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Post-ERCP Pancreatitis: Mechanisms, Risk Factors, and Prevention

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Abstract

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), occurring in up to 30 to 40% of high risk patients. The most prominent theories of post-ERCP pancreatitis (PEP) pathogenesis include mechanical trauma to the papillary orifice, hydrostatic injury, and enzymatic injury from activated proteolytic enzymes introduced from the duodenum. Investigators have proposed a number of patient-related, procedure-related, and physician-related risk factors for PEP. However, when evaluated in large prospective trials, the role of these factors in increasing risk of PEP is inconsistent. Placement of a pancreatic duct stent and administration of rectal non-steroidal anti-inflammatory drugs (NSAIDs) are the two interventions with the greatest body of evidence supporting efficacy in PEP prevention.

Keywords: Acute pancreatitis; PEP; Anti-inflammatory drugs

Background and Epidemiology

Acute pancreatitis is the most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP) [1,2]. The incidence of acute pancreatitis after ERCP in large prospective studies published over the last two decades ranges from 1.6 to 15.1% [3-13]. Most cases of post-ERCP pancreatitis (PEP) tend to be mild to moderate in severity. Only 0.4% of patients undergoing ERCP develop severe acute pancreatitis, and mortality resulting from PEP is estimated to only be 0.11%. However, the risk of PEP may be as high as 30-40% in patients with certain risk factors. Furthermore, pancreatitis is the single most common reason for ERCP-related lawsuits, accounting for up to 50% of all ERCP-related litigation [14].

Definition and Grading

Studies estimating the incidence of PEP are confounded by the lack of consistency in the definition of PEP utilized by investigators. In a large cohort of patients undergoing ERCP, Testoni el al demonstrated that the incidence of PEP ranged from 5.1% to 11.7% depending on the pain duration and amylase level required to diagnose PEP [15].

In an attempt to standardize the definition of PEP, Cotton et al published consensus criteria in 1991 that were based on review of over 15,000 cases. These consensus criteria require four components to diagnose PEP: elevation in serum amylase concentration greater than three times upper normal level, pancreatic-type abdominal pain, duration of pain greater than 24 hours after ERCP, and pain severe enough to require hospitalization. The consensus definition also graded PEP as mild, moderate, and severe based on hospital length of stay, and procedure complications (Table 1).

While the criteria proposed by Cotton et al have been widely employed in the published literature, alternative criteria have also been utilized by researchers in the field. The Atlanta criteria, one of the more commonly used alternative consensus classifications, were published in 1992 and recently revised, and defined severe acute pancreatitis based on the presence of local or systemic complications and organ failure [16] (Table 2).

Mechanisms

Although the exact mechanism of PEP is not known, several hypotheses have been proposed. Leading explanations identify mechanical trauma to the papillary orifice, hydrostatic injury, and enzymatic injury from activated proteolytic enzymes introduced from the duodenum as potential precipitants for PEP.

The mechanical trauma theory proposes that injury to the papillary orifice may cause sphincter of Oddi spasm or edema of the pancreatic orifice, thereby leading to obstruction of pancreatic juice outflow, and promoting pancreatic injury and inflammation. Papillary injury can occur during ERCP by prolonged or repeated attempts at cannulating the pancreatic duct , multiple contrast injections into the pancreatic duct [17], or thermal injury from electrocautery current during sphincterotomy [18].

The theory of hydrostatic injury is based on the possibility that over-injection of the pancreatic duct disrupts pancreatic cellular membranes and tight junctions between cells. As a result, intra-ductal contents backflow into the interstitial space and cause pancreatic injury [19].

Chemical injury from ionic high-osmolarity contrast media was suspected as a cause of pancreatic injury, but a meta-analysis of controlled trials did not show a significant difference between different contrast media [20, 21]. Regardless of the instigating mechanism, the conventional theory for progression of pancreatic injury to pancreatitis

Mild	Moderate	Severe
- Elevation in serum amylase concentration more than three times upper normal level - At least 24 hours after the procedure - Requiring admission or prolongation of planned admission to two to three days	- Hospitalization of four to ten days	- Hospitalization for more than ten days, - Patients with hemorrhagic pancreatitis, - Patients with newly developed phlegmon or pseudocyst, or - Patients who require intervention such as percutaneous drainage or surgery

Table 1: Consensus Criteria Grading System for Acute Pancreatitis.

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Mild	Moderate	Severe
- Lacking both organ failure and local or systemic complications	- Transient organ failure (organ failure <2 days), - Local complications[1], and/or exacerbation of co-existent disease	- Presence of persistent organ failure (> or =2 days)

[1]Local complications include acute peripancreatic fluid collections, pseudocysts, acute pancreatic or peripancreatic necrotic collection, and walled-off necrosis.

Table 2: Revised Atlanta Severity Classification for Acute Pancreatitis.

Operator related factors	Patient-related factors	Procedure-related factors
Low case volume	Suspected SOD[1] Female gender Previous pancreatitis Younger age Female Gender	Pre-cut sphincterotomy Pancreatic duct injection SOD manometry Pancreatic sphincterotomy Minor papilla sphincterotomy Difficult cannulation Biliary balloon sphincteroplasty Ampullectomy

[1]Sphincter of oddi dysfunction.

Table 3: Consensus-based risk factors for post-ERCP pancreatitis.

dictates that premature activation of proteolytic enzymes leads to auto-digestion of pancreatic cells. The resulting decrease in acinar duct secretion decreases protective flushing activity of the pancreatic duct, thereby activating the inflammatory cascade, ultimately leading to pancreatitis.

Risk Factors

Careful evaluation of a patient's risk for developing PEP is an essential component of pre-ERCP evaluation for a number of reasons. Patients with one or more factors that increase the probability of developing PEP risk must be counseled about their heightened risk. Alternative tests such as endoscopic ultrasound or magnetic resonance cholangiopancreatography may be an option for high-risk patients, particularly if the goal of the procedure is diagnostic rather than therapeutic. Prophylactic strategies could be employed to reduce risk of pancreatitis in high-risk patients with a strong indication for therapeutic ERCP.

Although multiple investigators have assessed the factors predicting PEP in individual studies, the studies are limited by significant heterogeneity in design, variation in PEP definition used, and candidate predictor variables studied [3,4,7,13,22,23]. Prior reviews have proposed a number of consensus-based factors that increased the risk of PEP (Table 3) [24,25]. However, when examined in larger prospective clinical studies, the role of these consensus-based factors in increasing risk of PEP is inconsistent. For instance, large prospective studies published in the 1990's identified lower case volume as an independent risk-factor for post-ERCP pancreatitis [3, 4]. Two large prospective studies in the subsequent decade failed to confirm this association [7,26]. Similarly, studies have yielded conflicting data regarding the risk of PEP after pre-cut sphincterotomy, biliary and pancreatic sphincterotomy, and sphincter of Oddi manometry [3,4,7,9,22,23,27,28].

In considering the totality of published data on the issue, a meta-analysis of 15 prospective clinic trials identified the following patient-related and procedure-related factors as predictors of PEP risk: suspected sphincter of Oddi dysfunction, female gender, previous PEP, pre-cut sphincterotomy, and pancreatic duct injection [23].

The risk of pancreatitis may increase synergistically in patients with multiple risk factors. For instance, multivariate regression yielded a 27% risk for PEP among patients who underwent biliary sphincterotomy for suspected bile duct stones if they were younger than age 60 and no stones were found [29].

Protease inhibitors	• 6 meta-analyses that included RCTs • Initial meta-analysis suggested efficacy • No overall benefit in 5 updated meta-analyses
Octreotide	• Bai 2008: 15 RCTs, no benefit with octreotide • Zhang 2009: 18 RCTs, benefit if dose >0.5 mg • Omata 2010: 17 RCTs, benefit with octreotide
Glyceryl trinitrate	• Chen 2010: 9 RCTs, benefit with GNT

Table 4: Pharmacologic agents that have been evaluated in multiple randomized trials of post-ERCP pancreatitis prevention.

Prevention

To date, numerous endoscopic and pharmacologic interventions have been studied in an attempt to reduce the occurrence of PEP. Among these, placement of prophylactic pancreatic stents and non-steroidal anti-inflammatory agents are the two interventions with the most robust evidence supporting efficacy in PEP prevention. Other interventions have either shown no evidence of efficacy, demonstrated conflicting results, or have not been rigorously evaluated in multiple large randomized trials (Table 4) [30-47].

Prophylactic Pancreatic Duct Stents

The rationale behind pancreatic duct stenting for prophylaxis of PEP is based on the mechanical trauma theory, with prophylactic pancreatic duct stenting presuming to remove the effect of obstruction to pancreatic duct.

Meta-analyses of randomized and non-randomized trials have consistently demonstrated a reduction in the incidence of PEP with placement of prophylactic pancreatic stents [48,49]. In the most recent meta-analysis of 8 randomized clinical trials and 10 non-randomized trials, the absolute risk reduction in the incidence of PEP with prophylactic pancreatic duct stenting was 13.3%, which translates to a number needed to treat of 8 patients to prevent one episode of PEP [48-51]. However, pancreatic stent placement does carry risks, such as occlusion, migration, perforation, infection, duodenal erosions, and development of stent-induced pancreatic duct strictures [52,53]. If a prophylactic pancreatic duct stent does not pass spontaneously, repeat endoscopy may be required. Failed attempts at pancreatic duct stenting may increase risk of pancreatitis compared to no attempt at stenting the pancreatic duct [54]. As a result, controversy exists regarding the criteria for utilization of prophylactic pancreatic duct stenting.

Randomized trials have used varying indications for prophylactic pancreatic duct stenting, ranging from the stenting of all patients undergoing ERCP, to restricting stent placement to patients with select high risk criteria [48]. A cost-effectiveness analysis using a third-party payer perspective identified a strategy of reserving prophylactic pancreatic stenting for high risk patients to have the highest incremental cost-effectiveness ratio when compared to a strategy of placing prophylactic pancreatic stents in all patients undergoing ERCP, or not placing prophylactic stents at all [55]. In this setting as before, consensus is lacking regarding which patient's to consider at high risk for PEP. For instance, a survey of 54 advanced endoscopists revealed significant disagreements in indications for prophylactic stent placement. While all of the physicians surveyed indicated they would place a stent after ampullectomy or pancreatic sphincterotomy, 30-40% of endoscopists did not feel a pancreatic stent was necessary in patients with prior PEP or suspected sphincter of Oddi dysfunction, factors which had been identified as increasing risk for PEP [56].

A second area of controversy is the optimal stent diameter for prophylactic pancreatic stents, where the aim is to maximize PEP prevention whilst maintaining a high stent migration rate Stent diameters varied from 3 French to 7 French in randomized trials assessing the efficacy of pancreatic stents. Although 5 French stents may be easier to place than 3 French stents, the larger stents may have a lower spontaneous migration rate into the duodenum. On the other hand, the smaller 3 French stents are less likely to be visible on X-ray, and may pose an increased risk of migration into side branches. In a retrospective analysis, PEP rates were similar in patients who received 4 French or 5 French stents but spontaneous migration rate was significantly higher in the 4 French group [57]. More recently however, a randomized trial comparing 5 French to 3 French stents was terminated early for futility, since no difference was noted in the primary outcome of stent migration [58]. Three French stents do not appear to impart a large advantage in migration rate, and are significantly more difficult to place, limiting their suitability in the setting of prophylactic pancreatic stenting. The published data therefore appears to favor use of 4 French or 5 French calibers for prophylactic stenting.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The rationale behind use of NSAIDs in prevention of PEP stems from their ability to inhibit a number of pathways involved in the pathogenesis of acute pancreatitis, including phospholipase A2 activity, prostaglandin synthesis, and neutrophil-endothelial cell attachment [59]. Experimental data supporting their beneficial effects in acute pancreatitis along with their low cost and ease of administration have spurred a number of clinical trials evaluating their efficacy in prevention of PEP [60-65].

In the most recently published meta-analysis of 10 randomized controlled trials, administration of NSAIDs was associated with a 6% absolute risk reduction in incidence of PEP, which translates to a number needed to treat of 17 [66]. The studies varied significantly in terms of which NSAID was used as well as dose, route, timing of administration and indications for administration of NSAIDs. The largest multicenter randomized trial of 602 patients utilized rectal indomethacin at a dose of 100 mg administered immediately after ERCP in high risk patients [63]. Over 80% of patients in this study also received a prophylactic pancreatic stent. The major indication for ERCP was suspected sphincter of oddi dysfunction. In this study, rectal indomethacin was associated with a 7.7% absolute risk reduction in post-ERCP pancreatitis rates. In post hoc analyses, rectal indomethacin appeared to be more efficacious than prophylactic pancreatic stents, and cost-benefit analysis favored a strategy of indomethacin alone for post-ERCP pancreatitis prevention [62]. The post hoc results are best viewed as hypothesis generating, and further investigation is necessary before a strategy of rectal NSAIDs without pancreatic duct stenting can be recommended for post-ERCP pancreatitis prevention.

In summary, acute pancreatitis remains the most common major complication of ERCP. Use of alternative imaging modalities like magnetic resonance cholangiopancreatography should be utilized preferentially for diagnostic purposes when pancreaticobiliary therapy is not anticipated. Among patients undergoing ERCP, pancreatic stents and NSAIDs should be considered to reduce risk of post-procedure pancreatitis. Further investigation is necessary to define the optimal indications for prophylaxis and the ideal prophylactic strategy.

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