

How to Prevent Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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ἀσκεῖν περὶ τὰ νοσήματα δύο, ὠφελεῖν ἢ μὴ βλάπτειν
—As to diseases, make a habit of two things: to help, or
at least, to do no harm.

Hippocrates, *Epidemics* (460 BCE–377 BCE)



Endoscopic retrograde cholangiopancreatography (ERCP) was developed in 1968 and almost instantly gained a key role in the diagnosis and management of many biliopancreatic disorders. Today, ERCP is predominantly a therapeutic procedure and its diagnostic

role has progressively vanished with the advent of important improvements in other imaging modalities such as computed tomography scanning, magnetic resonance cholangiopancreatography, and endoscopic ultrasound examination. The challenging nature of ERCP is not only due to the difficulty in learning and performing it, but mostly to the possible adverse events that are related to it. When approaching ERCP, one should know that post-ERCP pancreatitis (PEP) is the most common serious adverse event ($\leq 3.5\%$ of cases), and $\leq 10\%$ of those can be severe.^{1–3} It is also important to know that that PEP is associated with a high economic burden with annual estimated costs that exceed \$150 million in the United States.^{3,4} Other ERCP-related adverse are infections (1.4%), post-sphincterotomy bleeding (1.3%), and perforations (0.6%).^{3,4}

Appropriate Training in ERCP

Appropriate ERCP training is directly correlated to the control of ERCP-related adverse events. Usually, the endoscopic curriculum for a general gastroenterology fellowship does not include ERCP training. Therefore, to have effective ERCP training, one should find referral centers with structured training programs, availability of well-trained masters, ERCP simulators, adequate teaching materials, and

preferably centers with a multidisciplinary team including interventional endoscopists, surgeons, and interventional radiologists. In terms of competence, during training trainees should have reached selective cannulation in $\geq 90\%$ of procedures, should accurately interpret endoscopic and radiologic images, perform successful sphincterotomy, and stent placement.^{5,6} As far as numbers are concerned, approximately 255 ERCPs are required to achieve routine biliary ERCP competency.⁷ Decreasing the risk of PEP and other ERCP-related adverse events and “knowing how” to treat them should be part of the training curriculum

Correct Indication for ERCP: “The Lessons Are Clear”

The clinical appropriateness of ERCP is the key factor in the reduction of PEP. Therefore, the endoscopists should have excellent knowledge about the “indications to” the procedure and in “maneuvers to” reduce the risk of pancreatitis. Early recognition and prompt and appropriate management of PEP are critical in reducing morbidity and mortality. Peter Cotton,⁸ in an analysis of a series of 59 ERCP related lawsuits where he was an expert witness, concluded that the majority of them were related to the indication for the ERCP. Here we cite the conclusions: “The lessons are clear. ERCP should be done for good indications, by trained endoscopists with standard techniques, with good documented patient informed consent and communication before and after the procedure. Speculative ERCP, sphincterotomy, and pre-cuts are high-risk for patients and for practitioners.” The lessons are clear indeed.

Steps in Prevention of PEP: “Make a Plan, Check the Devices, and Be Prepared”

Planning the procedure and checking the availability and proper functioning of devices should be done routinely.

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Table 1. Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Patient-related factors	Suspected sphincter of Oddi dysfunction	
	Female gender	
	Obesity	
	Previous pancreatitis	
	Younger age	
	Non dilated extrahepatic bile ducts	
	Absence of chronic pancreatitis	
	Normal serum bilirubin	
	Procedure-related factors	Duration of cannulation attempts
		Pancreatic guidewire passages
Pancreatic injection		
Pre-cut sphincterotomy		
Biliary balloon dilatation		
	Failure to clear bile duct stones	

Subsequently, the following few simple steps should be considered.

The first step in PEP prevention, after a proper indication for ERCP, is identification of all patient- and procedure-related risk factors (Table 1). For instance, a young obese female patient with common bile duct stones and a previous episode of acute biliary pancreatitis is at much higher risk to develop PEP than other patients.

The second step in PEP prevention is the adoption of pharmacological prophylaxis (Table 2). Since 1977, >35 different drugs have been evaluated for the prevention of PEP with variable results.^{9,10} Finally, Elmunzer et al¹¹ in 2012 demonstrated that rectal nonsteroidal anti-inflammatory drugs (NSAIDs) were efficacious in PEP prevention. This finding was then followed by several randomized, controlled trials that confirmed the effectiveness of rectal NSAIDs.^{12,13} To have maximum efficacy, NSAIDs should be given shortly before the ERCP procedure.¹⁴ Generally, we give a single dose of indomethacin 100 mg, 20 minutes before the procedure.

The third step is to evaluate the papilla carefully, because every single papilla is different. First, the papilla should be clearly seen en face and its characteristics should be recognized (ie, presence of ectropion, long infundibulum), followed by selection of the best cannulation approach. This step is important in decreasing PEP. Recently, 2 prospective multicenter trials suggested that the macroscopic appearance of the papilla does influence bile duct cannulation.^{15,16} According to these studies, papillas were classified in 4 types: type 1, most common or “regular papilla”; type 2, “small papilla,” (small, often flat with a

diameter not greater than 3 mm); type 3, “protruding or pendulous papilla” (with the orifice oriented caudally); and type 4, “creased or ridged papilla,” (the ductal mucosa seems to extend distally out of the orifice either on a ridge or in a crease). The authors concluded that every type of papilla corresponded with some degree of difficulty in cannulation. From a practical standpoint, if an initial trainee is faced with a type 3 or 4 papilla, it would be logical to stop any attempt of cannulation and let the trainer continue. After cannulation by the expert, the trainee could continue with stent placement, stones extraction, and so on. Such a practical approach could also reduce PEP and other ERCP-related adverse events as well.

Fourth step: ready for cannulation? Contrast or wire? The literature suggests that guidewire cannulation is safer compared to contrast injection.^{17,18} However, the main biases of these studies are related to the contrast volume, concentration, and type, as well as the force of injection, factors that are extremely difficult to standardize. For instance, injection of a minimal quantity of contrast “to evaluate the direction of the ducts” provides important information regarding the anatomy of the ducts and choice of the type of wire. This approach, in our opinion, is very reasonable. Gentle guidewire maneuvering under fluoroscopy guidance and by trained assistants is also a key requirement.

The fifth step entails pancreatic stenting. Pancreatic stenting is another key factor in PEP prevention. This procedure should follow any unwanted high pressure main pancreatic duct (MPD) injection, multiple guidewire passages in the MPD, double wire cannulation, or endoscopic papillectomy. Pancreatic stenting should also be performed in all high-risk patients.^{19–21} Rescue MPD stenting has been reported to prevent the evolution of pancreatitis, and should be done 8–20 hours from the onset of PEP.^{22–24} Stents used for MPD stenting should be short (less than 5 cm, and small in diameter (5 French) and distally unflanged plastic stents. Unflanged stents can lead to spontaneous migration into the gastrointestinal tract, that occurs in 95% of cases within 10 days.¹⁸ If radiographs show evidence of stent persistence at 1 week, an upper endoscopy should be done for stent removal.¹⁸

Special Situations

In a patient with contraindication to rectal NSAIDs who is not at risk for fluid overload, and a pancreatic stent has not been placed, the suggested alternative is aggressive hydration with lactated Ringer’s solution (3 mL/kg/h during ERCP, a 20-mL/kg bolus after ERCP, 3 mL/kg/h for 8 hours after ERCP).²¹ In patients at high risk for PEP, the

Table 2. Prophylaxis of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Pharmacologic prophylaxis	Definitively effective: diclofenac and indomethacin
	Possibly effective: somatostatin, octreotide, gabexate; ulinastatin, epinephrine spraying over the papilla
	Other measures: aggressive hydration (Ringer lactate), topical epinephrine
Pancreatic stenting	To be performed in: any unwanted high pressure main pancreatic duct injection, multiple guidewire passages in the main pancreatic duct, double wire cannulation, endoscopic papillectomy or in all high-risk patients.

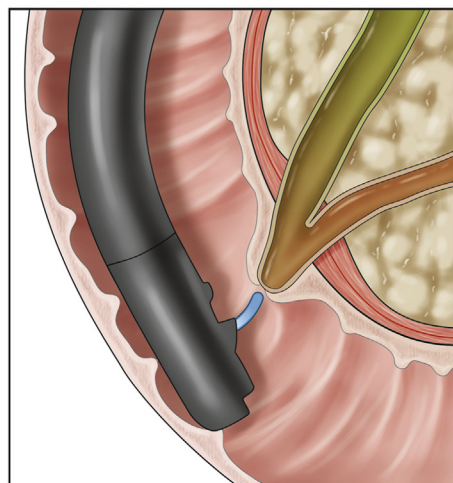


Figure 1. Steps in avoiding and prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

- Evaluate proper indication to ERCP
- Evaluate any existent risk factors for post-ERCP pancreatitis
- Give rectal NSAIDs (i.e., Indomethacin 100 mg) 20 minutes before ERCP
- Carefully evaluate the papilla (ectropion, location, and type)
- Choose the appropriate accessories for cannulation
- Place a pancreatic stent in all high-risk patients and situations
- Start aggressive hydration with lactated Ringer's solution in all high-risk patients
- Evaluate the patient after the procedure and, in case of complications, start the appropriate treatment as soon as possible

recommendation would be 100 mg of rectal NSAIDs before the procedure plus a pancreatic plastic stent in case of multiple accesses in the MPD, and of course, aggressive hydration with lactated Ringer's solution. Such high-risk ERCPs should be performed by experienced, expert endoscopists.

Postprocedural Care

How is the patient after the ERCP? The majority of ERCP procedures will not be associated with adverse events, but in the case of suspected PEP the first step is to establish the diagnosis. This is done with clinical, laboratory, and imaging examinations in preestablished timeframes. Appropriate treatment should start as soon as possible. Finally, it is very important to have an open, immediate, and comprehensive discussion with the patient and family members.

Conclusions

Prevention of PEP is a process and consists of several steps that should always be adopted (Figure 1). Having well-trained endoscopists and nurses in the ERCP team is extremely important and is the basis of this process. A solid indication for the ERCP is fundamental in avoiding adverse events. The procedure should be preferably done in a tertiary referral center with the availability of a multidisciplinary team. Prophylaxis of PEP should be done using NSAIDs 20 minutes before the procedure. Before attempting cannulation, the papilla should be well-evaluated and cannulation accessories and type of cannulation should be chosen accordingly. Pancreatic stent should be placed in all high-risk patients and situations and whenever it is deemed necessary. Finally, considering the rapid evolution of deep learning and artificial intelligence it is a matter of time when we will have software capable of identifying high-risk patient and high-risk papilla.

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Conflicts of interest

The authors have made the following disclosures: Professor Guido Costamagna is consultant for Cook Medical, Boston Scientific, and Olympus, and has Olympus research grant. Dr Ivo Boškoski is consultant for Cook Medical, Boston Scientific, and Apollo Endosurgery; is an Apollo Endosurgery research grant holder; and is Scientific Board member of Endo Tools.