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## Best practices for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

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### 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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**Core Tip:** Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) represents an important etiology of acute pancreatitis and is the most common

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major adverse event post-ERCP. Nevertheless, gaps in knowledge remain, as do large variations in clinical practice. Best practices with respect to the prevention of PEP continue to evolve as new evidence becomes available. Herein, we review the literature regarding PEP to increase awareness of this entity, facilitate best practices in PEP prevention and subsequent management, and ultimately improve clinical outcomes.

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## INTRODUCTION

Acute pancreatitis is an acute, inflammatory disease of the pancreas, responsible for over 100000 hospital admissions annually in the United States[1,2]. It represents a major cause of morbidity and healthcare consumption in the United States and indeed worldwide[1-3]. There are numerous established etiologies of acute pancreatitis, among which gallstones and alcohol are generally the most common[4]. A number of other etiologies have been elucidated and better appreciated over the last several decades, including acute pancreatitis which arises as an adverse event (AE) following endoscopic retrograde cholangiopancreatography (ERCP), *i.e.* post-ERCP pancreatitis (PEP)[5]. PEP is the most common major AE of ERCP and has garnered significant interest from the biomedical community. However, its pathogenesis has yet to be fully understood, and its clinical management remains heterogeneous[1,6]. Identifying those at high-risk for PEP is critical to formulating an individualized prophylactic and therapeutic approach[6,7]. A multitude of pharmacological and endoscopic measures have been studied to mitigate the risk of PEP[7], include the use of rectal non-steroidal anti-inflammatory drugs (NSAIDs), aggressive intravenous (IV) hydration, and pancreatic duct stenting[8]; which of these is most effective or appropriate, however, remains a subject of ongoing study and debate. Herein, we review the current prophylactic and therapeutic measures for the prevention and management of PEP in attempt to provide evidence-based clinical guidance for best practices.

## 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

the back); (2) Serum pancreatic enzyme levels  $> 3 \times$  the upper limit of normal; and (3) Imaging findings consistent with acute pancreatitis (Table 1), as indicated by the revised Atlanta classification[8]. Although this criteria will accurately lead to the diagnosis of acute pancreatitis from other etiologies, these criteria are not always accurate in patients following ERCP. As a result of the biliary trauma caused by ERCP, many times these patients will meet two of these criteria but in reality lack acute pancreatitis. Nevertheless, the revised Atlanta criteria has been shown to more accurately predict PEP severity as compared to the consensus criteria[9]. The Cotton criteria used to diagnose PEP was developed in 1991 and has since been modified to specify whether the post-procedural abdominal pain is “new or worsened” (Table 1) [8]. Additional criteria to be classified as *mild* PEP includes an amylase level  $> 3 \times$  the upper limit of normal within 24 h post-procedure and any hospitalization of at least 2 d, while moderate disease requires 4-10 d. Severe PEP is characterized by: (1) Hospitalization for  $> 10$  d; (2) The development of a complication (*e.g.*, necrosis/abscess); or (3) The need for intervention (surgery)[8].

Of note, the diagnosis of PEP in the post-ERCP patient can sometimes be challenging, potentially leading to over- or under-diagnosis. In acute pancreatitis, epigastric pain is typically constant and radiates to the back; conversely, bowel distention and painful spasms occurring after ERCP are episodic and fleeting in nature, though the two may be difficult to distinguish. Elevations in serum pancreatic enzyme levels can occur post-ERCP in the absence of abdominal pain or imaging features of acute pancreatitis, rendering routine post-ERCP ordering of these tests of unclear (or no) clinical significance; however, marked elevations of serum amylase and/or lipase  $> 1000$  units/L at two hours after ERCP are highly predictive of PEP[8, 10-12]. The adoption of a uniform definition for the diagnosis of PEP will not only aid in its early diagnosis but also impact its subsequent treatment, though an individualized management approach would likely still be needed given the potential nuances of such procedures.

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## PREDICTORS OF PEP

Predicting which patients are at high risk for PEP is crucial. Several factors have been regarded as important predictors of a patient’s risk of developing PEP. These risk factors are additive and can be categorized as: (1) Patient-; (2) Procedure-; or (3) Operator-related[8]. Patient-related risk factors include age (younger and older), female sex, normal serum bilirubin, recurrent pancreatitis, prior PEP, or those with sphincter of Oddi dysfunction[13]. While controversy surrounds age as risk factor for PEP, data have illustrated that pancreatitis in the elderly population could present differently and even be associated with different outcomes[14,15]. Of note, patients with pancreas divisum may be at higher risk of acute pancreatitis which might influence clinical decision making with regard to the prophylactic measures taken to prevent PEP in this population[16]. Procedure-rated factors include difficult cannulations, pancreatic duct injection, sphincter of Oddi manometry, or precut sphincterotomy. Hospital and endoscopist procedure volume also seems to correlate with outcomes[17]. In fact, a database study involving nearly 200000 ERCPs performed in the inpatient setting found a significantly lower procedural failure rate and shorter length of stay in hospitals performing  $\geq 200$  ERCPs per year[4]. Additional factors such as pancreatotoxic drugs, biliary stents, or bile duct stones may influence the risk of PEP but their roles are not yet fully established (Table 2)[13].

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## ENDOSCOPIC TECHNIQUE AS A PREVENTATIVE STRATEGY

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-guidewire 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 | New or worsened abdominal pain and amylase > 3 × upper limit of normal within 24 h after the procedure and requiring hospital stay/extension by 2-3 d |
| Moderate                       | Transient organ failure (resolves within 48 h). Local or systemic complications without persistent organ failure  | All the above with requiring 4-10 d hospitalization   |
| Severe                         | Persistent organ failure (> 48 h). Single/multiple organ failure  | > 10 d hospitalization or requiring intervention. Development of a complication (pseudocyst, necrosis) or Need for surgical intervention              |

**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                       | Pancreatic sphincterotomy                 | Endoscopist inexperience                |
| Age (young or old)                                  | Recent sphincter of Oddi manometry        | Lower ERCP case volume                  |
| Normal bilirubin                                    | Difficult biliary cannulation             | Poor fluoroscopic imaging               |
| Female sex  | Papillary balloon dilation                | Aggressive attempts at cannulation      |
| History of PEP                                      | Numerous pancreatic duct cannulations     | Poor ancillary services                 |
| History of pancreatitis                             | 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, anasarca, 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 of 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[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[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[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[47]. However, at this time the results of its usefulness in PEP prevention are inconclusive [18]. Notably, a study from 2010 found that the main protease inhibitors, gabexate mesylate and ulinastatin, had no effect on PEP[48]. As such, it is not recommended to administer protease inhibitors for PEP prophylaxis[2,18,43].

Nitrates can also be used as a form of prophylaxis, with sublingual administration being the best studied route[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[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[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[54,55]. Topical administration of epinephrine onto the papilla for PEP prophylaxis is not recommended[18].

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## BEST PRACTICE

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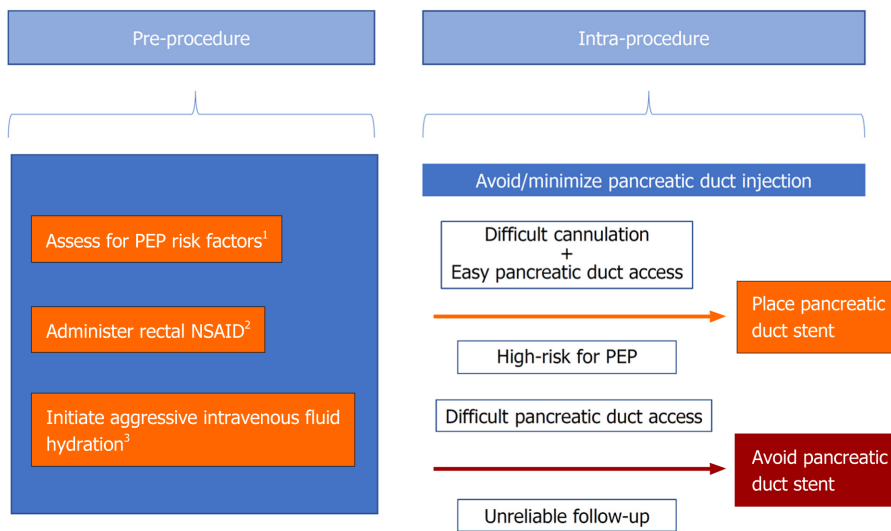
Best practice with respect to the prevention of PEP continues to progress as the literature evolves and new evidence becomes available. First, we suggest that prior to ERCP, clinicians should conduct a thorough assessment for possible risk factors for PEP. Second, rectal indomethacin (or diclofenac) 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).

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## CONCLUSION

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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. <sup>1</sup>Younger age, female sex, normal bilirubin, recurrent pancreatitis, prior post endoscopic retrograde cholangiopancreatography pancreatitis, sphincter of Oddi dysfunction; <sup>2</sup>Rectal indomethacin or diclofenac; <sup>3</sup>Lactated 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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