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# What Are the Predictors of Post-ERCP Pancreatitis, and How Useful Are They?

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## Summary

Acute pancreatitis is one of the major complications of ERCP. It is of paramount importance that we accurately identify which patients will go on to develop post-ERCP pancreatitis. As most ERCPs are performed on an outpatient basis, early evaluation can allow safe discharge of the majority of patients who will not develop post-ERCP pancreatitis or develop only mild symptoms that will be self-limited. Alternatively, early detection of those patients who will go on to develop moderate or severe post-ERCP pancreatitis can guide decisions regarding hospital admission and aggressive management and can help direct the use of targeted therapies that have the potential to prevent or mitigate pancreatic inflammation. Thus, significant efforts have focused on trying to identify predictors of post-ERCP pancreatitis. These parameters can be organized into three categories of tests: 1) pancreatic enzymes as markers of pancreatic injury: serum amylase/urine amylase; 2) markers of proteolytic activation: trypsinogen, trypsinogen activation peptide; 3) markers of systemic inflammation: C-reactive protein, various interleukins such as IL-6 and IL-10. A serum amylase level greater than 4-5 times the upper reference limit in conjunction with clinical symptoms has been shown to be an accurate and reliable predictor of post-ERCP pancreatitis. However, the exact timing and level of amylase elevation remains debatable. Urine testing of amylase and trypsinogen-2 in post-ERCP patients has also been shown to be highly sensitive and specific for detecting pancreatitis. The main advantage of these urinary markers is that they are available as rapid dipstick tests. Serum trypsinogen-2 levels have also been studied in post-ERCP pancreatitis patients; high levels seem to correlate with severity of disease. Among the markers of systemic inflammation, serum CRP is an accurate and readily available laboratory test for predicting severity of post-ERCP pancreatitis, but it appears to be helpful at 24-48 hours and, therefore, is not an early marker. Several other markers remain investigational and have not yet found wide clinical applicability.

## Introduction

Acute pancreatitis is a major and not uncommon complication of ERCP. According to a large, multicenter study reported by Freeman *et al.* [1], the incidence of post-ERCP pancreatitis (PEP) is 6.7%. Although most episodes of PEP are mild (about 90%), a small percentage of patients (about 10%) may develop severe pancreatitis resulting in a prolonged hospitalization, intensive unit care and utilization of major hospital resources; these patients have a significant morbidity and mortality [2].

It is of paramount importance that we accurately identify which patients will go on to develop PEP. As most ERCP is performed on an outpatient basis, early evaluation can allow safe discharge of the majority of patients who will not develop PEP or develop only mild symptoms that will be self-limited.

Alternatively, early detection of those patients who will go on to develop moderate or severe PEP can guide decisions regarding hospital admission and aggressive management. Additionally, early detection can help direct the use of targeted therapies that have the potential to prevent or mitigate pancreatic inflammation. Thus, significant efforts have focused on trying to identify predictors of post-ERCP pancreatitis that allow for earlier detection and also help in gauging severity.

Clinical assessment alone has been shown to be unreliable in predicting the development of pancreatitis [3]. In search for more objective criteria to accurately predict PEP, many studies have looked at pancreatic enzyme elevations alone or in conjunction with clinical assessment [3, 4, 5, 6]; a combined clinical and laboratory approach has been shown to be much more reliable than serologic testing alone.

The pathogenesis of PEP is still poorly understood, but inappropriate activation of proteases within the pancreas is thought to have a central role. Trypsin is a potent activator of pancreatic proenzymes, such as phospholipase A2, procarboxypeptidase, proelastase as well as proinflammatory cascade systems. The localized pancreatic inflammation and resultant tissue injury leads to a systemic inflammatory response [7]. Since trypsin is a principal instigator, variables that measure trypsinogen activation have been examined as predictors of pancreatic injury. Additional biochemical markers that have been proposed as predictors of PEP include acute phase reactants or markers of systemic inflammation, such as serum C-reactive protein (CRP), procalcitonin and various interleukins. These parameters can be organized into three categories of tests:

1. pancreatic enzymes as markers of pancreatic injury: serum amylase/urine amylase;
2. markers of proteolytic activation: trypsinogen, trypsinogen activation peptide;
3. markers of systemic inflammation: CRP, various interleukins.

## Category 1: Markers of Pancreatic Injury

*Serum Amylase*

Serum pancreatic enzymes rise in reaction to manipulations during ERCP in the majority of patients [8, 9, 10]. In the absence of pancreatitis, serum amylase levels peak at 90 minutes to 4 hours after ERCP and return to normal levels within 48 hours. Although serum amylase is commonly elevated in uncomplicated ERCPs, the swiftness and degree of elevation is much more marked in patients who develop PEP. Thus, studies were done to evaluate the effectiveness of serum amylase as a potential predictor of PEP.

Early work by LaFerla *et al.* [9] documented elevated serum amylase levels at 2 hours after ERCP. Of the 20 post-ERCP patients evaluated, only 7 went on to develop pancreatitis. In these 7 patients, serum amylase levels rose quickly and were significantly higher than in those patients who did not develop pancreatitis. Thus, they concluded that amylase elevations 2 hours post-ERCP could accurately predict those patients that were at risk of developing pancreatitis. Further studies supported these early findings [3, 11]. Gottlieb *et al.* [3] prospectively evaluated 231 patients in whom serum amylase and lipase determinations were made 2 hours after ERCP. Additionally, these patients underwent clinical evaluation specifically addressing the symptoms of abdominal pain, nausea and emesis. This study demonstrated that clinical assessment alone was unreliable in predicting PEP; one third of patients who developed pancreatitis had no pain 2 hours after the end of the procedure whereas one third of patients who did not develop pancreatitis did complain of pain. These authors also found that values of serum amylase and lipase below 276 IU/L and 1000 IU/L, respectively, were highly predictive in ruling out pancreatitis with negative predictive values of 0.97 and 0.98 respectively. Serum amylase values (2 hours post ERCP) more than 6 times the upper reference limit (URL) predicted a greater than 90% probability of developing pancreatitis.

In an effort to more thoroughly characterize post procedure amylase elevations, Testoni *et al.* [5] conducted a study in which they evaluated 409 patients who underwent endoscopic sphincterotomy and measured serum amylase levels before the procedure and at 2, 4, 8 and 24 hours afterwards. These investigators recommended using serum amylase levels greater than 5 times the URL as a cut-off so as not to miss cases of PEP. They found that sensitivity of serum amylase levels in predicting PEP was most accurate at 4 hours (68%) and 8 hours (100%), not at 2 hours (26%).

In a recent study from Australia, evaluating 263 patients who had undergone ERCP and/or endoscopic sphincterotomy, a 4-hour post ERCP amylase level was found to be a rapid and useful predictor of pancreatitis: Thomas and Sengupta [6] proposed an algorithm for patient management based on stratification by the 4-hour serum amylase level. If the amylase level is less than 1.5 times the URL (negative predictive value 100%), then the patient could be safely discharged home. If the amylase level is greater than 3.0 times the URL (positive predictive value 36.8%) then the patient should be admitted to the hospital. If the value falls between 1.5 and 3.0 times the URL, then clinical assessment, concerns or risk factors should govern decisions on management.

The aforementioned studies have advocated using serum amylase elevations at 2 or 4 hours post-ERCP but two recent studies have suggested that serum amylase levels greater than 4-5 times the URL at 24 hours may be more predictive. Additionally, they emphasized that the combination of pain at 24 hours in conjunction with elevated amylase levels is more effective in predicting the occurrence of pancreatitis [4, 12].

In conclusion, a post-ERCP serum amylase level has been suggested as a rapid and reliable predictor of pancreatitis. The ideal time and cut-off is still uncertain, but studies suggest that a 4-hour level that is greater than 4-5 times the URL is reliable. The above strategy proposed by Thomas and Sengupta is one that could be employed in the management of outpatient ERCPs [6].

*Urine Amylase*

In efforts to develop a reliable, inexpensive, and rapid test to predict pancreatitis, two studies evaluated a bedside urine amylase test called Rapignost™ [13, 14]. Once a test strip is placed in urine, the urine moves by capillary action across a colored-starch region. If amylase is present, it degrades the starch compound into soluble colored products that leave a purple discoloration on a white paper zone. The intensity of the purple color is proportional to the amylase content.

Initial studies evaluating the utility of Rapignost™ in predicting acute pancreatitis have suggested that it is reliable. Kampaainen *et al.* [13] looked at 500 patients who presented to the emergency department with abdominal pain and found that the Rapignost™ test was 79% sensitive and 89% specific for the diagnosis of acute pancreatitis. Hegewald *et al.* [14] focused mainly on patients with hyperamylasemia post ERCP. They found that Rapignost™ was highly specific at 0 hours and 16-24 hours (100%), but not as sensitive (78%) in predicting hyperamylasemia. At 4 hours, the sensitivity and specificity were lower: 50% and 95%, respectively. Out of 75 patients, only three developed PEP: although the urine test was positive in all three patients, the small numbers did not allow for statistically significant conclusions regarding this test's ability to predict PEP.

**Category 2: Markers of Proteolytic Activation**

Pancreatic acinar cells contain proenzymes (zymogens) including trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidases A and B and phospholipase A2. Trypsinogen is the main protease in pancreatic fluid: it can activate all of the other proenzymes, including itself. Conversion of trypsinogen to active trypsin

occurs by cleavage of a peptide called the trypsinogen activation peptide. There are two isoenzymes of trypsinogen: trypsinogen-1 and trypsinogen-2. Alpha-1-antitrypsin and alpha-2-macroglobulin are the two major trypsin inhibitors; these proteins inactivate trypsin by binding to it and subsequently eliminating it from the normal circulation. Acinar cell injury and local tissue damage from the activation of trypsinogen and the other zymogens is thought to be an essential event in the pathogenesis of acute pancreatitis.

*Trypsinogen Activation Peptide*

Trypsinogen Activation Peptide (TAP) is generated in the pancreas when trypsinogen is converted to its active form, trypsin. Plasma and urine levels of TAP have been found to be elevated and predictive of the development of acute pancreatitis [15]. However, this finding was not validated in other reports [16].

In a study looking specifically at post-ERCP patients, urinary TAP was not found to be useful in predicting mild PEP. Banks *et al.* [17] prospectively enrolled 107 consecutive patients in a study to evaluate the utility of urine TAP assay 4 hours post procedure. Ten of the 107 patients developed mild PEP; urinary TAP levels were not significantly increased.

*Trypsinogen-2*

In patients with acute pancreatitis, trypsinogen-2 has been found to be markedly elevated in the serum and urine [18]. Several studies have investigated rapid urinary tryspsinogen-2 test strips that utilize monoclonal antibodies and immunochromatography [13, 19, 20, 21]. These studies have shown high sensitivities and negative predictive values, suggesting that the urinary trypsinogen-2 test can exclude pancreatitis with high probability. Kemppainen *et al.* [22] examined the utility of the rapid urinary trypsinogen-2 test in the diagnosis of PEP 6 hours post-procedure. These investigators looked at 106 patients, 11 of whom went on to develop PEP. The urine dipstick test was positive in 9 of the 11 patients and the sensitivity and specificity were 81% and 90%, respectively. They concluded that a negative urine dipstick test 6 hours after the procedure was highly reliable for excluding PEP.

Trypsinogen-2 levels in the serum as well as bound trypsin 2-alpha-1-antitrypsin complex (trypsin 2-AAT) have also been investigated as potential markers [18, 23]. Kemppainen *et al.* [24] prospectively evaluated 308 patients who underwent ERCP, 31 of whom developed PEP. Blood samples for assay of trypsinogen-2, trypsin 2-AAT and amylase were collected at 1, 6, and 24 hours after ERCP in all patients. The investigators found elevated trypsinogen-2 levels as early as 1 hour after ERCP; this peaked at 6 hours in patients with pancreatitis. Additionally, the rise in level seemed to correlate with the severity of the pancreatitis. The trypsin 2-AAT complex, however, did not show a clear rise until 24 hours after ERCP. The sensitivity of a three-fold rise in trypsinogen 2 at 1 hour was 74% and the specificity was 87%. These numbers were comparable to the 2-hour amylase and lipase elevations reported in the study by Gottlieb *et al.* [3].

A drawback of using these markers is the lack of specificity, as many other conditions, including biliary and pancreatic malignancies, pseudocysts and cholangitis can cause elevations [19]. Despite this, an elevated serum trypsinogen-2 levels seen early in the course of PEP holds promise as a marker that can rapidly detect and reliably gauge the severity of PEP.

**Category 3: Markers of Systemic Inflammation**

Several studies have focused on markers that measure the degree of systemic inflammation as predictors of the development of PEP.

*C-Reactive Protein and Interleukins*

C-reactive protein (CRP) is an acute phase reactant synthesized by hepatocytes. It has

been shown to be elevated in patients with acute pancreatitis. Kiviniemi *et al.* [25] studied CRP response in uncomplicated and complicated ERCPs. They prospectively evaluated 42 patients and measured amylase, lipase, and CRP values before ERCP, and at 6 and 24 hours post-procedure. After about half of the uncomplicated ERCPs, serum amylase and lipase became elevated; however, no rise in CRP was seen. In the 3 patients who developed PEP, CRP levels were greatly elevated at 48 hours post procedure.

In another study, Kaw and Singh [26], measured CRP and interleukin-6 (IL-6) levels in 85 patients. Serum levels were measured before ERCP and at 12-24 hours and 36-48 hours after ERCP. In the 20 patients who developed PEP, serum levels of CRP and IL-6 correlated with severity of PEP. Thus, studies have shown that serum CRP is an accurate and readily available laboratory test for predicting severity of PEP, but it appears to be a late marker.

Oezcueruemez-Porsch *et al.* [27] evaluated a number of inflammatory markers and acute phase reactants, including procalcitonin, serum amyloid A, interleukin-1 receptor antagonist, solubilized tumor necrosis factor-alpha receptor II, interleukin-6, and interleukin-10 in 94 patients who underwent ERCP. Twelve patients developed PEP. The authors found that among all of the parameters that were evaluated, only peak IL-6 and IL-10 showed significant correlations with clinical data: i.e. pain score and duration of ERCP. They concluded that these two interleukins might prove useful for monitoring patients post-ERCP.

## Conclusions

Pancreatitis is a recognized complication of ERCP. While most cases of PEP are mild and self-limited, approximately 10% of patients develop severe pancreatitis. Identification of specific parameters that can rapidly and reliably predict the development of pancreatitis has been a major focus of research [28]. In addition to accurately predicting PEP, the ideal marker should also provide prognostic information regarding the severity of the pancreatitis. Many predictors of PEP have been described: serum amylase, urine amylase and trypsinogen-2 levels, trypsinogen activation peptide, trypsinogen-2-alpha-1-antitrypsin complex, and various acute phase reactants.

Although no single available test has been shown to be 100% reliable, several have been shown to have potential value. A serum amylase level greater than 4-5 times the URL in conjunction with clinical assessment has been shown to be an accurate and reliable predictor of PEP. However, the exact timing and level of elevation still remains debatable. Urine testing of amylase and trypsinogen-2 in post-ERCP patients has also been shown to be highly sensitive and specific for detecting pancreatitis. The main advantage of these urinary markers is that they are available as rapid dipstick tests. Serum trypsinogen-2 levels have been studied in PEP patients; high levels seem to correlate with severity of disease. Although this test appears to be a good predictive marker, it is not widely available. C-reactive protein is an inexpensive and readily available test that is commonly used in assessing severity of pancreatitis however, it is most helpful at 24-48 hours and thus is not an early marker. Serum interleukin levels seem to be indicative of the level of pancreatic injury and inflammation, but these markers are still considered investigational and do not yet have wide clinical applicability.

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**Key words** Acute Disease; Amylases; C-Reactive Protein; Cholangiopancreatography, Endoscopic Retrograde; Interleukins; Pancreatitis; Predictive Value of Tests; Sensitivity and Specificity; Trypsinogen

**Abbreviations** PEP: post-ERCP pancreatitis; trypsin 2-AAT: trypsin 2-alpha-1-antitrypsin; URL: upper reference limit

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