a clinical suspicion of sphincter of Oddi disorder, particularly women, are not only at increased risk for PEP, but appear more predisposed to severe pancreatitis and death.[e8–e10] When considering the risk-benefit ratio of ERCP in this patient population, not only should the patient's overall risk of PEP be assessed, but their probability of experiencing a more dramatic clinical course should also be considered and discussed.

### Procedure-Related Risk Factors for PEP

The most common procedure-related risk factors for PEP include ampullectomy, difficult cannulation, and planned or unplanned intervention in the pancreas. The definition of a difficult cannulation varies between studies, ranging from $>$5 attempts to $>$10 minutes of attempted cannulation.[e11,e12] Using the $>$10 minutes definition, the odd ratio for PEP was 1.76 (95% confidence interval [CI], 1.13–2.74).[e2] Similarly, repeated pancreatic wire passages – which is another marker of difficult cannulation and appears harmful in itself – is associated with an even higher risk of PEP (OR, 2.77; 95% CI, 1.79–4.30).[e2] Indeed, some evidence suggests that even a single pancreatic wire passage is an independent predictor.[e13] Other interventions that increase risk are aggressive or repeated pancreatic injection and pancreatic sphincterotomy.[e14] Short-duration (60 seconds or less) balloon dilation of an intact biliary sphincter is also associated with PEP, but longer duration dilation is not as dangerous[e15] and dilation after biliary sphincterotomy does not increase risk at all.[e16] Precut sphincterotomy has traditionally been associated with a higher incidence of PEP, but more rigorous investigation has shown that early use of precut to reduce the number of cannulation attempts is actually protective.[e17]

### Pharmacoprevention With Agents Other Than Rectal NSAIDs and IVF

Many other pharmaceutical agents have been studied for the prevention of PEP with largely negative or conflicting results, partly because of inadequate methodologic rigor and sample sizes in RCTs. Non-NSAID agents with the most promise are bolus-administered somatostatin, nafamostat, and nitrates.[e18] Nitrates are the most attractive because of their widespread availability, ease of administration, and safety as a one-time dose. They function as a smooth muscle relaxant that reduces intraductal pressures after ERCP through their effect on the pancreaticobiliary sphincter complex. Trials of nitrates, however, have shown mixed results,[e18] although the combination of rectal indomethacin and sublingual nitroglycerin may be promising.[e19,e20] As we await stronger data on these and other agents, NSAIDs remain the only medication in widespread clinical use.

### Technical Considerations to Reduce Risk of PEP

The double-wire technique has become a popular second-line cannulation approach when initial attempts result in unintentional pancreatic wire passage, which is a risk factor for PEP. Although evidence showing that this technique is effective overall is conflicting, double-wire cannulation appears particularly helpful when access is impeded by difficult anatomy, such as when there is a malignant biliary stricture or the ampulla is intra-diverticular.[e12] A RCT of difficult cannulation cases requiring this technique demonstrated that prophylactic pancreatic stent placement reduced the incidence of PEP in this patient population.[e21] Additionally, in a recent large-scale RCT of indomethacin alone vs indomethacin plus a prophylactic pancreatic stent to prevent PEP – the SVI trial – PSP was particularly effective in patients undergoing the double-wire technique.[e11]

Studies have attempted to define the optimal rescue technique for difficult cannulation, but, in practice, each of these methods could be most appropriate depending on anatomic factors and operator experience. Conceptually, the safest of these is fistulotomy, during which electrosurgical current is used to create access into the duct through its intraduodenal portion, but away from the pancreatic orifice, minimizing the risk of PEP. On this basis, when the anatomy is conducive (ie, prominent intraduodenal portion of the bile duct), fistulotomy may be the most cogent approach. Because electrocautery-based access techniques can be dangerous in the hands of inexperienced endoscopists, European guidelines recommend these be used by practitioners with >80% cannulation success using standard techniques.[e22]

### *Controversies Surrounding Prophylactic Pancreatic Stent Placement*

Several controversies around the technical approach to PSP remain, such as how long to try, whether to chase after the pancreatic duct when the procedural objective is achieved before pancreatic access, and which prosthesis to choose. A secondary analysis of the SVI trial concentrating on patients who underwent successful PSP showed no strong association between PEP and 5 modifiable technical factors: whether pancreatic wire access was achieved for the sole purpose of PSP (vs occurring naturally; OR, 0.82; 95% CI, 0.37–1.84), whether substantial effort expended on stent placement (vs nonsubstantial effort; OR, 1.58; 95% CI, 0.73–3.45), stent length (>5 cm vs ≤5 cm; OR, 1.01; 95% CI, 0.63–1.61), stent diameter (≥5 French vs <5 French; OR, 1.13; 95% CI, 0.65–1.96), or guidewire caliber (0.035 inch vs 0.025 inch; 0.83; 95% CI, 0.49–1.41).[e23] Although these findings are based on post hoc analysis comprising relatively small subgroups of patients and are thus likely imprecise, the lack of a strong association between PEP and any one of these factors suggests that endoscopists should use their best judgment in individual cases without being overly committed to any specific approach. For example, generally speaking, our preference is to place a 5-French, long (to at least the midbody) prophylactic stent, but we pivot to a shorter prosthesis when wire access to the upstream duct is anticipated to be challenging (eg, tight pancreatic Ansa loop).

## Additional Considerations for ERCP-Related Bleeding

From a technical point of view, operator inexperience (≤1 sphincterotomy/wk)[e9] and choice of electrosurgical current (pure-cut) have traditionally been considered the main risk factors.[e24] However, recent randomized trials have brought the previously established advantages of blended current into question.[e25,e26] Although these data have not resulted in a practice change away from blended/smart current in our units, we are following the evolution of this evidence.

When placing a hemostatic clip through a duodenoscope, straightening the scope to the greatest extent possible (while still maintaining adequate alignment and visualization) and dropping the elevator immediately before deployment maximize the probability of successful placement. In some situations, switching to a gastroscope with a clear cap can achieve a more mechanically favorable approach for deployment, provided the location of the pancreatic orifice is clear and can be avoided by the jaws of the clip.

Direct tamponade after sphincterotomy can be achieved by external compression of the bleeding site using an extraction balloon that has been inflated in the duodenum or by inflating the balloon within the duct (above the sphincterotomy) and capturing the sphincterotomy site between the balloon and scope face. Typically, tamponade for 30–45 seconds using either approach is sufficient to arrest bleeding or at least provide improved visualization for additional hemostatic therapy.

## Additional Considerations for ERCP-Related Perforation

A recent consensus-based document defines ERCP-related perforation as a transmural defect or the presence of foreign material (eg, gas, intestinal or pancreaticobiliary fluid, contrast, or a foreign body) outside of the lumen that leads to an unplanned or extended healthcare encounter or admission.[e27]

The Stapfer classification is the most widely used system for ERCP-related perforations.[e28] A type 1 perforation is defined as a lateral or medial duodenal wall injury, typically due to the tip of the endoscope; type 2 is defined as a peri-ampullary injury, often secondary to sphincterotomy; type 3 is an injury to the distal bile duct; and type 4 is defined as retroperitoneal air alone (Supplementary Figure 1). Traditionally, this system was used to determine which patients require surgical repair vs repeat ERCP vs conservative management, but the implications are less concrete now with the evolution of endoscopic treatment of luminal perforations.

To avoid sphincter-related perforation in the management of particularly large bile duct stones, some experts intentionally perform an incomplete biliary sphincterotomy, leaving a safety margin of intact sphincter, to minimize the risk of retroperitoneal extension of the cut by large-volume balloon dilation or forceful extraction of a large stone.

## Additional Consideration for ERCP-Related Infectious Complications

Placement of a fcSEMS in a patient with an intact gallbladder may lead to acute cholecystitis by jailing off the cystic duct orifice and impeding the flow of bile from the gallbladder, whereas self-expanding metallic stent (SEMS) placement across a malignant extrahepatic biliary stricture may jail off the gallbladder by compression of an infiltrated cystic duct, even when the stent is uncovered. For benign strictures, meta-analyses suggest that this phenomenon occurs in only 1% of patients after fcSEMS placement, although this rate is likely an underestimate because SEMSs are not typically used when the cystic takeoff cannot be avoided by the stent.[e29] A large prospective cohort study found that cholecystitis occurred in 3 of 43 (7.0%) chronic pancreatitis patients with intact gallbladders if the cystic takeoff was covered compared with no cases among the 58 chronic pancreatitis patients if the cystic duct orifice could be avoided.[e30] For malignant strictures, the risk of cholecystitis after SEMS placement ranges from 5%–10%.[e31–e34] Randomized trials comparing uncovered SEMS to fcSEMS for the relief of malignant extrahepatic biliary obstruction have not clearly demonstrated a statistically significant difference in cholecystitis.[e35,e36] Although some large cohort studies do show an association between fcSEMS and acute cholecystitis,[e34,e37] others do not.[e31,e33] Of note, cholecystitis can occur even with coaxial plastic stents or when no stent has been placed at all. Functionally, any process that limits outflow from the gallbladder after ERCP, including cystic duct stones and edema, can result in this phenomenon.

There is at present no “ideal” strategy for duodenoscope-related infections that optimizes the competing factors of infection reduction (ideally, elimination), technical performance, cost, and carbon footprint, but the next logical step could be the development of “high-risk” patient criteria to support restricted use of more costly devices (Supplementary Table 1).

## Rare and Underappreciated Complications, and Special Populations

### Gas Embolism

Gas embolism is extremely rare, but a high index of suspicion can be lifesaving. Gas entry into the circulation has been attributed to the formation of a bilio-venous fistula due to the combination of intraductal trauma and forceful insufflation of gas.[e38] This phenomenon has most commonly been described in association with direct peroral cholangioscopy because of insufflation through an endoscope that has been introduced into the bile duct.[e39] The use of carbon dioxide – as opposed to room air – is believed to mitigate risk,[e40] but does not eliminate it.[e41,e42]

Gas embolism can be localized (confined to the portal circulation) or systemic. Localized embolism is identified on cross-sectional imaging or x-ray and typically resolves within 24 hours with conservative management.[e38,e43–e45] Systemic gas embolism, on the other hand, has a reported mortality rate of >60% and neurologic deficits are evident in a substantial proportion of survivors.[e38]

Gas embolism should be suspected any time a patient’s condition deteriorates rapidly from a cardiopulmonary standpoint during ERCP.[e46–e54] When there is any suspicion, the patient should be placed in the Trendelenburg position (to minimize gas travel to the brain) and given 100% oxygen and IVF.[e38,e46–e54] CT scan of the chest and head along with transthoracic echocardiogram are important for making the diagnosis and assessing the extent of cerebral impact. When the diagnosis is certain, in addition to supportive measures, central venous catheter–guided aspiration of intracardiac air and hyperbaric oxygen therapy have been reported as therapeutic options.[e38,e48,e49,e51–e53]

### Contrast-Associated Complications

A minute fraction of contrast injected during ERCP, especially into the pancreas, is absorbed systemically. However, clinically important contrast-associated allergic reactions are extremely rare, even in patients with known contrast allergies.[e55,e56] The role of premedication to prevent these events is controversial[e57] and practice guidelines in the United States have not addressed this issue in almost 20 years. It is unclear what fraction of units have a protocol for premedication of at-risk patients, and whether there is true value in implementing one. Some units premedicate with oral prednisone/diphenhydramine and inject only low-osmolality contrast media in patients with a prior allergy. In one of our units, we only premedicate patients with a prior severe reaction such as anaphylaxis or laryngospasm, but not those with milder reactions such as urticaria. When premedication is offered, it should resemble a typical radiology protocol that is initiated on the day prior because single intravenous doses of prednisone/diphenhydramine immediately before ERCP are not protective. When a significant contrast-associated event does occur, it resembles a typical anaphylactic reaction occurring within 20 minutes of contrast injection.[e55] Such patients are stabilized hemodynamically and managed with supportive measures, typically in the intensive care unit.

### ERCP-Associated Radiation Exposure

Fluoroscopy is necessary for ERCP, but both deterministic and stochastic effects associated with radiation exposure can lead to increased endoscopist, staff, and patient risk.[e58,e59] The main risk to the patient, occurring with very prolonged exposure, is cutaneous injury. Therapeutic ERCP has been reported to have an effective radiation dose of 12.4 mSv, higher than the 10 mSv exposure of an abdominal CT scan—a dose that would lead to an estimated 1 in 1700 lifetime cancer risk.[e60] However current ERCP-associated radiation exposure is likely lower than this reported level, attributable to evolution of fluoroscopy equipment and technology, including settings for radiation optimization.[e61–e64] An important metric in maximizing the quality of ERCP is the measurement, tracking, and reduction of radiation exposure to patients and the ERCP team. Brief educational interventions regarding modifiable factors to minimize radiation exposure have been associated with immediate and significant radiation exposure reductions for both high- and low-volume ERCPists.[e65] Some modifiable factors to minimize radiation exposure include the use of collimation, the use of low magnification settings when possible, and capturing only the fluoroscopy images that are absolutely necessary for each procedure.[e65]

### Stent Migration

Up to 6% of plastic stents placed during ERCP have been reported to migrate either proximally into the duct or distally into the duodenum.[e66] The most common result of distal migration of a plastic stent out of the duct is eventual passage in the stool without complication. However, any migration event can result in recurrent obstruction because the stent no longer serves its intended purpose.[e67] Additionally, distally migrated stents can result in perforation, bowel wall inflammation, and even penetration into regional vasculature or organs.[e68–e72] Several approaches have been reported for the removal of proximally migrated plastic stents, including directly grasping and removing the stent with forceps,[e67] intrastent balloon extraction,[e73] and sweeping the stent out using a retrieval balloon inflated proximal to the migrated stent.[e67] Cholangioscopy using a compatible micro-snare and forceps devices are also effective.[e74,e75]

### Basket Impaction

A mechanical lithotripsy basket can become impacted within the duct when the device fails to fragment the stone and the duct opening is too small for extraction. This has been reported in up to 6% of ERCPs in which a basket is used.[e76] Impaction is now less common because newer baskets are designed to detach at their distal tip, facilitating removal even when the stone does not crush. When impaction occurs, cutting the basket catheter outside of the accessory channel to expose the wires is the next step. This enables the use of a through-the-scope or outside-of-the scope (fluoroscopically guided) salvage lithotripter. These instruments will result in either adequate stone fragmentation or fracture of the lithotripsy basket, both of which will allow removal.

If neither are available, at the very least, cutting the catheter allows the removal of the duodenoscope to allow salvage maneuvers alongside the impacted basket, including large-volume balloon dilation and cholangioscopy-assisted lithotripsy.[e76,e77] Other approaches include using rat-toothed forceps traction on the basket wire[e78] or a second basket.[e79] These are the only options when the basket is designed for extraction and not lithotripsy and use of a salvage lithotripter is not possible. If endoscopic efforts are unsuccessful in the bile duct, an antegrade approach involving percutaneous transhepatic biliary drainage and a snare/catheter to dislodge the basket can be used.[e80]

### Pediatrics

ERCP can be safely and effectively performed in neonates, children, and adolescents, but studies have reported a higher adverse event rate relative to adults.[e81] Several challenges associated with ERCP in this population exist. First, the lower incidence of pancreaticobiliary disease in children restricts most pediatric ERCPists to a low-volume practice. Second, duodenoscopes and other accessories are designed for adults. Indeed, younger age predisposes to adverse events in pediatric ERCP, likely attributable to smaller working space, smaller pancreaticobiliary orifice, and lack of dedicated equipment. The previously available dedicated infant duodenoscope has been discontinued and an alternative is not available for patients under 10 kg or 12 months of age,[e82] leading to a scenario in which inappropriate scopes are used in the smallest patients. Novel duodenoscope designs have not concentrated on the pediatric population and devices tested only in adults can have unanticipated adverse events when used off-label in children. For example, novel duodenoscopes with single-use endcaps were associated with more difficulty cannulating and higher rates of adverse events in pediatric patients.[e83] This is an area for which disposable duodenoscope technology can be leveraged to fill an important unmet need. Finally, the impact of radiation exposure in children is magnified across their longer post-ERCP lifespan. Data indicate that pediatric ERCPs performed by low-volume endoscopists are associated with increased radiation exposure and this raises concern that the patients most susceptible to radiation effects are undergoing ERCPs with higher levels of radiation exposure.[e84]

Nevertheless, ERCP plays an important and salutary role when performed by well-trained pediatricians or adult endoscopists with pediatric experience. In children 2 years of age or older who are of typical stature, a standard adult duodenoscope can be used safely. Whenever ERCP is performed in children, great caution should be exercised while advancing the scope through the duodenal sweep because this area appears most susceptible to perforation.

### Pregnancy

Cholelithiasis is found in up to 12% of pregnant women,[e85] and a subset of these patients will develop symptomatic choledocholithiasis during pregnancy. Although ERCP during pregnancy poses unique challenges – anesthesia concerns, radiation exposure to the fetus, and apparent increase in the risk of PEP[e86] – inaction is associated with gallstone pancreatitis and cholangitis, both of which could threaten the pregnancy.[e87] Thus, when indicated, ERCP can and should be performed during pregnancy, ideally during the second trimester. Efforts to reduce fetal radiation exposure to the greatest extent possible should always be implemented. Nonradiation ERCP has been described in this context,[e88,e89] but in our experience, ERCP for pregnant patients is best performed using a very limited amount of fluoroscopy to increase the chance of a highly efficient procedure that minimizes time under anesthesia and the risk of PEP. An obstetrics team should always be involved throughout the entire process. Additional best practices for performing ERCP during pregnancy include positioning the patient in the left lateral decubitus position during the late second and third trimesters of pregnancy, lead drapes placed over the lower abdomen and pelvis to minimize fetal radiation exposure, and placement of the grounding pad on the right upper thorax or arm to avoid electrical current conduction through amniotic fluid.

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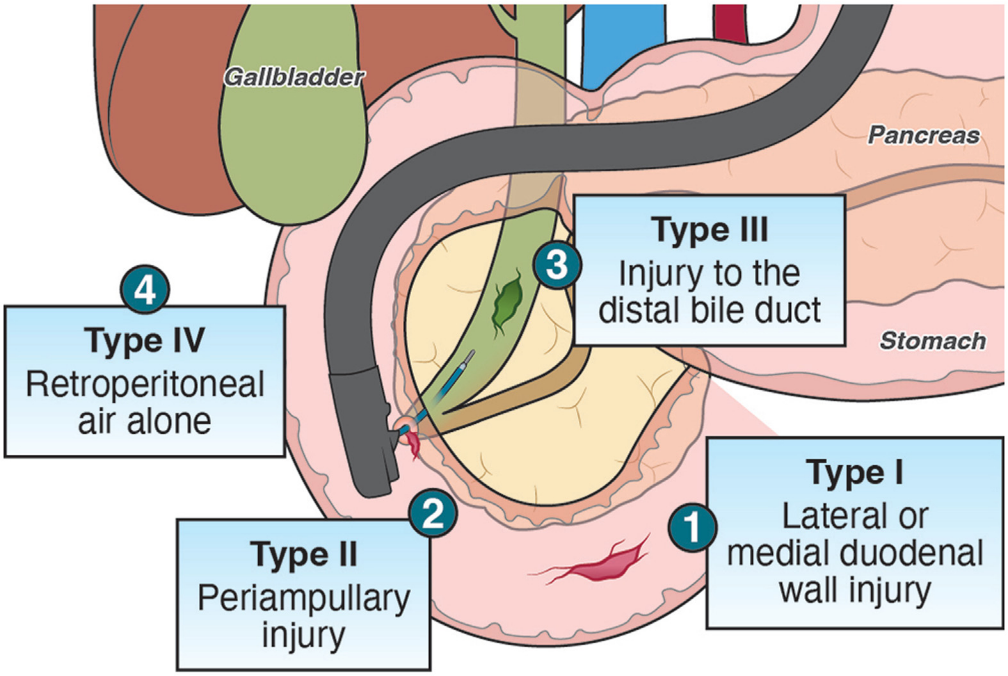


**Supplementary Figure 1.** The Stapfer classification for ERCP-related perforations.

**Supplementary Table 1.** Potential Scenarios for Single-Use Duodenoscope

| Patients at high risk for transmitting MDRO | Patients who are highly susceptible to infection |
|---|---|
| MDRO colonized | Post–solid organ transplantation |
| Acute cholangitis | Chemotherapy |
| Cholangiocarcinoma | Immunosuppression for systemic disease |
| Primary sclerosing cholangitis | Immunocompromised due to systemic disease |

MDRO, multidrug-resistant organisms.