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Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Review Article

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Endoscopic retrograde cholangiopancreatography (ERCP) is a critical procedure for diagnosing and treating biliary and pancreatic diseases, but it carries the risk of post-ERCP pancreatitis (PEP), a major complication leading to significant morbidity and healthcare costs. PEP varies widely in severity, from mild discomfort to life-threatening conditions like pancreatic necrosis and multi-organ failure. The incidence of PEP is influenced by both patient-related factors (e.g., gender, history of pancreatitis) and procedural factors (e.g., cannulation difficulty). Preventive measures include careful patient selection, the use of non-steroidal anti-inflammatory drugs (NSAIDs), aggressive hydration, and pancreatic stenting. Despite these strategies, challenges remain in early diagnosis and management, emphasizing the need for vigilant post-procedural monitoring and tailored interventions. This review summarizes the epidemiology, pathophysiology, risk factors, and prevention strategies of PEP, highlighting the latest guidelines and research to optimize patient outcomes.
Keywords: ERCP, Post-ERCP Pancreatitis, Risk Factors, Prevention.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP), developed in 1968, is commonly used to diagnose and treat biliary and pancreatic diseases. The most prevalent major consequence of ERCP is pancreatitis (PEP), which causes significant morbidity and mortality and costs over 200 million yearly (Obeidat et al., 2022).

Therapeutic ERCP

ERCP is the major treatment for pancreatobiliary diseases, including stone clearing and biliary blockages. It also has the highest risk of complications and mortality among endoscopic procedures, with post-ERCP pancreatitis (PEP) being the most common after anaesthesia (Arain and Freeman, 2015).

PEP Clinical Presentation and Severity

PEP is usually minor, however some patients experience multi-organ failure, pancreatic necrosis, and death (Cahyadi et al., 2022). Abdominal discomfort, lipase or amylase levels above three times normal, and imaging abnormalities are needed to diagnose acute pancreatitis in Atlanta (Smeets et al., 2019). The PANCREA alliance classifies pancreatitis into four severity levels based on local and systemic consequences (Petrov et al., 2013).

Pathophysiology of PEP

PEP is caused by chemical, mechanical, hydrostatic, enzymatic, and microbiological stresses that cause inflammation and enzyme activation. Injection pressure and high-osmolarity contrast medium increase papilla trauma risk (Freeman et al., 2001; Zhang et al., 2022).

PEP risk factors

Both patient and procedural factors affect PEP risk. Female gender, younger age, pancreatitis history, and problematic cannulation are patient risk factors. Multiple pancreatic guidewire passes and extended cannulation are procedure risks (Sajni, 2022; Testoni et al., 2016). Temporary stenting prevents, especially in high-risk patients (Olsson et al., 2017).

PEP prevention

In high-risk instances, NSAIDs, hydration, and pancreatic stenting prevent PEP. ESGE recommends rectal administration of 100 mg diclofenac or indomethacin for all ERCP patients, with glyceryl trinitrate or somatostatin in high-risk instances when NSAIDs are contraindicated (Cotton and Elmunzer, 2020)

Aggressive hydration shows a protective effect against PEP, highlighting the need to address patient- and procedure-related risk factors (Table 1) (Radadiya et al., 2019; Wang et al., 2021).

Table 1: Excerpt of patient and ERCP-related risk factors for PEP

Patient-Related Factors	OR	Procedure-Related Factor	OR
- Previous history of PEP	3.2–8.7	- Difficult cannulation	1.7–15
- Non dilated common bile duct	3.8	- Multiple pancreatic duct Cannulation	2.1–2.7
- Female gender	1.4–2.2		
- Previous history of pancreatitis	2.0–2.90	- Pancreatic injection	1.6–2.7
- Suspicion of SOD	2.04–4.4	- Biliary balloon dilatation on an intact biliary sphincter	4.5
- Younger age	1.6–2.9		
- Black race	1.1*	- Failure to clear bile duct stones	4.5
- Obesity	1.1*	- Precut Papillotomy	2.1–3.1
- Congestive heart failure	1.3*	- Transpancreatic septotomy	1.2–3.1
- End stage renal disease	1.9*	- Intraductal ultrasound	2.4
- Cocaine use	1.5*		
- Alcohol use	1.1*		

Patient-Related Factors

Patient factors associated with higher risk of post-ERCP pancreatitis (PEP) include female gender, previous pancreatitis or PEP, suspected sphincter of Oddi dysfunction (SOD), younger age, a non-dilated common bile duct, normal bilirubin, and end-stage renal disease (Karyampudi et al., 2021).

Modifiable and Non-Modifiable Factors

Additional modifiable factors such as alcohol and cocaine use, as well as non-modifiable factors like race, obesity, and congestive heart failure, may also contribute to PEP risk (Mutneja et al., 2021).

High-Risk Classification

The ESGE classifies risk factors as “definite” or “likely.” An ERCP is considered high-risk for PEP if one definite risk factor or two likely risk factors (either patient- or procedure-related) are present (Table 2).

Table 2. Definite and likely procedure- and patient-related factors for post-ERCP pancreatitis (Dumonceau, et al. 2020) (PD: pancreatic duct. PEP: post-ERCP pancreatitis. SOD: Sphincter of Oddi Dysfunction).

	Patient-Related	Procedure-Related
Definite risk factors	-Suspicion of SOD -Previous PEP -Previous pancreatitis -Female sex -Younger age -Non-dilated biliary duct	- Difficult cannulation - >1 PD cannulation - Pancreatic injection - Failure to complete stone clearance -Biliary balloon dilatation of the native papilla
Likely risk factors	-Absence of chronic pancreatitis -Normal serum bilirubin -End stage renal disease	- Precut or pancreatic sphincterotomy - Intraductal ultrasound

Factors Related to Endoscopy

Endoscopist experience affects PEP and AEs. Due to difficulties including bile duct cannulation, less experienced endoscopists have higher PEP rates, according to Lee et al. (2020) with an OR of 1.63 (95% CI, 1.05–2.53). PEP risk increases with longer cannulation times and less expertise (Lee et al., 2021).

In a meta-analysis, Keswani et al. (2017) revealed high-volume endoscopists had 60% greater ERCP success and 30% fewer AEs, while PEP rates were identical. Annual procedure cutoffs ranged from 25 to 156 for "high volume".

Mixed results from trainee participation studies. Desai et al. (2019) found higher PEP and post-ERCP sepsis rates during the "July effect" (1.2% vs. 1.1%, $p = 0.004$; 9.4% vs. 8.8%, $p < 0.001$), while European and Chinese studies found similar AE rates with and without trainee involvement (Voiosu et al., 2020; Wang et al., 2022). Safety is ensured via supervised hands-on training until learners are autonomous (Siau et al., 2022).

Procedure-Associated Factors

Assessing papilla manipulation, a PEP risk, is crucial. Later studies indicated increased problematic cannulation and PEP rates for some forms of papilla, but multivariable models found no significant risk (Chen et al., 2020; Haraldsson et al., 2019). Zuber-Jerger et al. (2009) found that steady scope location and good papilla visualisation predict success more than

morphology (Figure 1).

The "5-5-1" guideline defines "difficult cannulation" by the ESGE: >5 min, >5 papilla contacts, or one unintentional pancreatic duct (PD) cannulation (Testoni et al., 2016). According to Lee et al. (2021), PEP rates increased with longer cannulation attempts: 3.9% for 3–5 minutes, 11.9% after 5 minutes, and up to 16% with both prolonged duration and PD cannulation. Training endoscopists using the "15-10-2" rule (15 minutes, 10 papilla contacts, and 2 PD cannulations) had similar results to those utilising the "5-5-1" rule (Wang et al., 2022).

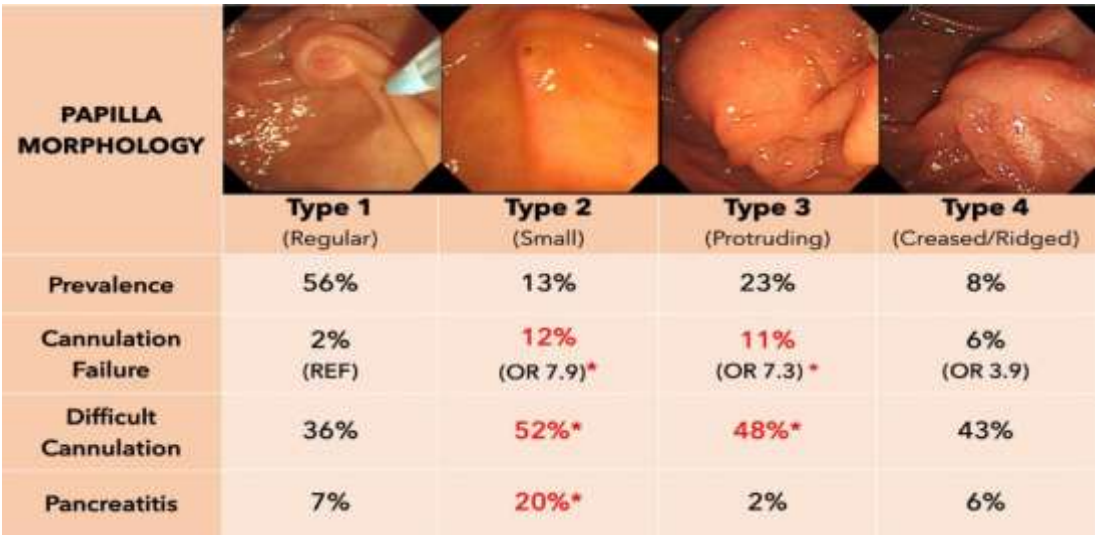

Figure 1. A proposed classification of the papilla morphology and the associated difficulty during bile duct cannulation. * Significantly higher risk vs. Type 1 papillae. (Haraldsson, et al. 2019)

PD Control and PEP Rates

PEP rates rise with PD modification, particularly in individuals with CBD <9 mm. Intervention rates vary: 4.6% without PD modification, 8.3% with contrast, 16.9% with guidewire, and 22.1% with both (Nakai et al., 2015).

PEP diagnosis criteria

Severe, persistent abdominal pain, typically radiating to the back, serum amylase or lipase levels at least three times the upper limit of normal (ULN), and imaging signs of acute pancreatitis are used to diagnose PEP in the Atlanta classification (Banks et al., 2013). Organ failure duration and local/systemic consequences determine severity.

Clinical Signs and Early Testing

PEP has epigastric discomfort and increased blood enzymes like other acute pancreatitis. ESGE recommends evaluating amylase or lipase levels 2–6 hours post-ERCP for symptomatic individuals. Below 1.5 and four times the ULN indicate safe discharge (Dumonceau et al., 2014). Early post-ERCP stomach discomfort makes PEP difficult to distinguish from

transitory pain (Tryliskyy and Bryce, 2018).

Diagnostic Markers and Serum Amylase Trends

Amylase levels above double the ULN at 3 hours suggest PEP, prompting re-evaluation at 6 hours. Lower levels indicate no PEP (Obeidat et al., 2022). In the first six hours, a randomised experiment suggests visual analogue scale pain evaluation for diagnosis (Park et al., 2018).

Alternative indicators for PEP include trypsinogen, C-reactive protein, and interleukins including IL-6 and IL-10, discovered in smaller studies (Koksal et al., 2016; Jin et al., 2013).

Define consensus and severity

Cotton defines PEP as fresh pancreatic-type discomfort with a threefold amylase rise within 24 hours of ERCP, requiring hospitalisation. CT or MRI may confirm PEP when ambiguous, but moderate instances may show normal imaging (Cotton et al., 1991). The 2020 ESGE update defines PEP as pain with increased enzymes (≥3x ULN) resulting in hospitalisation or protracted stays (Dumonceau et al., 2020).

Severity Classification

Mild PEP has no problems, moderate has transitory organ failure or local/systemic issues, and severe has sustained organ failure >48 hours. About 5% of PEP cases are severe (Kochar et al., 2015). The new Atlanta criteria add complications and 48-hour organ failure status to severity (Derrick et al., 2020).

The revised Atlanta classification appears to better predict the severity and mortality of PEP compared to the consensus criteria (Table 3) (Smeets, et al. 2019).

Table 3. Comparison of severity grade according to the consensus paper and the Revised Atlanta Classification

Severity	Consensus Paper	Revised Atlanta Classification
Mild	Hospital stay up to 2–3 days	_ No organ failure _ No systemic or local complication
Moderate	Hospital stay up to 4–10 days	_ Organ failure * that resolves within 48 h (transient organ failure) and/or _ Local or systemic complications without persistent organ failure
Severe	Hospitalization > 10 days or necrotizing pancreatitis or pseudocyst or intervention (percutaneous drainage or surgery)	_ Persistent organ failure * > 48 h - Single organ failure - Multiple organ failure

* Organ failure based on modified Marshall score defined as any of the following: PaO2/FiO2 < 300, systolic blood pressure < 90 mmHg despite fluid resuscitation, serum creatinine > 170 _mol/L (>1.9 mg/dL).(Wang, et al. 2014)

Prevention of Post-ERCP Pancreatitis (PEP)

1. Patient Selection

Preventing PEP requires careful patient selection. Avoiding needless ERCPs, referrals, and multidisciplinary review can assist endoscopists avoid high-risk or unsuitable patients (Siau et al., 2022). When available, EUS or MRCP confirm choledocholithiasis more safely (Khan et al., 2023). EUS discovered stones in 35% of patients with negative MRCP in Japan (Suzuki et

al., 2022). Stone removal can also be done laparoscopically during cholecystectomy using CBD exploration (Cahyadi et al., 2022). To decrease adverse events, surgically fit patients with resectable malignant strictures should have early surgery (Tol et al., 2016). PEP risk reduction requires anaesthesia review, pre-procedure planning, imaging evaluation, and procedural roadmap.

2. Medical PEP Prevention

A. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Rectal diclofenac and indomethacin greatly reduce PEP, with NNT values of 8–21 (Dumonceau et al., 2020). A meta-analysis of 17 RCTs indicated their bioavailability outperformed pancreatic duct stents, especially when given rectally (Patai et al., 2017). Pre-ERCP timing and dosage (100 mg) were helpful, whereas high-risk patients did not benefit from 200 mg (Fogel et al., 2020).

b. Intravenous Fluids

When NSAIDs are prohibited, IV fluids help. Two meta-analyses show that intensive hydration lowers PEP by 56% and hospital stays (Radadiya et al., 2019; Wu, 2021). According to ESGE standards, ERCP should begin with 3 mL/kg/hour, followed by a bolus and post-procedure hydration (Patel et al., 2022).

c. Other Agents

Topically applied GTN and somatostatin may reduce PEP. Somatostatin decreased PEP in high-risk patients by 4% against 7.5% in controls (Bai et al., 2015). With little effectiveness, glucocorticoids, protease inhibitors, and epinephrine have been investigated.

3. PEP Prevention Procedures

a. Approaches to Difficult Biliary Cannulation

Wire-guided cannulation avoids pancreatic duct contrast injection, lowering PEP risk. Cannulation method planning, stable placement, and pre-procedure imaging evaluation are crucial (Facciorusso et al., 2022). Early precut-papillotomy or needle-knife fistulotomy can minimise PEP in difficult cannulation but need advanced training (Tang et al., 2018).

b. Inadvertent Pancreatic Duct Cannulation

Early double-guidewire (DGW) or transpancreatic biliary septotomy (TPS) pancreatic guidewire-assisted procedures improve unintentional PD cannulation success. TPS had an 84.6% cannulation success rate against 69.7% for DGW (Kylänpää et al., 2021). Prophylaxis with a pancreatic stent after surgery benefits both techniques (Sugiyama et al., 2018).

c. Prophylactic Pancreatic Duct Stenting (PPS)

In high-risk PEP cases, PPS reduces severe PEP risks (RR = 0.39) and sequelae including necrotising pancreatitis (Dubravcsik et al., 2020). PPS hazards include stent migration and infections (Donnellan and Byrne, 2012).

Post-ERCP Pancreatitis Management

Identification Challenges

PEP can be difficult to distinguish from other causes of post-ERCP stomach discomfort and high amylase or lipase values, delaying treatment. PEP is treated with strong IV fluid hydration and pain management like other acute pancreatitis (Sahakian et al., 2014).

Fluid Therapy

Early, vigorous IV fluid resuscitation prevents SIRS and organ failure (de-Madaria et al., 2022). Wu et al. (2011) stated that lactated Ringer's solution, which is pH-balanced, may be better than regular saline because it reduces inflammation. However, lactated Ringer's vs normal saline is still contested (Zhou et al., 2021). An review of three RCTs and five retrospective investigations advised an infusion rate of 200–300 mL/h, totalling 4800–7200 mL on the first day, as rates higher or below 200 can be hazardous (Huber et al., 2020).

Monitoring and Severity Assessment

Mild PEP can cause life-threatening necrosis, therefore organ failure must be monitored. ICU treatment may be needed for severe PEP (Sahakian et al., 2014). The updated Atlanta classification classifies PEP severity by local consequences or chronic organ failure beyond 48 hours. High-risk patients must be identified early, even if categorisation is usually retroactive. The APACHE-II, Ranson, and Pancreatitis Outcome Prediction scoring systems can predict severe PEP (Tang Faghih et al., 2018).

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