Best practices for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

Simcha Weissman, Mohamed Ahmed, Matthew R Baniqued, Dean Ehrlich, James H Tabibian

Abstract
Acute pancreatitis is one of the most common gastroenterology-related indications for hospital admissions worldwide. With the widespread reliance on endoscopic retrograde cholangiopancreatography (ERCP) for the management of pancreaticobiliary conditions, post-ERCP pancreatitis (PEP) has come to represent an important etiology of acute pancreatitis. Despite many studies aiming to better understand the pathogenesis and prevention of this iatrogenic disorder, findings have been heterogeneous, and considerable variation in clinical practice exists. Herein, we review the literature regarding PEP with the goal to raise awareness of this entity, discuss recent data, and present evidence-based best practices. We believe this manuscript will be useful for gastrointestinal endoscopists as well as other specialists involved in the management of patients with PEP.

Key Words: Post-endoscopic retrograde cholangiopancreatography pancreatitis; Endoscopic retrograde cholangiopancreatography; Pancreatitis; Practice guidelines; Pharmacology; Prevention

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PATHOGENESIS OF ACUTE PANCREATITIS

The pathogenesis of acute pancreatitis is centered around direct acinar cell injury with subsequent activation of proteolytic pancreatic enzymes. Inciting injuries include obstruction (e.g., from stone or tumor), alcohol and other toxins, and trauma, among others[9]. In PEP, activation of inflammatory pathways can occur for multiple reasons, which similarly include mechanical obstruction, direct trauma, or toxic injury[9,10]. When bile duct cannulation is difficult, prolonged papillary manipulation and repeat instrumentation can lead to mechanical injury and edema, impairing flow of pancreatic enzymes from the exocrine pancreas into the small intestine[8]. Electrocautery can also cause edema and similarly impair flow of pancreatic enzymes. Hydrostatic injury can occur secondary to intraductal water or contrast injection[8]. Contrast agents themselves can potentially cause chemical injury (even without significant changes in hydrostatic pressure); however, their role in this regard in the pathogenesis of PEP remains controversial and may depend on the chemical properties of the specific contrast agent[11]. The ensuing sequence of inflammation and recruitment of cytokines can manifest locally or go on to activate a systemic inflammatory response syndrome, resulting in higher severity of acute pancreatitis.

APPROACH TO DIAGNOSING PEP

The diagnosis of acute pancreatitis (of any etiology) can be made with at least two of the following three criteria: (1) Typical epigastric abdominal pain (often radiating to
Prophylactic measures that may help curtail PEP [18]. Several well-designed meta-analyses have found an association between early needle-knife precutting and lower rates of PEP, as compared to persistent attempts at cannulation [19,20]. A recent study showed that prophylactic pancreatic stenting following a double-guide wire technique reduces the rate of PEP, as double-guide wire technique alone was associated with higher PEP [21]. As such, international endoscopic societies recommend early needle-knife precut sphincterotomy (or papillotomy) and double-guide wire technique with prophylactic pancreatic duct stenting, especially in difficult biliary cannulation, to prevent ERCP-related AEs [2,18,22-29].
**Table 1** Mild, moderate, and severe acute pancreatitis as delineated by the revised Atlanta classification and the post-endoscopic retrograde cholangiopancreatography pancreatitis-specific Cotton criteria

| Revised Atlanta classification | Cotton criteria |
|-------------------------------|-----------------|
| Mild                          | Requires 2 out of 3: Epigastric abdominal pain; amylase/lipase > 3 × normal limit; abdominal image findings; no organ failure; no local or systemic complications |
| Moderate                      | Transient organ failure (resolves within 48 h). Local or systemic complications without persistent organ failure |
| Severe                        | Persistent organ failure (> 48 h). Single/multiple organ failure |

**Table 2** Reported patient-, procedure-, and operator-related risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis

| Risk factors for post-ERCP pancreatitis by category | Patient-related | Procedure-related | Operator-related |
|-----------------------------------------------------|-----------------|-------------------|-----------------|
| Sphincter of Oddi dysfunction                        | Age (young or old) | Pancreatic sphincterotomy | Endoscopist inexperience |
| Normal bilirubin                                     | Recent sphincter of Oddi manometry | Difficult biliary cannulation | Lower ERCP case volume |
| Female sex                                           | Papillary balloon dilation | Numerous pancreatic duct cannulations | Poor ancillary services |
| History of PEP                                       | Inadvertent/high-pressure pancreatography | Unfamiliarity with preventative methods |

PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

**INTRAVENOUS FLUIDS AS A PREVENTATIVE STRATEGY**

The use of IV fluids, in particular aggressive periprocedural IV hydration, has been recommended for the prevention of PEP[18,22]. Two meta-analyses found that the use of aggressive hydration with lactated Ringer’s Solution, 35-45 mL/kg administered over 8-10 h, decreased the incidence of PEP[30,31]. Another more recent study found similar results when comparing aggressive to standard IV hydration[32]. There is evidence that suggests lactated Ringer’s solution may be preferable as compared to normal saline[33,34]. Of note, aggressive hydration should be tempered in patients that are at risk of fluid overload (those with heart failure, anisarca, poor renal function, ascites etc.) and may be less impactful in those that have a prophylactic pancreatic duct stent placed[18].

**PHARMACOLOGICAL PREVENTION**

Numerous pharmacological approaches have been studied as a means to preventing (or decreasing the severity of) PEP. These include: NSAIDs, somatostatin, protease inhibitors, antibiotics, nitrates, heparin, and others. Prophylactic NSAIDs are perhaps the most studied pharmacological tool found to help prevent PEP[35-42]. Indeed, numerous meta-analyses have examined the effect of NSAIDs, and while the overwhelming majority found a significantly lower incidence of PEP — a few found a nonsignificant difference[35-42]. As such, it has been recommended to use 100 mg of diclofenac or indomethacin (per rectum) before ERCP in all patients who do not have a contraindication[18]. Of note, the use of NSAIDs in combination with other pharmacologic measures to prevent PEP is not recommended by the European society of gastrointestinal endoscopy[18]. However, recommendations from other societies do not support or deny the use of NSAIDs with other pharmacological measures[2,43]. Studies to better understand the role and optimal timing, route, and dose of NSAIDs in this regard are ongoing[44].
Somatostatin is a cyclic peptide that has an inhibitory effect on multiple systems of the body\cite{45}. There are a few studies that have shown that its use is associated with an overall reduction in the incidence of PEP; however, these studies may be biased by a small sample size and have had conflicting results with other studies\cite{18}. Additionally, octreotide, a somatostatin analogue, was shown to have no significant difference in PEP incidence when compared to a placebo, unless used at a dose higher than 0.5 mg\cite{46}. Thus, this somatostatin is not recommended for PEP prophylaxis.

Protease inhibitors can be used to inhibit the activation of proteolytic enzymes that are released from the pancreas and play a role on the pathogenesis of PEP\cite{47}. However, at this time the results of its usefulness in PEP prevention are inconclusive\cite{18}. Notably, a study from 2010 found that the main protease inhibitors, gabexate mesylate and ulinastatin, had no effect on PEP\cite{48}. As such, it is not recommended to administer protease inhibitors for PEP prophylaxis\cite{2,18,43}.

Nitrates can also be used as a form of prophylaxis, with sublingual administration being the best studied route\cite{49}. This most recent meta-analysis showed that the use of glyceryl trinitrate reduces the overall incidence of PEP, which was consistent with four previously published meta-analyses\cite{49-53}. It is currently recommended that sublingual glyceryl trinitrate be considered in patients with a contraindication to NSAIDs or to aggressive hydration for prevention of PEP\cite{18}.

Epinephrine has also been proposed as a method for PEP prevention. It is administered by spraying the papilla to reduce the edema and prevent PEP. However, there are conflicting results in two randomised controlled trials which compared epinephrine and saline\cite{54,55}. Topical administration of epinephrine onto the papilla for PEP prophylaxis is not recommended\cite{18}.

**BEST PRACTICE**

Best practice with respect to the prevention of PEP continues to progress as the literature evolves and new evidence becomes available. First, we suggest that prior to ERCP, clinicians should conduct a thorough assessment for possible risk factors for PEP. Second, rectal indomethacin (or diclofenac) should be considered for all patients undergoing ERCP. Third, IV fluids (lactated Ringer's solution or alternatively normal saline) should be given pre-, intra-, and post-procedure to those who do not have a contraindication to high-volume hydration, particularly in those with a contraindication to NSAIDs. Fourth, pancreatic duct stenting should be performed prophylactically in cases of difficult cannulation and when pancreatic duct access is readily achieved. Fifth, in patients without a prior sphincterotomy who are at high-risk for PEP, cannulation with needle-knife precut techniques (e.g., suprapapillary fistulotomy) should be progressed to early or considered as a primary approach so as to avoid trauma to the pancreatic duct orifice. Finally, pancreatic duct injections should be minimized (Figure 1).

**CONCLUSION**

Despite advances in collective knowledge of the mechanisms of and risk factors for PEP, it remains the most common major AE of ERCP and incompletely understood. Best practice with regards to prevention is through careful patient selection, sound endoscopic technique, and evidence-based prophylactic measures. Thoughtful attention to risk factors for PEP is vital in order to guide specific procedural and other preventative techniques and to optimize outcomes. Preventive measures include administration of (rectal) NSAIDs, aggressive IV hydration, various procedural techniques aimed at avoiding trauma to the papillary region, pancreatic duct stenting, and avoiding contrast injection into the pancreatic duct. The optimal choice and/or combination of these measures often requires individualized decision-making. Future high-quality studies are needed to better evaluate these and other approaches and thereby decrease the incidence and severity of PEP.
Figure 1 Flow chart illustrating the best-practice approach to post-endoscopic retrograde cholangiopancreatography pancreatitis prevention and management. Notably, in patients with complications of underlying advanced liver disease and/or comorbidities such as portal hypertension, coagulopathy, renal dysfunction, and volume overload, the selection of these prophylactic options should be made on a case-by-case basis and, when available, based on clinical evidence. ¹Younger age, female sex, normal bilirubin, recurrent pancreatitis, prior post endoscopic retrograde cholangiopancreatography pancreatitis, sphincter of Oddi dysfunction; ²Rectal indomethacin or diclofenac; ³Lactated Ringers preferred, 35-45 mL/kg administered over 8-10 h. PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; NSAID: Non-steroidal anti-inflammatory drug.

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