Diagnosis of Post- Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Endoscopic retrograde cholangiopancreatography (ERCP) is the primary therapeutic approach for disorders affecting the pancreatobiliary tree. It carries the highest risk of complications and mortality among other endoscopic modalities, with post-ERCP pancreatitis (PEP) being the most frequent complication, even after a seemingly straightforward procedure. Its incidence lies between 2–10%, which could be as high as 30–50% in high-risk cases. PEP is severe in up to 5% of cases, with potential for life-threatening complications, and death in up to 1% of cases. The risk of PEP is potentially predictable and may be modified with pharmacological measures and endoscopic techniques, also patient selection plays an important role. The therapy for PEP is like that of acute pancreatitis. Analgesia and supportive care with moderate fluid therapy are often sufficient in most patients. In conclusion, PEP is a potentially life-threatening complication of ERCP which can be mitigated through a correct patient selection, combination of pharmacological and intraprocedural measures as well as prompt diagnosis and early management.

post-ERCP pancreatitis ERCP pancreatic stenting NSAIDS endoscopic transsphinteric septotomy PEP

1. Diagnosis of PEP

A consensus paper in 1991 defined post-ERCP (endoscopic retrograde cholangiopancreatography) pancreatitis (PEP) as “clinical evidence of pancreatitis” after ERCP associated with a three-fold increase of serum amylase at ≥24 h and necessitating hospital admission or prolonged hospital stay [1]. Thereafter, in 1996, Freeman added pain (i.e., new or worsening abdominal pain) as a further criterion to the PEP definition [2]. The 2020 ESGE guideline on ERCP-related adverse events defines PEP as a condition that is associated with new or worsened abdominal pain combined with elevated pancreatic enzymes (amylase or lipase ≥ 3 times upper limit of normal), thus prolonging a planned hospital admission or necessitating hospitalization after an ERCP [3].

In terms of diagnosing PEP, abdominal discomfort is common after ERCP; thus, clinical assessment, in combination with serum amylase and/or lipase, is essential to differentiate between transient post-procedural bloating; PEP; and other complications, e.g., perforation, cholangitis and unresolved biliary obstruction (such as from retained CBD stones). Early cross-sectional imaging can be helpful for diagnosis and to exclude a structural cause for PEP, e.g., retained stone, which may necessitate early repeat ERCP. The management of PEP (discussed below) is similar to that of acute pancreatitis. Endoscopists should be encouraged to clearly document

the difficulty level of ERCP, type of ampulla, number of attempts required to achieve selective biliary cannulation, biliary cannulation technique, use of air vs. carbon dioxide and time required to complete the procedure, because these factors are predictors of difficult ERCP and possible PEP.

PEP can be classified by severity. The consensus paper initially defined mild and moderate PEP solely on the duration of the hospitalization (i.e., hospital stay to 2–3 days or 4–10 days, respectively). Severe PEP was defined as hospitalization > 10 days or hemorrhagic pancreatitis or pseudocyst requiring intervention (percutaneous drainage or surgery). The revised Atlanta classification sees local complications, systemic complications and organ failure and its duration or the absence thereof at 48 h as factors to stratify the severity of acute pancreatitis [4]. Severe pancreatitis occurs in approximately 5% of PEP cases [5] and is defined by the presence of persistent (>48 h) organ failure, moderate as transient (≤48 h) organ failure or local or systemic complications and mild as the absence of complications [4]. The revised Atlanta classification appears to better predict the severity and mortality of PEP compared to the consensus criteria (**Table 1**) [6].

Table 1. 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 µmol/L (>1.9 mg/dL).

2. Pathophysiology of PEP

PEP is thought to result from an interplay of mechanical obstruction and/or hydrostatic injury, which causes early activation of pancreatic enzymes, leading to local and potentially systemic inflammation [7]. Obstruction can be caused by oedema or trauma to the papilla most often through over-manipulation. Thus, it is crucial to recognize this and to consider alternative cannulation techniques when standard attempts fail. Hydrostatic injuries can be

induced by pancreatic duct (PD) injection with the use of contrast agents or water, especially in the case of acinarization. Further causes for injuries include perforation of the pancreatic duct side branch with guidewire, use of electrocautery and possibly allergic reaction to the contrast agent [8].

3. Incidence and Mortality of PEP

Cotton and colleagues (1991) analyzing the complications of biliary sphincterotomy (EST) in over 11,400 ERCP reported a PEP rate of 2.1% and a mortality rate of 0.2% [1]. Freeman and colleagues (1996) analyzing over 2300 ERCP showed a PEP rate of 5.4% with a mortality rate of <0.1% [2]. A systematic review of RCTs in 2015 with almost 13,300 patients revealed a PEP rate of 9.7% and an overall mortality rate of 0.7% with an interestingly differing PEP and mortality rate according to geographic locations with 8.4% and 0.2% in Europe, 9.9% and 0% in Asia, and 13% and 0.1% in North America, respectively [5]. Another systematic survey of prospective studies with almost 17,000 patients reported a lower PEP incidence of 3.47% [9]. A large American retrospective study comprising over 1.2 million patients between 2011 and 2017 concluded that the mortality rate increased from 2.8% of PEP patients to 4.4% at the end of study period, despite the PEP rate being 4.5% and thus comparable to previous publications. In patients with Sphincter of Oddi dysfunction (SOD), the reported PEP rate was as high as 15% [10][11]. A recent Japanese RCT with 370 patients undergoing biliary stenting revealed that patients without biliary sphincterotomy conveyed a PEP rate of 20.6% compared to 3.9% in patients with prior sphincterotomy [12]

4. Risk Factors Associated with PEP

Because of the potentially severe but modifiable nature of PEP, it is important to recognize its risk factors, most of which can be patient-related or procedure-related (**Table 2**).

Table 2. Excerpt of patient and ERCP-related risk factors for PEP (adapted from Dumonceau 2020 and * Mutneja 2020). OR: Odds Ratio; PEP: post-ERCP pancreatitis; SOD: Sphincter of Oddi Dysfunction.

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	Pancreatic injection	1.6–2.7
Previous history of pancreatitis	2.0–2.90	Biliary balloon dilatation on an intact biliary sphincter	4.5
Suspicion of SOD	2.04–4.4	Failure to clear bile duct stones	4.5
Younger age	1.6–2.9	Precut Papillotomy	2.1–3.1
Black race	1.1 *	Pancreatic sphincterotomy	1.2–3.1
Obesity	1.1 *	Intraductal ultrasound	2.4

Patient-Related Factors	OR	Procedure-Related Factor	OR
Congestive heart failure	1.3 *		
End stage renal disease	1.9 *		
Cocaine use	1.5 *		
Alcohol use	1.1 *		

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