A Review of Prevention of Post-ERCP Pancreatitis

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Abstract: Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic procedure employed in the management of disorders of the biliary system. Post-ERCP pancreatitis (PEP) is the most common complication of ERCP and can lead to significant morbidity as well as occasional mortality. In addition to adequate procedural training, therapeutic endoscopists who perform ERCPs should possess a thorough understanding of patient- and procedure-related risk factors for PEP. This knowledge can inform patient selection for ERCP and allow for appropriate management efforts to be performed in high-risk cases. Procedural techniques promoting minimally traumatic biliary cannulation should be employed when initial standard techniques are unsuccessful. In high-risk patients, several measures can be undertaken to limit the risk of PEP, including administration of rectal nonsteroidal anti-inflammatory drugs, prophylactic placement of pancreatic duct stents, and liberal administration of lactated Ringer solution. When PEP does occur, appropriate management with aggressive intravenous hydration, pain control, and early enteral nutrition should be administered. Additional research is needed to further define risk factors for PEP, optimal procedural techniques used during ERCP, and ideal prevention and treatment strategies to limit the incidence and severity of PEP in patients.

Endoscopic retrograde cholangiopancreatography (ERCP) is a specialized procedure used for the diagnosis and treatment of pancreatic and biliary system disorders. This procedure was developed as a diagnostic modality in the late 1960s and early 1970s.[1,2] The first biliary sphincterotomy was performed in 1974,[3] and since then, the use of ERCP as a tool for therapeutic interventions within the biliary tract has been rapidly evolving.

Post-ERCP pancreatitis (PEP) is the most common complication of ERCP and occurs in 3% to 15% of ERCP cases, with roughly 5% of these patients developing a severe course of the condition. In high-risk cases, the risk of PEP can be as high as 25%.[4] PEP can lead to significant morbidity, occasional mortality, and substantial costs to the health care system. It is estimated that more than $200 million

is spent annually on treating PEP.[4] Other complications of ERCP, including postsphincterotomy hemorrhage, perforation, and the development of cholangitis or cholecystitis, are comparatively rare.

Commonly accepted definitions of PEP are found in the consensus criteria, which were developed by Cotton and colleagues[5] in 1991, and the 2012 revisions of the Atlanta Classification.[6] The consensus criteria include new or increased abdominal pain consistent with acute pancreatitis, pancreatic enzyme elevation to more than 3 times the upper limit of normal within 24 hours of the procedure, and the necessity for new or continued hospitalization for at least 2 nights.[5] The Atlanta Classification lists abdominal pain consistent with acute pancreatitis, amylase or lipase elevation to more than 3 times the upper limit of normal, and evidence of pancreatic inflammation revealed by abdominal imaging.[6] Under both definitions, 2 of the 3 criteria are required for a diagnosis. Given the differences in practice among providers and hospital systems, there is concern that the length of hospital stay cited in the consensus criteria might lead to intraprovider and intrafacility variability in PEP rates. The Atlanta Classification eliminates this criterion and is generally thought to be more sensitive; however, it promotes the use of computed tomography imaging, which is not necessarily required for diagnosis in many clinical situations.

Appropriate Patient Selection for Endoscopic Retrograde Cholangiopancreatography

Given the risks of ERCP, namely bleeding, perforation, cholangitis, and PEP, therapeutic endoscopists should be judicious in identifying the appropriate patients for the procedure. Diagnostic ERCP has become extremely limited due to the increase in the use of less-invasive biliary diagnostic modalities, particularly magnetic resonance cholangiopancreatography and endoscopic ultrasound, as a result of their accuracy in detecting biliary disease.[7-9] ERCP should be reserved for patients who have a high pretest probability that a therapeutic intervention will be required. Furthermore, the benefits and probability of a successful therapeutic intervention should be weighed carefully against the risks of complications on a case-by-case basis.

Appropriate indications for ERCP include high suspicion of biliary obstruction as a result of choledocholithiasis, biliary stricture, or biliary malignancy, or high suspicion of a bile duct injury such as a bile leak after cholecystectomy. Prior to ERCP, these indications are typically suggested by the clinical course and laboratory values of the patient as well as by imaging modalities. A plan should be put in place to intervene upon the expected finding before proceeding with ERCP. Additionally, all of the needed supplies, a well-trained staff, and an experienced endoscopist should be present in order to maximize the chances of a successful intervention.

ERCP should be avoided if other procedures can be performed or if the condition can resolve on its own. For example, in patients presenting with possible choledocholithiasis in the setting of cholecystitis or cholelithiasis who require cholecystectomy and do not have clinical evidence of cholangitis, it may be reasonable to perform a cholecystectomy first with intraoperative cholangiogram to assess for the presence of persistent choledocholithiasis. In cases where the common bile duct stone passes of its own volition, ERCP (and, thus, the risks of this second procedure) can be avoided. Conversely, in cases of persistent choledocholithiasis, ERCP can safely be performed following, or at the same time as, cholecystectomy.[10] Overall, the scope of indications for ERCP has narrowed in recent years. The recently published EPISOD (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction) trial recommends avoiding ERCP in patients with unexplained pancreaticobiliary pain. During this trial, patients with what was previously known as type III sphincter of Oddi dysfunction (SOD) were randomized to receive either a combination of ERCP, biliary manometry, and sphincterotomy or a sham procedure. This study found no significant difference in terms of pain reduction in these high-risk patients.[11]

Risk Factors for Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis

In identifying high-risk cases, it is important to consider both patient- and procedure-related risk factors for PEP (Table 1). Pathophysiologically, PEP is thought to be a result of increased pressure that develops within the main pancreatic duct from periampullary inflammation caused by the trauma of ERCP. Thus, the majority of described risk factors are those that lead to increased inflammation at the ampulla and the head of the pancreas. A thorough understanding of these risk factors allows for therapeutic endoscopists to cater management decisions to the particular risks of each case.

Patient-Related Risk Factors

Patient characteristics that increase the risk of the development of PEP include female sex, young age (<55 years), a history of pancreatitis, a history of PEP, normal bilirubin, nondilated bile ducts, suspicion of SOD, and the presence of intraductal papillary mucinous neoplasm. Advanced age and the presence of a periampullary diverticulum or choledocholithiasis have not been shown to increase the risk for PEP.[11-13] Research demonstrates that patients with more than 1 risk factor have a significantly

Table 1. Risk Factors for the Development of PEP

Patient-Related Risk Factors	Procedure-Related Risk Factors
Female sex	Difficult cannulation of the biliary orifice
Young age (<55 years)	Biliary, pancreatic, or precut sphincterotomy
History of pancreatitis	Balloon dilation of an intact sphincter
History of PEP	Wire cannulation into the main pancreatic duct
Normal bilirubin	Contrast injection into the main pancreatic duct
Nondilated bile ducts	Placement of a self-expanding metal stent
Suspicion of sphincter of Oddi dysfunction	Ampullectomy
Presence of IPMN	

IPMN, intraductal papillary mucinous neoplasm; PEP, post–endoscopic retrograde cholangiopancreatography pancreatitis.

higher risk than those with a single risk factor[12]; therefore, patient characteristics should be considered in regard to both appropriate patient selection for ERCP and efforts aimed at prophylaxis against PEP.

Several protective patient-related factors have been described. Patients who have undergone previous ERCP with sphincterotomy are at lower risk of developing PEP, as prior sphincterotomy frequently leads to separation between the common bile duct and the main pancreatic duct, thereby theoretically reducing the chances of pancreatic duct cannulation or injection and allowing for easier and more efficient cannulation of the common bile duct.[4] Patients with chronic pancreatitis are also thought to be at lower risk given the presence of gland atrophy and calcification.[12] Atrophy of pancreatic parenchyma may also be protective in older patients,[14] and post–pancreatic atrophy obstruction is thought to reduce the risk of PEP in patients with pancreatic head masses.[15]

Procedure-Related Risk Factors

Procedural factors that have been associated with PEP include difficult cannulation of the biliary orifice, biliary sphincterotomy, pancreatic sphincterotomy, precut sphincterotomy (ie, sphincterotomy to assist with biliary cannulation), balloon dilation of an intact sphincter, wire cannulation into the main pancreatic duct, contrast injection into the main pancreatic duct, placement of a self-expanding metal stent, and ampullectomy. Factors that have not been shown to increase the risk of PEP include endoscopic nasobiliary drainage, therapeutic ERCP, endoscopic biliary stenting, and biliary stone removal.

The volume of ERCPs performed by therapeutic endoscopists may also be protective, but data remain controversial. Logically, more experienced therapeutic endoscopists would have less difficulty with biliary orifice cannulation and other technical aspects of the procedure; however, it is also likely that higher-volume therapeutic endoscopists would be tasked with higher-risk cases. There remains a strong recommendation to refer high-risk patients or patients who require high-risk interventions to tertiary medical centers with high-volume therapeutic endoscopists. These centers are not only the most prepared to perform the desired procedure, but also the most prepared to appropriately manage any complications that may arise. Involvement of trainees in ERCP procedures is a possible risk factor for PEP, as trainees typically require more time to achieve cannulation and have a lower rate of success. Ensuring that trainees achieve a sufficient number of closely supervised procedures prior to independent practice is very important to protect patient safety.[14]

Procedure Techniques

Difficulties with cannulation of the common bile duct, placement of a wire into the pancreatic duct, and injection of contrast dye into the pancreatic duct all independently increase the risk of developing PEP. Difficult cannulation is defined as failure to successfully cannulate the biliary orifice using standard cannulation practices, which include contrast-assisted and guidewire-assisted techniques. In a multicenter, prospective, randomized study of selective bile duct cannulation performed by multiple endoscopists (the BIDMEN study), Kawakami and colleagues compared guidewire-assisted to non–guidewire-assisted attempts at cannulation. The authors reported a significant reduction in time to successful cannulation and in fluoroscopy time when using the guidewire-assisted technique.[16] Despite a slightly higher risk of injury to the pancreatic duct using guidewire assistance, this approach is recommended as the first procedure to use for cannulation.[4]

When the standard approaches to common bile duct cannulation are not successful, advanced maneuvers and alterations to the ERCP technique should be sought in a timely manner to avoid excessive trauma to the ampulla or missteps into the pancreatic duct. Generally, it is not advisable to continue with a guidewire-assisted approach after 2 to 3 unsuccessful attempts at cannulation with this technique. Several advanced techniques have been proposed to achieve efficient cannulation when guidewire-assisted cannulation fails, including a double-wire

technique,[17] wire cannulation alongside a pancreatic duct stent,[4] needle-knife precut sphincterotomy,[4] transpancreatic septotomy,[18] and fistulotomy.[4] These alterations in technique are typically used in the setting of difficult anatomy (eg, in the presence of malignant biliary obstructions). Although these approaches increase the rate of successful biliary cannulation, they often carry their own risks. Both the needle-knife precut sphincterotomy technique and the double-wire technique requiring wire cannulation of the pancreatic duct can increase the risk of PEP.[19] In light of this risk, and because these alternative methods are generally used in the setting of difficult anatomy, prophylactic pancreatic duct stent placement and rectal nonsteroidal anti-inflammatory drugs (NSAIDs) should be strongly considered in these cases. Overall, the risk of PEP is reduced by cannulating the common bile duct efficiently with minimal trauma and by minimizing the frequency and pressure of pancreatic duct injection and cannulation.

Prophylactic Pancreatic Duct Stent Placement

Evidence has been growing in recent years regarding the use of pancreatic duct stent placement to prevent the development of PEP. Pancreatic duct stent placement is thought to allow for reduction in pressure within the pancreatic duct. In 1998, a randomized, controlled trial of patients with SOD and high pancreatic sphincter pressures on manometry demonstrated that pancreatic duct stent placement after biliary sphincterotomy significantly reduced the rate of PEP.[20] A 2002 retrospective study of patients with SOD undergoing ERCP found a significant reduction in PEP with pancreatic duct stent placement and biliary sphincterotomy when compared with biliary sphincterotomy alone, independent of biliary manometry findings.[21] Since then, multiple randomized, controlled trials have consistently shown that pancreatic duct stent placement reduces the risk of PEP in a variety of settings. Two meta-analyses have shown that pancreatic duct stent placement helps to reduce the risk of pancreatitis and should be performed particularly in high-risk cases.[22,23] In addition to SOD, frequent indications for pancreatic duct stent placement during ERCP include pancreatic sphincterotomy, precut sphincterotomy, pancreatic duct wire cannulation, pancreatic duct contrast injection, ampullectomy, pancreatic duct intervention, and difficult cannulation.

Despite substantial evidence supporting prophylactic pancreatic duct stent placement, there are several limitations to consider. A reported increased risk of PEP exists in cases in which pancreatic duct stent placement is attempted but is unsuccessful.[24] Presumably, the attempt at pancreatic duct stent placement leads to additional trauma and inflammation of the pancreatic duct without the benefit of pancreatic duct pressure reduction by the stent. Additionally, injury to the pancreatic duct as a result of pancreatic duct stent placement is a major concern. Damage can lead to stenosis or even disruption of the pancreatic duct, precipitating cases of severe and relapsing pancreatitis.[25] Furthermore, although the majority of pancreatic duct stents will pass on their own within a few weeks of placement, there is a risk of prolonged retention of the stent. In some cases, stent retention can lead to chronic injury to the pancreatic duct and to pancreatitis. It is common practice to perform a radiograph within a few weeks of pancreatic duct stent placement in order to ensure that the stent passes.[26] To better avoid these challenges, endoscopists should be experienced and have a thorough understanding of the proper technique for pancreatic duct stent placement.

The choice of pancreatic duct stent size should also be carefully considered. Whereas larger-caliber stents tend to allow for more reliable pancreatic duct pressure reduction, smaller-caliber stents are less likely to damage the pancreatic duct during insertion. Data on optimal pancreatic duct stent size are limited. Reports have suggested that larger stents have a higher rate of successful placement than smaller stents (eg, 5-Fr stents vs 3- or 4-Fr stents),[27] but also a higher rate of pancreatic duct injury.[28] Softer stents have also been developed to limit damage from pancreatic duct stent placement.

Rectal Nonsteroidal Anti-Inflammatory Drugs as Pharmacoprevention

PEP is, in itself, a proinflammatory condition leading to numerous complications, including patient morbidity, pancreatic necrosis, and, in rare cases, death. The exact mechanism for PEP remains unclear, but is thought to develop from a proinflammatory cascade originating from pancreatic acinar cell injury that leads to systemic cytokine release. Phospholipase A2 is an established key modulator of the signaling cascade. NSAIDs are known potent phospholipase A2 inhibitors. Over the past decade, numerous clinical trials have investigated rectal NSAID use for the prevention of PEP. The underlying theory is that prophylactic anti-inflammatory agents can block or moderate the initial cascade that leads to clinical PEP.

In 2003, rectal diclofenac was investigated as a preventive agent for PEP.[29] Two hundred patients were randomized to receive either rectal diclofenac or placebo; the diclofenac group had a significantly reduced rate of PEP. A follow-up 2007 study investigated the use of rectal indomethacin for PEP prevention.[30] The 490-patient study revealed significantly reduced rates of PEP in the rectal

indomethacin group. In 2012, a landmark multicenter, double-blinded, randomized, controlled trial was performed investigating the efficacy of rectal indomethacin for PEP prevention.[31] The rectal indomethacin group had significantly lower rates of PEP as well as reduced rates of moderate to severe pancreatitis. One of the common criticisms of this trial is the characteristics of the study population; 82% of the patients were suspected of having SOD, a condition that is associated with an increased PEP risk compared to the general population. Because this study contained particularly high-risk patients, the results may not necessarily extrapolate to the general population.[31] A 2014 randomized, controlled trial studying high-risk patients with difficult biliary cannulation noted significantly reduced PEP rates compared to placebo.[32] In 2016, a randomized, controlled trial sought to investigate the role of rectal indomethacin for PEP prevention in the average-risk patient. Seventy percent of study participants were deemed to have average risk.[33] High-risk patients were characterized by pancreatic duct stent placement, SOD, history of PEP, difficult cannulation, pancreatography, biliary or pancreatic duct sphincterotomy, and/or trainee involvement. The results noted no significant differences in PEP rates between the placebo and the rectal indomethacin groups, suggesting that rectal indomethacin may not be necessary for PEP prevention in average-risk patients. Another 2016 randomized, controlled trial sought to investigate the timing of rectal indomethacin use for PEP prevention.[34] The study, performed in China, randomized 2600 patients to universal preprocedural rectal indomethacin administration vs a risk-stratified, postprocedural indomethacin administration for high-risk patients. Study results noted significantly reduced PEP rates in the universal preprocedural indomethacin group. Subanalysis noted significantly reduced PEP rates in the high-risk population of the preprocedural indomethacin group compared to the postprocedural indomethacin group. In average-risk patients, there were also significantly reduced rates of PEP in the indomethacin group. The study conclusions suggest preprocedural rectal indomethacin use for all patients undergoing ERCP when possible. A subsequent large retrospective study of 4017 patients revealed a reduction in PEP in both average- and high-risk patients.[35] A 2017 meta-analysis of all rectal NSAID, randomized, controlled trials noted reduced PEP rates in both average- and high-risk patients.[36] However, these studies are not entirely conclusive given the inherent limitations related to the select study methodology.

Ultimately, these authors suggest the use of rectal indomethacin unequivocally for all high-risk patients. For the average-risk patient, based on the current data, we defer rectal NSAID use to operator preference. Although it is not unreasonable to consider rectal indomethacin in these patients, we would not support unequivocal guidelines that advocate for the standard use of rectal NSAIDs in the average-risk patient.

Aggressive Lactated Ringer Solution as Pharmacoprevention

Aggressive intravenous fluid administration has been the mainstay of pancreatitis treatment for many years.[37] Lactated Ringer (LR) solution has been shown in a small randomized, controlled trial to be more effective than normal saline in the reduction of systemic inflammation in patients with acute pancreatitis.[38] It has been theorized that acidosis can perpetuate systemic inflammation seen in cases of pancreatitis; thus, the pH-neutral LR solution would be a more appropriate resuscitation fluid than normal saline, which can cause a hyperchloremic metabolic acidosis.[38] Because intravenous hydration is important in treating pancreatitis, aggressive administration of intravenous fluids during ERCPs may help to prevent or limit the severity of PEP. Several trials have demonstrated this result.[38-40] A randomized, controlled trial published in 2017 showed a reduction in rates of PEP as well as in hospital readmission at 1 month when both LR solution and rectal indomethacin were used compared to normal saline and placebo.[41] Regarding the optimal volume of LR solution that should be administered, some studies suggest an initial bolus of 10 to 20 mg/kg followed by 3 mg/kg/hr,[39,40] but more data are needed to further refine these recommendations. Although the ideal volume of LR solution to administer in these cases is unknown, in our opinion, it is better to give some than none at all. In our practice, we routinely administer a 1-L bolus of LR solution at the beginning of each ERCP procedure, and an additional 1 to 3 L of LR solution for high-risk cases, depending on the procedure length and patient weight.

Treatment of Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis

Even in optimal circumstances when every appropriate precaution has been taken, it is well known that PEP will still occur in some patients. The treatment of PEP does not vary significantly from the treatment of acute pancreatitis of other etiologies, with the exception that the timing and etiology of the inciting incident are known. Standard treatment of pancreatitis, including early aggressive intravenous hydration, symptom management, and early enteral nutrition, should be implemented. Clinical signs of severe complications of pancreatitis, such as infected pancreatic necrosis and cholangitis, should be closely monitored and managed appropriately.[42]

Table 2. Summary of Recommendations

• The risks and benefits of ERCPs should be weighed carefully on a case-by-case basis to assist with appropriate patient selection.
• A thorough understanding of patient- and procedure-related factors that increase the risk of PEP informs peri- and intraprocedural decision-making.
• Guidewire-assisted techniques are preferred over non–guidewire-assisted techniques in initial attempts at bile duct cannulation.
• If difficulty with cannulation is encountered, alternative cannulation techniques should be attempted.
• Rectal NSAIDs should be administered in all high-risk cases and considered in average-risk cases.
• Prophylactic pancreatic duct stent placement should be performed in all high-risk cases and considered in average-risk cases.
• Liberal administration of lactated Ringer solution should be administered, and higher volumes should be given in high-risk cases.

ERCP, endoscopic retrograde cholangiopancreatography; NSAID, nonsteroidal anti-inflammatory drug; PEP, post–endoscopic retrograde cholangiopancreatography pancreatitis.

Summary

Although PEP remains the most common complication of ERCP, leading to significant morbidity and rare mortality, there is much that can be done to prevent or limit the severity of PEP (Table 2). Appropriate patient selection, guided by an understanding of PEP risk factors, is exceedingly important. Once the procedure is underway, a guidewire-assisted cannulation technique is preferred, and alternative techniques should be sought when initial attempts are not imminently successful. Finally, rectal NSAIDs, prophylactic pancreatic duct stent placement, and liberal administration of LR solution should be considered in high-risk patients. These recommendations have already been shown to improve outcomes; however, additional research efforts are needed to further reduce the burden of PEP.

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