

Controversies in ERCP: Indications and preparation

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ABSTRACT

The aim of the series of papers on controversies of biliopancreatic drainage procedures is to discuss the pros and cons of the varying clinical practices and techniques in ERCP and EUS for drainage of biliary and pancreatic ducts. The first part focuses on indications, clinical and imaging prerequisites before ERCP, sedation options, post-ERCP pancreatitis (PEP) prophylaxis, and other related technical topics. In the second part, specific procedural ERCP-techniques including precut techniques and its timing as well as management algorithms are discussed. In addition, controversies in EUS-guided bile duct and pancreatic drainage procedures are under preparation.

Key words: bile stones, EUS, magnet resonance cholangiopancreatography, pancreaticolithiasis, primary sclerosing cholangitis, tumor

INTRODUCTION

Indications, clinical pathways, training, sedation practice, and techniques used for ERCP and EUS may vary in different cultural contexts, countries, and endoscopic centers.¹⁻³¹ EUS and ERCP are often practiced by the same operators with a hepatopancreaticobiliary

skill set. EUS is an important diagnostic tool to establish the indication for ERCP, complementary to computed tomography (CT) and magnet resonance cholangiopancreatography (MRCP), and imaging methods have taken over the diagnostic role of ERCP.

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EUS also steadily emerges as a therapeutic alternative to ERCP in some cases of biliary drainage. Therefore, it seems advisable to reflect on current indications, safety aspects, and techniques of ERCP.

In this paper, important practical issues regarding performance and controversies of ERCP are discussed from different perspectives. Practicing endoscopists from various regions across the world contributed to this review and discussed their standard practices in the context of currently available evidence. The aim of this paper is to discuss the pros and cons of the varying clinical practices and techniques in ERCP. The first part focuses on indications, clinical and imaging prerequisites before ERCP, sedation options, post-ERCP pancreatitis (PEP) prophylaxis, and other related topics. More specific procedural techniques including precut techniques and its timing as well as management algorithms are reviewed and discussed in the second part.

The authors declare that this paper is not intended as a guideline, but rather as an opportunity to document current practice, allowing readers to evaluate their own procedures and to stimulate further discussion.

DO WE NEED OTHER IMAGING/ ESOPHAGOGASTRODUODENOSCOPY/ OTHER PROCEDURES BEFORE ERCP?

Is esophagogastroduodenoscopy before ERCP mandatory?

Introduction and review of the literature

ERCP is a high-risk endoscopic procedure requiring deeper sedation than conventional esophagogastroduodenoscopy (EGD). It is therefore a key that an endoscopist has assessed all available information to ensure that the procedure is appropriately planned. Essential knowledge before ERCP includes clinical information, patient's fitness to tolerate the procedure, as well as adequate preprocedural imaging. Imaging should not be limited to cross-sectional modalities. Some patients may be suitable to proceed to ERCP on the basis of ultrasound (US) alone. However, should preparation for ERCP always or in special circumstances include EGD?

Do we need esophagogastroduodenoscopy?

Complication risks for diagnostic EGD are very low (<1:10,000) and are mostly due to over sedation.^[4] Little is known about the evidence supporting EGD

before ERCP as all recommendations in textbooks originate from personal opinions of the authors. It seems logical to assume that a prior EGD could reduce the complication rate of some ERCPs due to better visualization of the esophagus, stomach, and duodenum, thereby facilitating detection and evaluation of any preexisting pathology. On the other hand, EGD, although low risk, is not devoid of complications.

Arguments in favor of esophagogastroduodenoscopy before ERCP

There is no evidence-based literature to support performing EGD in all patients pre-ERCP. As stated above, in some circumstances, there is a logical rationale to start with EGD. First, in patients with presumed upper gastrointestinal strictures, benign or malignant, EGD to assess the anatomy using a forward viewing scope could be informative. The second group includes patients with clinical dysphagia without known strictures. In addition, EGD could be informative in patients with unclear postsurgical anatomy, especially where cross-sectional imaging is inconclusive. At last, if advancement of the side-viewing scope is met with resistance or the intubation of the esophagus or second part of the duodenum is difficult, assessment with EGD before re-attempting with the side-viewing scope seems sensible. Additional groups that might warrant mentioning include patients with suspected esophageal diverticulae, large hiatal hernias, and esophageal/duodenal varices. We therefore recommend having a gastroscope available during ERCP lists in case such uncommon and unexpected circumstances occur.

Arguments against

In patients with preserved normal anatomy and without dysphagia, performing EGD would be an unnecessary added risk. In addition, it exposes the patient to prolonged sedation, certainly in countries where ERCPs are not necessarily performed with propofol or general anesthesia (GA). At last, it adds to unnecessary costs to the national healthcare systems or the patient in private care settings.

Conclusion

In general, there is no indication to perform routine EGD pre-ERCP in patients without dysphagia, known or presumed strictures, or altered anatomy of the upper gastrointestinal tract. If anatomical assessment is imperative or if unclear obstructions are encountered, then EGD is easy and safe owing to its low complication risks.

Do we need ultrasound or other radiological imaging modalities before ERCP

Introduction and review of the literature

In general, before ERCP, blood tests and noninvasive imaging such as US, CT scan, and/or magnetic resonance imaging (MRI) are performed.^[5,6] More recently, EUS has emerged as a valuable addition to the armamentarium. This will be discussed separately.

Arguments in favor of radiological imaging before ERCP

In patients where choledocholithiasis is not proven on abdominal US or CT, European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend MRCP or EUS to establish a clear indication for ERCP.^[6-8] Patients with symptomatic chronic pancreatitis (CP) may also be candidates for endoscopic therapy in selected instances.^[9] For CP and jaundiced patients with suspected cancer, cross-sectional imaging in the form of a multidetector CT is recommended before ERCP to image the pancreatic and biliary tract and surrounding vessels.^[10-12] This is to detect, characterize, and stage the masses/tumors adequately before ERCP because artifacts and inflammation around metal stents or complications such as PEP might hamper the image quality and subsequent correct interpretation. CT, MRI, and contrast-enhanced US have further advantage of potentially detecting distant metastases.^[13,14] US and, in particular, MRI with MRCP are helpful to characterize lesions of the hepatic hilum according to the Bismuth–Corlette classification.^[15] Preprocedural staging, classification of the anatomical level of biliary tract obstruction, and treatment planning are important as this may influence intraprocedural decision-making.

Arguments against radiological imaging before ERCP

In acute cholangitis due to stones or blocked stents, the diagnosis and therefore indication for ERCP might already be clear and would not warrant cross-sectional imaging *per se*. In those circumstances, an US might suffice. Most patients would have had some forms of imaging during admission to the hospital.^[6] At last, unnecessary costs as well as potentially harmful events, *e.g.*, radiation and application of contrast agents, should be avoided when CT is considered.

Conclusion

In selected cases, in addition to abdominal US, further cross-sectional radiological imaging is needed to establish the diagnosis and thereby the indication for

ERCP. It may also provide additional information to guide management decisions during the performance of ERCP. The most common indication for immediate ERCP is in those with a clear clinical diagnosis of cholangitis with dilated bile ducts on US.

Do we need EUS before ERCP?

Introduction and review of the literature

Existing guidelines do not suggest that EUS should necessarily be performed before ERCP in either benign (choledocholithiasis, CP) or malignant disease (cholangiocarcinoma, gallbladder cancer, pancreatic cancer, and ampullary cancer).^[11,16] There are however some circumstances when performing EUS before biliary intervention with ERCP is justified; this will be discussed below.

Clear indications of EUS before ERCP

In cases with obstructive jaundice where MRCP is unavailable or not possible (for example, due to cardiac pacemaker) or where imaging (US/CT/MRCP) and laboratory findings are equivocal for the presence of bile duct obstruction or stones, EUS should strongly be considered to establish an indication for ERCP.^[8] For small stones, in particular, EUS was found to have a better diagnostic yield compared with MRCP.^[17,18] EUS outperformed MRCP in patients with suspected choledocholithiasis and negative CT findings.^[19] In patients with intermediate risk of choledocholithiasis and a negative MRCP result, EUS results in detection of choledocholithiasis in a substantial percentage of cases.^[20] In jaundiced patients with double duct dilatation but without a mass on cross-sectional imaging, EUS before ERCP and stent insertion offers a window of opportunity to find a discrete mass to explain the clinical picture, perform fine needle biopsy where appropriate and to justify an ERCP. In cases of isolated biliary dilatation where a focal point of obstruction suggests a possible cholangiocarcinoma, EUS examination before ERCP allows identification of the level of obstruction without interference by a stent or loss of dilatation following decompression. This is particularly relevant in cholangiocarcinoma given the small size of these lesions and the significant artifact or mural alterations that can be produced by metal stents.

Oncological indications

In suspected cancer of the pancreatic head without tissue diagnosis, ERCP-guided metal stenting (SEMS) was shown to increase the occurrence of incorrect EUS-guided tissue diagnosis of the tumor by an odds

ratio of 1.96.^[21-29] Therefore, EUS and biopsy should ideally be performed before SEMS placement in such cases. Plastic stents do not seem to have the same limitation;^[22] however, because they tend to occlude over time, SEMS has become the preferred treatment modality for malignant biliary obstruction in most units.^[22-29] Other reasons to perform EUS before ERCP would be to assess for vascular involvement of the tumors, which could be otherwise impaired by the presence of metal stents.^[23,26] Previous studies suggest a role for EUS to stage the vascular involvement when CT proves equivocal.^[30,31] Combining the EUS biopsy with ERCP and biliary stenting in one session as a “one-stop-shop” is attractive for patients with malignant distal biliary obstruction as it reduces hospital visits or hospital stay. It has been shown that performing EUS and ERCP in a single session has no disadvantages compared to performing both procedures in separate, sequential sessions but shortens the time interval before starting treatment of pancreatic head cancer.^[32] Moreover, in patients with suspected malignant bile duct obstruction, both in pancreatic head cancer and in biliary malignancy, the diagnostic yield of the combined procedure was higher compared to EUS-guided fine needle aspiration alone.^[33] From the endoscopic team, it requires expertise in both, EUS and ERCP. Combining EUS-guided biopsy and ERCP stenting in one session is more feasible when propofol sedation is available as opposed to conventional sedation with opiates and benzodiazepines where patients’ time-dependent tolerance is the limiting factor.

Suspected choledocholithiasis

For the management of suspected bile duct stones, recent guidelines include EUS and MRCP as investigation tools that should be considered.^[5-8] According to the aforementioned European guideline, the only exception to not necessarily having previous cross-sectional imaging would be in patients who present with cholangitis or common bile duct (CBD) stones confirmed on abdominal US. Of note, abdominal US has a sensitivity of only 73%^[34-36] [Figure 1]. The latter is almost comparable to CT scans. When a CT was performed to detect stones, it was found to have 81.2% accuracy in a retrospective study, but this decreased to 56.5% when stones were <5 mm.^[37]

For EUS, the sensitivity ranges between 75% and 100% to diagnose choledocholithiasis.^[38] Especially in patients

with biliary pancreatitis, EUS is an important gatekeeper procedure: according to a systematic review, a strategy of performing EUS before decision on ERCP avoids ERCP with its associated complications in 71% of cases.^[39] An important management approach included in the British Society of Gastroenterology (BSG) guidelines is that of laparoscopic cholecystectomy with intraoperative cholangiography or laparoscopic US for patients with an intermediate likelihood of CBD stones.^[5] If calculi are identified within the CBD, these can be extracted laparoscopically or by intraoperative ERCP in the same session. This latter approach has been shown to be safe and effective with obvious benefits in terms of hospital stay and cost.^[40] An important aspect of this approach is that a guide wire can be passed antegradely via the cystic duct across the ampulla, facilitating endoscopic CBD cannulation and avoiding inadvertent pancreatic duct cannulation with its associated risk of pancreatitis. This approach requires close cooperation between the surgical and endoscopic teams.

Chronic pancreatitis

EUS is not required pre-ERCP once painful CP is established and confirmed. Performing a high-quality pancreatic CT and/or MRI with cholangiopancreatography to rule out pancreatic cancer before planning treatment is the recommended imaging modality. Based on a meta-analysis,^[41] the European guideline states that ERCP, EUS, CT, and MRI/MRCP are comparable in diagnosis of CP, but among noninvasive examinations, EUS has the highest diagnostic sensitivity.^[42] It has a role in diagnosing CP (particularly, in the early stages of the

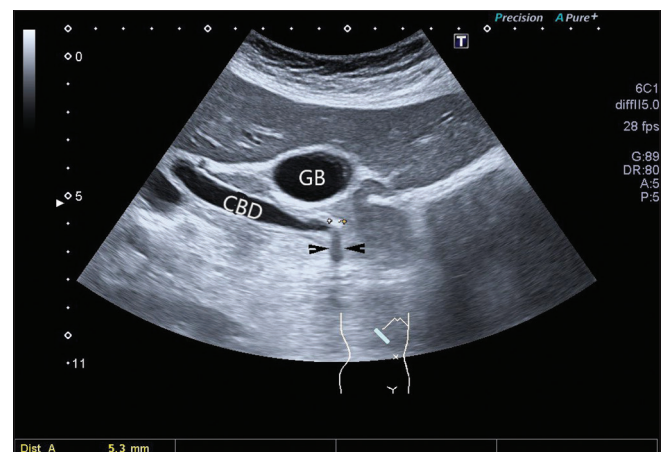


Figure 1. Small stone of the distal common bile duct (echogenic stone between markers, 5 mm), detected with transabdominal ultrasound using a convex robe (2–6 MHz). Please note the postacoustic shadow (arrowheads)

disease), in diagnosing and managing complications that may be attributed to disease progression, and in planning endoscopic treatment. Its value lies principally in diagnosing/differentiating calculi and strictures, establishing concurrent malignancy and treating complications such as pseudocysts.^[43] However, EUS alone has its limitations and should not be used alone to diagnose CP.^[44] To overcome some of these limitations, EUS elastography can be used to evaluate tissue strain (stiffness) to improve accurate diagnosis.^[45,46] Although EUS elastography may help in diagnosis of CP, further prospective and histopathological-matched studies are required.^[47]

Conclusion

EUS before ERCP is not conventionally recommended. It is helpful in suspected CBD stones when cross-sectional imaging cannot provide the diagnosis and single-stage cholecystectomy with intraoperative ERCP is not available. In malignant distal bile duct obstruction requiring staging completion or tissue diagnosis in addition to biliary drainage, EUS should ideally be performed before ERCP and stenting. In CP, EUS may be used in addition to cross-sectional imaging if pancreatic malignancy is suspected or for detailed planning of endoscopic treatment.

ARE ROUTINE COAGULATION TESTS REQUIRED BEFORE ERCP?

Against routine anticoagulation tests before ERCP

As the incidence of bleeding diathesis in the general population is low, routine coagulation screening tests add rarely to the management of nonjaundiced patients undergoing ERCP.^[48] In addition, prothrombin time will not detect the presence of the more common hereditary coagulopathies such as von Willebrand disease and hemophilia A and B. Routine blood tests increase costs and might cause time delays. The ESGE guidelines do not see the need for routine coagulation tests in patients who are not on anticoagulation or who are not jaundiced.^[49]

Arguments in favor of routine anticoagulation tests before ERCP

ERCP with sphincterotomy is considered a high-risk procedure for adverse events of bleeding which occur in 0.1%–2%.^[50,51] Therefore, the BSG guidelines recommend stopping antiplatelet agents (clopidogrel, prasugrel, and ticagrelor) and warfarin 5 days before ERCP in patients with low thrombotic risk.^[52] Direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban should be discontinued 48 h before the

procedure in patients with low thrombotic risk and normal renal function. In patients on warfarin at high risk of thromboembolic events (mitral metal valve, atrial fibrillation, and prosthetic heart valve or mitral stenosis, less than 3 months after a venothromboembolic event), bridging with low-molecular-weight heparin is started 2 days after stopping warfarin and hold 24 h before the procedure. Deeply jaundiced patients with biliary obstruction often will benefit from intravenous (IV) Vitamin K to optimize the international normalized ratio (INR) because Vitamin K absorption is impaired due to cholestasis.

Conclusion

Costs for full blood count and coagulation studies are low, and these tests are quickly available in high-volume centers where ERCPs should be performed. Platelets >50,000 and INR <1.5 are widely accepted criteria before considering sphincterotomy. In patients with coagulopathy due to liver cirrhosis, endoscopic papillary balloon dilatation may be advantageous compared to endoscopic sphincterotomy.^[53,54]

SEDATION IN ERCP. DO WE NEED AN ANESTHETIST TO PROVIDE SEDATION DURING ERCP?

Introduction and review of the literature

Advanced endoscopic procedures such as ERCP require optimal sedation for the safety and comfort of the patient and to complete technically demanding procedures with precision and calmness, resulting in acceptable success rates. Traditional sedation agents include the combination of benzodiazepines and opiates, most often midazolam and fentanyl.^[55,56] Propofol (2,6-di-isopropylphenol) is an ultra-short-acting sedative agent with rapid onset. Compared to traditional sedating agents, propofol allows shorter recovery times and better sedation and amnesia levels without an increased risk of cardiopulmonary complications, as demonstrated in a meta-analysis of nine prospective randomized trials with a total of 969 patients.^[57] A German multicenter study (ProSed 2) including more than 300,000 patients undergoing endoscopy concluded that sedation-related complications were generally low (0.01%) and were lowest among patients receiving propofol monotherapy.^[58] The quality of sedation seems to have an effect on the therapeutic success of the ERCP. In a nation-wide analysis in Sweden including 31,001 ERCP procedures with

native papillae,^[59] propofol sedation resulted in higher cannulation rates (89.0% *vs.* 86.7%; $P < 0.0001$) and less intraprocedural complications (2.9% *vs.* 3.7%; $P < 0.0001$) than traditional sedation with benzodiazepine and opiates. The rate of post-ERCP complications was expectedly similar. It is therefore obvious that adequate sedation improves the outcome of the ERCP procedure.^[60] There remains controversy^[61] and a huge variance in national and international legislations^[62] as to whether propofol should be administered only by anesthetists or whether properly trained nonanesthetists^[63] can apply propofol sedation safely. Nurse-administered,^[64] patient-controlled,^[65] or computer-assisted, target-controlled infusions are alternative means of delivering propofol sedation during endoscopy with prolonged procedure times or complex interventions.^[66] Comparing the safety of nonanesthetist-administered propofol sedation (3018 patients) in advanced endoscopic procedures with those of anesthetist provided propofol sedation (2374 patients) in a meta-analysis of 26 prospective observational studies, the safety of nonanesthetist-administered propofol sedation compared favorably, possibly because anesthetists tended to give more propofol and aimed at deeper sedation levels.^[67]

Arguments in favor of anesthetist restricted propofol sedation

Deep sedation improves the technical outcome and completion rate of procedures.^[60] Anesthetists are trained to manage respiratory and cardiopulmonary complications, should they occur. Patients with ASA classes >III have a higher rate of adverse events requiring unplanned interventions during ERCP and would thus benefit from anesthetic support.^[68] Having the luxury of an anesthetic team providing GA with endotracheal intubation or monitored deep propofol sedation without intubation allows the endoscopic team to fully concentrate on the technical part of the endoscopic procedure.

Arguments in favor of nonanesthetist-administered propofol sedation

Anesthetists have usually no exposure to sedation for endoscopic procedures during their training and are not familiar with the challenges the endoscopist faces and the sedation level required for endoscopy.^[69] In addition, for ERCP, the rate of sedation-related adverse events in nonanesthetist provided propofol sedation is small. Although no reversal exists, the effect of propofol resolves very rapidly and rarely requires transient mask

and bag ventilation. Anesthetist-led deep sedation is expensive and subsequently restricts the provision of propofol sedation for ERCP patients, due to capacity, funding, and staffing issues.

Conclusion

Propofol sedation is preferable to benzodiazepine/opiate combinations for sedation in endoscopy due to shorter recovery times, higher satisfaction levels by patients, improved success rates, and lower adverse event rates. There is overwhelming evidence that nonanesthetist-administered propofol sedation for advanced endoscopic procedures is safe, cost-effective and results in high levels of patient and endoscopist satisfaction. Clearly, adequate patient selection and appropriate training are mandatory to maximize safety.

ERCP AND EUS: SHOULD THE EXAMINER BE THE SAME?

ERCP should be performed by the same examiner as EUS

The option of EUS before ERCP has many advantages for the endoscopist trained in both.^[70] In biliary pancreatitis, for example, ERCP is only indicated in the setting of persistent calculi within the CBD, usually evidenced by co-existing cholangitis or persistently elevated liver function tests. EUS can confirm their presence before attempted biliary cannulation. Benign stenosis of the papilla of Vater, especially in patients after cholecystectomy (so-called adenomyomatosis of the papilla of Vater) cannot be discriminated by cross-sectional imaging,^[71] but easily using EUS^[72] [Figure 2].

This condition renders guide wire introduction often very challenging and frequently leads to an unsuccessful procedure. Being aware of the condition or of a stone impacted in the papilla or floating in the bile duct can inform the ERCPist how to best approach the papilla [Figure 3].

Written information of the condition does not match the amount and quality of information about the individual anatomy the endoscopist takes in if the EUS was performed by him/herself. The endoscopist can better decide whether and how deep to cut, if precut papillotomy is necessary. In the end, the endoscopist can decide how much risk to take in precutting according to the clinical picture. An impacted stone warrants immediate relief whereas a free floating stone can be delayed to the next day(s). In certain

clinical conditions, ERCP can be performed without fluoroscopy but with EUS alone. This could shorten the therapeutic setup and avoid radiation.^[73] Another advantage of the endoscopist being proficient in both EUS and ERCP is the knowledge and assessment of suitability for alternative EUS interventions should ERCP fail. In the case of initial failed biliary cannulation, the EUS-ERCP-ist is better disposed to weigh up the technical aspects and risks related to intra- or extra-hepatic biliary access using EUS as opposed to persisting with ERCP techniques, including precut sphincterotomy. If the EUS approach seems a low-risk procedure, the switch of methods can be made earlier and might even be possible within the same procedure, if the endoscopist is well trained in EUS interventions and the patient was consented for this and is tolerating the procedure from a sedation point of view. A further major advantage to the ERCP

practitioner also being trained in EUS is the ability to perform biliary drainage and tissue acquisition as a one-stage procedure in the setting of malignancy. This reduces the number of invasive procedures these patients must undergo [Figures 4-7].

ERCP could be performed by any other examiner

If the ERCP-ist and endosonographer are highly specialized endoscopists, it is not necessary to insist that they have to be one and the same person. Working closely together and understanding the other person's EUS report can be as good as being the same endoscopist. One essential precondition to prevent information loss in case of different examiners is high-quality standardized EUS reports.^[74-76] The most important factor for being successful is to involve the other endoscopist in good time in case of difficulties and knowing each other's skills. Short communication pathways and the availability of the EUS expert are crucial to be able to switch methods immediately as necessary.

SUPINE, PRONE, OR LEFT LATERAL POSITION?

Introduction and review of the literature

The optimal positioning of a patient during ERCP depends on many factors.

First, it relates to the capability of the available X-ray equipment. Most X-ray machines can only be moved two dimensionally. If the machine is able to move three

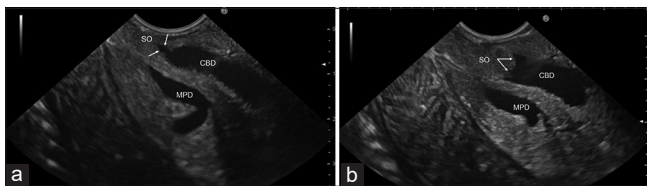


Figure 2. Longitudinal endosonography in a patient with elevated liver enzymes and recurrent right upper quadrant abdominal pain: typical finding of benign stenosis of the papilla of Vater with slight dilatation of the CBD and the MPD. Relaxation of the SO with the typical “champagne flute sign” (a, arrows) and contraction of the SO with a polypoid appearance of the sphincter apparatus protruding into the ductal lumen (b, arrows). CBD: Common bile duct; MPD: Main pancreatic duct; SO: Sphincter of Oddi

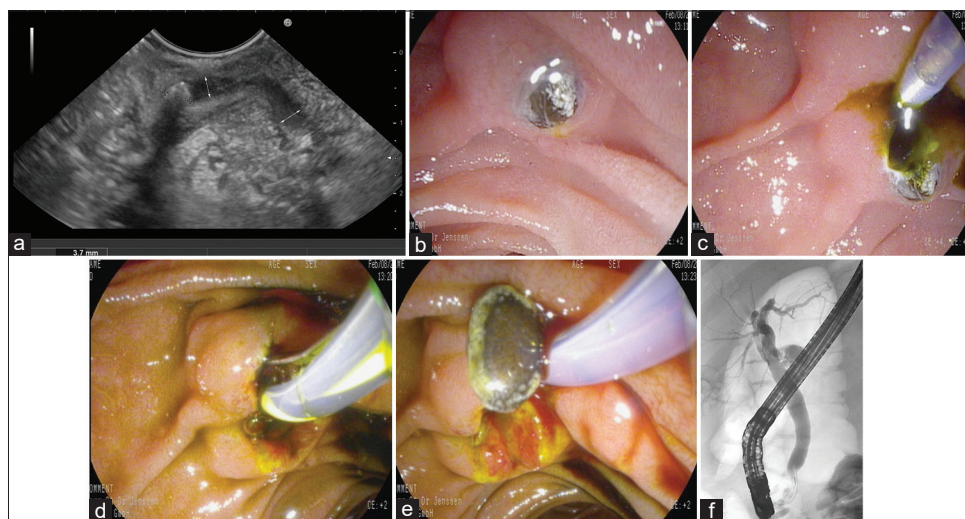


Figure 3. Small common bile duct stone in the orificium of the papilla of Vater. The stone (3.7 mm, between markers) was detected using longitudinal EUS in a non-dilated common bile duct with hypoechoic luminal content (double head arrows, a). The stone was visible on side-viewing endoscopy in the orificium of the papilla (b). Needle knife precut was performed, leading to flow of dark bile fluid (c). Biliary sphincterotomy was completed in wire-guided standard technique (d) allowing spontaneous passage of the stone (e and f)

dimensionally around the patient, then the endoscopist does not have to move the patient to change to a different angle.

Second, it depends on the patient's condition. Some patients cannot be placed onto the stomach or the back or the side because of pain or co-existing restricting physical conditions.

Third, the sedation method used. In the case of IV sedation only, there is no difference between left lateral and prone positioning of the patient. In our experience,



Figure 4. EUS and ERCP in a patient with PSC. EUS demonstrates the thickened bile duct walls (a) and (b) as well as dilatation and narrowing of the bile duct lumen (c). The corresponding ERCP reveals multiple strictures (d). PSC: Primary sclerosing cholangitis

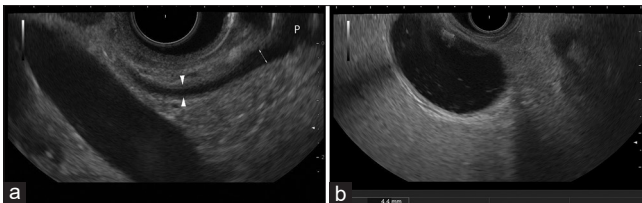


Figure 5. EUS in acute biliary pancreatitis (radial endosonography): Slim common bile duct (lumen: double arrow) with slightly thickened wall (arrow heads), the stone has already passed (a). A small gallbladder stone (4 mm; between markers) is found (B): ERCP can be avoided before laparoscopic cholecystectomy.

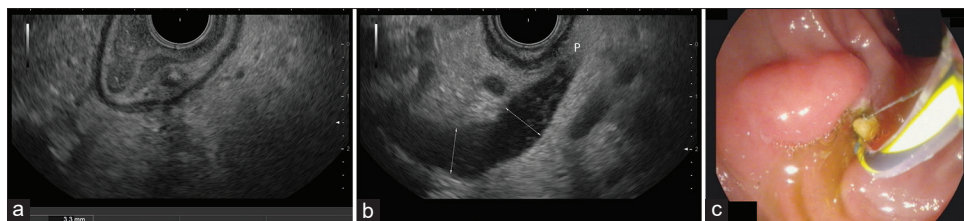


Figure 6. EUS and ERCP in acute biliary pancreatitis: a 3 mm stone is found within the ampullary part of the common bile duct (between markers; a). The common bile duct is slightly dilated (double head arrow) with non-anechoic content (sludge) (b; P = Papilla of Vateri). Following biliary sphincterotomy, the small stone is born (c).

the supine position should be avoided because of a higher possibility of aspiration during long procedures. A recent meta-analysis showed a higher technical success rate in prone ERCP at the cost of a higher number of adverse events.^[77] In a study comparing alternate positions, however, there was no statistical difference between prone and supine position, especially if the patient was placed at a slight angle with elevation of the head.^[77-80]

Fourth, anatomical factors relating to the patient. Sometimes, it can be difficult to intubate the duodenum in the prone or supine due to angulation of the stomach in a patient with a morbid body mass index. Left lateral position of the patient can make it easier to introduce the tip of the scope into the duodenum. Another confounder can be the presence of a duodenal diverticulum. In this instance, sometimes, the left lateral position, and sometimes, the prone position of the patient can be helpful.

Arguments in favor of left lateral position

The majority of therapeutic ERCPs deal with stones in the CBD. In these cases, the left lateral position of the patient is easier for the endoscopist because that is the main position for other endoscopic procedures.^[81] This makes it easier for the endoscopist to introduce the scope in a familiar way and avoids aspiration in an intravenously sedated patient. The adequacy of fluoroscopic imaging is not impaired in left-sided positioning, and the papilla region and the CBD as well as the pancreatic duct can be traced easily with rotation of the C-arm. If necessary, the left lateral positioning of the patient can be resolved into a prone position by simply turning the patient.^[79]

Arguments against left lateral position

If only two-dimensional X-ray equipment is available, then left lateral positioning of the patient results in inadequate differentiation of the intrahepatic bile ducts. Equally, the length of a pathology involving the pancreatic duct from the papilla can be massively under- or overestimated.

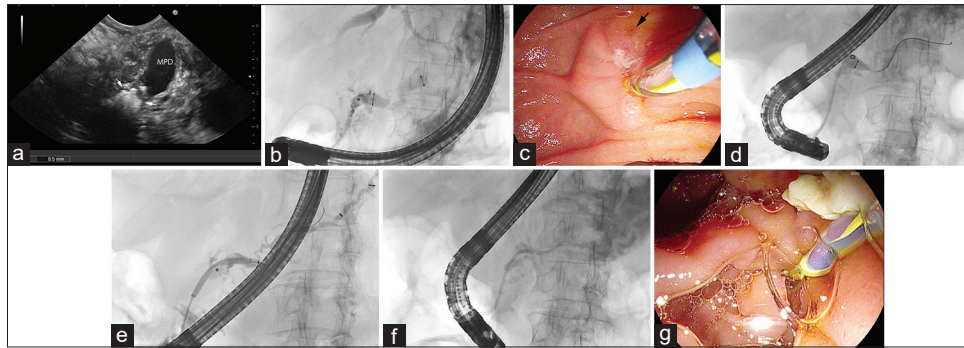


Figure 7. EUS and ERCP in chronic pancreatitis: EUS (a) shows a dilated MPD (8.5 mm between markers) caused by a larger obstructing stone (arrowheads). On ERCP, the obstructing stone (*) is seen within the dilated MPD (double head arrows; b). Pancreatic sphincterotomy is performed (directed to the 1 o'clock position), the pancreatic duct ostium is found 10 mm below the biliary ostium (arrow; c). After passing the obstructing stone with a guide wire, bougienage (d) and balloon dilatation (e) are performed by the placement of a pancreatic plastic endoprosthesis (f). Extraction of the fragmented pancreatic stone was possible following extracorporeal shock wave lithotripsy (g). MPD: Main pancreatic duct

Prone or supine positioning of the patient makes it easier to interpret pathology correctly. In addition, prone positioning renders the patient more stable, so moving artifacts are less of a problem. Supine positioning of the patient does not appreciably alter imaging from the prone position and is mostly preferred in patients undergoing GA.^[80,82] In intubated patients, the supine position is ideal for intubation and extubation of the patient while the risk of aspiration is minimized.

Conclusion

Decisions regarding positioning of the patient should be made according to the aim of the procedure and the patient's condition. If only the CBD is of interest, left lateral positioning of the patient may be preferable. If differentiation of the intrahepatic ducts or imaging of the pancreatic duct is of interest, prone position seems preferable. If the investigation is performed under GA, the supine position is as good as the prone position. Most endoscopists perform ERCP according to their own routine – if they are used to a specific positioning of the patient, they should not change their habits. In terms of the literature, there are no real differences in outcome according to patient positioning.

PANCREATITIS PROPHYLAXIS, POST-ERCP PANCREATITIS

Introduction and review of the literature

PEP is the most common potentially severe complication of ERCP and is associated with significant morbidity and occasionally death. While there are well-recognized patient (including female sex; younger age; previous PEP; normal caliber CBD; suspected sphincter Oddi dysfunction) and procedural (including

difficult cannulation; pancreatic duct injection of contrast; repeated wire insertion in pancreatic duct) factors that increase the risk, no procedure is risk free. The incidence reported in the literature varies widely.^[83,84] In high-risk patients/procedures, it may be as high as 25%–30% with an incidence of 1%–10% in low-risk settings. While a figure of 2%–5% is widely quoted as the rate in average-risk patients undergoing routine ERCP, prospective studies of PEP have invariably documented a higher rate 7%–19%.^[85-87] This probably reflects the more careful case assessment of a prospective study compared to retrospective studies or audits^[88,89] and is more likely to reflect the true figure. PEP is associated with significant healthcare costs, estimated at \$150 million annually in the USA.^[90] PEP is likely to be multifactorial with a combination of hydrostatic, mechanical, and enzymatic factors.^[84] The most important opportunity for prevention occurs preprocedure and involves careful review of individual risks and benefits to ensure that ERCP is only offered to those in whom there is clear potential benefit that outweighs the risk. An ideal PEP prevention strategy would be inexpensive, with minimal inherent risk, not prolong the procedure or postprocedure stay, and not require follow-up intervention.

PEP prophylaxis can be broadly considered in three categories:^[91] (1) endoscopic intervention; (2) systemic pharmacotherapy; and (3) IV fluid therapy. The perhaps most important fourth category is prevention of diagnostic ERCP, *e.g.* by proper pre-ERCP diagnostics (using US and EUS) and careful consideration of patient- and procedure-related risk factors to tailor an individual strategy for PEP prevention.^[91]

Endoscopic intervention

Guide wire technique

Cannulation technique is a recognized factor relating to PEP. Insertion with a guide wire first instead of direct cannulation and contrast injection reduces the risk of PEP and has become common practice.^[92] Whether the sphincterotome is placed against the papilla (touch technique) or does not have physical contact and only the advanced wire is used to insert (no touch technique) does not differ in the rate of PEP, but the cannulation rate is significantly higher with the touch technique.^[93-95]

Pancreatic duct stents

Pancreatic duct stents have been shown to reduce the risk of PEP in high-risk cases.^[96] A network meta-analysis of studies in high-risk patients found 5-Fr stents to be more efficacious than 3-Fr stents^[97] and 3-cm 5-Fr stents were associated with a lower risk of PEP than a 5-cm stent in a randomized controlled trial (RCT).^[98] However, pancreatic stent placement can be challenging and is associated with complications such as inward stent migration and duct perforation. In addition, a failed attempt at pancreatic stent placement is associated with an increased risk of pancreatitis of 35%.^[99,100] If a pancreatic duct stent is placed, follow-up imaging is mandatory to ensure spontaneous dislodgement. Reported dislodgement rates vary with one study reporting a rate of spontaneous dislodgement within 14 days as high as 98%.^[99] However, in two other studies, 89%^[101] and 60%^[102] of patients required endoscopy for stent removal. A retained pancreatic duct stent is associated with risk of duct damage and CP. The role of fast degrading biodegradable pancreatic stents in this setting remains unclear.

Topical epinephrine

Epinephrine sprayed onto the ampulla has been investigated as potential prophylaxis; a recent meta-analysis^[103] suggested that this was effective in reducing PEP and suggested that it as an alternative therapy if nonsteroidal anti-inflammatory drugs (NSAIDs) were contraindicated. However, this recommendation and the quality of the studies included in the meta-analysis have been questioned.^[104] Two recent RCTs have investigated the combination of topical epinephrine and rectal NSAIDs; The INDIEH trial found no difference in incidence and severity of PEP,^[105] while the other was stopped at the interim analysis for safety concerns and futility due to a higher incidence of PEP in the combination

group.^[106] We therefore do not recommend topical epinephrine.

Systemic pharmacotherapy

Rectal nonsteroidal anti-inflammatory drugs

Many pharmacological agents have been investigated for the prophylaxis of PEP, with attention focusing latterly on NSAIDs.^[86,87,90,107] NSAIDs are potent inhibitors of phospholipase A2, cyclooxygenase, and neutrophil–endothelial interactions, which are believed to play an important role in the pathogenesis of acute pancreatitis.^[90,108] A landmark RCT (in high-risk patients)^[90] documented that rectal indomethacin confers protection in addition to pancreatic duct (PD) stenting. Subsequent *post hoc* analysis^[102] demonstrated that after adjusting for imbalances in risk factors for PEP between the groups, the patients who received indomethacin alone had the lowest risk of PEP. Similar results were found in a network meta-analysis that indirectly compared the efficacies of NSAIDs and PD stenting.^[83,109] The latest network meta-analysis showed equipotency of NSAIDs and PD stenting and favored indomethacin alone due to lower costs and feasibility. Subsequent studies have demonstrated efficacy of rectal NSAIDs in average-risk as well as high-risk patients and that when PEP occurs, severity is reduced.^[110] In addition, pre-ERCP administration is more effective compared to post-ERCP administration^[111] (6% *vs.* 12% PEP rate). Dose escalation beyond 100 mg did not confer any advantage in a recent RCT.^[112] Rectal NSAID is the mainstay of PEP prophylaxis and its use is advocated by a number of societies.^[49,91,113,114] The issue of whether the addition of PD stenting confers any advantage is under investigation in the ongoing stent *versus* indomethacin trial.^[115]

Sublingual nitrate

Nitrates relax smooth muscle and increase pancreatic parenchymal blood flow.^[116] A meta-analysis reported that glyceryl trinitrate reduced the overall incidence of PEP (relative risk 0.67, 95% confidence interval 0.52–0.87) while subgroup analysis found that sublingual administration (2–5 mg before ERCP) was superior to transdermal or topical application.^[117] Whether or not sublingual nitrate has an additive effect to rectal NSAIDs remains unresolved. A single-center study^[118] in predominantly high-risk patients has reported that the combination of 5 mg sublingual isosorbide dinitrate and 100 mg rectal indomethacin given before ERCP was more effective than indomethacin alone in reducing the incidence

of PEP (6.7% *vs.* 15.3%, $P = 0.0016$). A subsequent multicenter RCT^[119] also reported superiority of the combination in reducing PEP (5.6% *vs.* 9.5%, $P = 0.03$) although hypotension occurred in 8% of patients who received the nitrate. There were also several limitations to the latter study; in addition to utilizing a nonstandard dose of indomethacin (50 mg), there was no blinding and all patients received a urinary trypsin inhibitor, ulinastatin, as an additional pancreatitis prophylaxis measure.

Aggressive hydration

Aggressive hydration with lactated Ringer's solution has been documented to reduce the systemic inflammatory response and C reactive protein in patients with acute pancreatitis compared to normal saline.^[120] An acidic environment favors trypsinogen activation and the development of pancreatitis in experimental models.^[121] Ringer's lactate solution is less likely to induce metabolic acidosis than saline, which may explain its protective effect. Consequently, Ringer's lactate solution is the recommended fluid for resuscitation in the International Association of Pancreatology guidelines.^[122] The above has led to interest in the potential role of aggressive hydration in the prevention of PEP. A small, randomized study^[123] documented that aggressive hydration with Ringer's solution significantly reduced the incidence of PEP (17% *vs.* 0%) in a cohort of inpatients undergoing ERCP. No other prophylactic agent was used. A recent^[124] meta-analysis of nine RCTs investigating aggressive hydration (utilizing both normal saline and Ringer's lactate solution) reported a significant 56% reduction in the incidence of PEP with 17 patients treated to prevent one case of PEP.

There is great interest in the potential of a combination of aggressive hydration and rectal NSAIDs for PEP prophylaxis. Secondary analysis of the INDIEH trial^[105] found that higher fluid volume and the use of lactated Ringer's solution were associated with a decreased risk of PEP and length of hospital stay when used in conjunction with rectal indomethacin in high-risk patients.^[125] In two recent network meta-analyses, the combination of rectal Indomethacin and aggressive hydration was found the most effective strategy to prevent PEP.^[126,127] The results of RCTs such as the Fluyt trial^[128] investigating the combination of aggressive hydration plus rectal NSAIDs in average-risk to high-risk patients are awaited with interest.

The majority of studies have involved a long-course regimen of hydration extending for 8 h postprocedure,

thereby potentially necessitating a postprocedural inpatient stay. An effective regimen combining short-course per-procedural aggressive hydration and rectal NSAIDs thereby not prolonging patient stay would be ideal; however, high-quality data supporting this approach are lacking. A previous study^[129] found no difference between a combination of bolus Ringer's lactate solution and rectal indomethacin compared to bolus normal saline and rectal indomethacin. Although of good methodological design, this study has been criticized for being underpowered.^[130]

Specialist society recommendations

The ESGE^[49] guidelines published in 2020 recommend rectal NSAIDs for all patients unless contraindicated with consideration of a PD stent if biliary cannulation is difficult and PD stenting easy (*e.g.*, inadvertent wire in PD). If rectal NSAIDs are contraindicated, aggressive hydration is recommended for 8 h postprocedure unless a PD stent is placed (difficult biliary cannulation, easy PD stenting) when aggressive hydration can be stopped after the procedure. In the event that both IV hydration and rectal NSAID are contraindicated, 5 mg sublingual GTN and consideration of PD stenting is recommended. The ASGE^[13] guidelines on adverse events related to ERCP published in 2017 recommend PD stents or rectal NSAIDs for high-risk individuals and suggest that rectal NSAID may be beneficial in average-risk individuals. The evidence for PD stents is categorized as high quality while that for NSAIDs in high-risk patients is moderate and in average-risk patients is low. They also suggest that there is insufficient evidence that rectal NSAIDs plus PD stenting is superior to either technique alone. Japanese guidelines on prevention of PEP focus on the proper indication of ERCP and careful consideration of patient- and procedure-related risk factors. Rectal application of NSAIDs is recommended immediately before ERCP and PD stenting only in high-risk patients.^[91]

Arguments in favor

Rectal NSAIDs are inexpensive in most healthcare systems, the cost of a 100 mg indomethacin suppository being less than 3 euros in the UK. However, in the USA, diclofenac suppositories are not available and indomethacin suppositories are only available from one manufacturer; consequently, the cost has increased from \$2 to \$340 over the last 15 years; with the addition of hospital charges, the total cost can be several thousand dollars.^[131] Unless the individual has a history of NSAID allergy, rectal NSAIDs are

safe and easy to administer. Use of rectal NSAIDs for ERCP prophylaxis (where drug cost is not inflated) is a “no brainer.” The same is true to aggressive pre-ERCP hydration unless there are contraindications, *e.g.* congestive heart failure.

Arguments against

There is no plausible clinical reason not to administer diclofenac or indomethacin suppositories in patients who have no contraindications. The evidence for combination of interventions is weak; in fact, there are data indicating no additional benefit of a PD stent if a rectal NSAID has been administered and in the authors view the extra costs (of the stent as well as repeat endoscopy for stent removal) and risks (stent misplacement, migration, and retention due to loss to follow-up) strongly mitigate against PD stent placement instead of or as well as rectal NSAID in most patients in whom a rectal NSAID can be safely administered. The ESGE guidelines definition of difficult cannulation (>5 contacts with the papilla or 5 min of cannulation attempts or >1 unintended PD cannulation) and suggestion that additional PD stenting (if PD stenting is easy) is warranted in this setting may lead to placement of PD stents in a significant proportion of cases without clear evidence of benefit but with additional costs and potential harm. Before an aggressive hydration strategy is ordered, contraindications should be considered on an individual basis.

Conclusion

Rectal indomethacin or diclofenac should be administered ideally preprocedure to all patients undergoing ERCP unless there is a clear contraindication. The evidence for combination with any other intervention is weak. Until more evidence is available, any additional prophylaxis should be considered on an individual basis and tailored accordingly. Periprocedural aggressive hydration where safe should be considered in high-risk patients and concomitant PD stenting should be restricted to the highest risk cases and where such stenting is readily achieved. In cases where an NSAID cannot be administered, aggressive hydration (with the rate and duration tailored to patient comorbidity and PEP risk) should be considered along with PD stenting for high-risk cases.

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Conflicts of interest

Siyu Sun is the Editor-in-Chief of the journal, Christoph F. Dietrich is the Co-Editor-in-Chief, and Michael Hocke and Christian Jenssen are Editorial Board Members. The article was subject to the journal's standard procedures, with peer review handled independently of these Editors and their research groups.

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