Post-ERCP pancreatitis: Pathophysiology, early identification and risk stratification

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Abstract

Acute pancreatitis is the most common and feared complication of endoscopic retrograde cholangiopancreatography (ERCP). The aim of the study was to review the current knowledge on the nomenclature, etiology, pathophysiology, clinical presentation, diagnostic workup, and risk stratification of post-ERCP pancreatitis (PEP). A structured search in PubMed and Scopus databases was performed using search terms related to the subject of diagnosis, pathophysiology, risk stratification of post-ERCP pancreatitis, including full text articles and abstracts in the English language. Several causes, operating both at a local and systemic level, might play an important role in the pathogenesis of PEP. Different patient-related risk factors can help predict post-ERCP pancreatitis; diagnosis depends on clinical presentation, imaging and laboratory investigations. As an outpatient procedure, post-ERCP pancreatitis may be safe in a selected group of low-risk patients. Further investigation of the etio-pathogenesis of post-ERCP pancreatitis is required in order to improve diagnosis and treatment. Early identification and severity stratification of post-ERCP pancreatitis greatly affects the patient's outcome. There is still controversy concerning the risk factors related to PEP. More studies are needed to clarify early and definite diagnosis, risk and severity stratification, as well as treatment of post-ERCP pancreatitis.

Key words: pancreatitis, ERCP, risk score, post-ERCP pancreatitis

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Introduction

Acute pancreatitis is the most common post-procedural complication following endoscopic retrograde cholangiopancreatography (ERCP). Its incidence is reported between 2.1% and 24.4%, with such variability being attributable to heterogeneous patient populations, differing levels of endoscopic expertise, procedural differences, disparate definitions of post-ERCP pancreatitis (PEP) and its severity.[1–13] Although, whilst the final pathogenic mechanisms of pancreatic damage are similar regardless of the causative factor, it has been suggested that non-ERCP-induced acute pancreatitis and PEP are different clinical entities with different outcomes in both mild and severe forms.[14] PEP prevail over acute pancreatitis developed under the influence of factors other than ERCP in rates of developing infected necrosis; the rate of postoperative pancreatic and enteric fistula is also higher in PEP compared to acute pancreatitis due to other causes than ERCP; patients suffering PEP constitute a younger cohort and have increased residual long-term morbidity compared to non-ERCP acute pancreatitis. On the other hand, the mortality rate is higher in cases of acute pancreatitis induced by non-ERCP related causes compared to PEP.[15] This review summarizes and critically appraises recent major published studies devoted to the issue of pathophysiology, early identification and risk stratification of PEP. This review was prepared as part of the 3rd year of the MSc in Surgical Sciences or Edinburgh Surgical Sciences Qualification.

The pathophysiology of PEP

The pathophysiology of PEP is not entirely clear with a multi-factorial concept being held. This involves a combination of chemical, thermal, mechanic, hydrostatic, enzymatic, allergic, and microbiological insults that result from papillary instrumentation and/or hydrostatic injury from the overfilling of the pancreatic duct with contrast material. The influence of these factors leads to a cascade of events resulting in premature intracellular activation of pancreatic proteolytic enzymes, autodigestion, and the release of inflammatory cytokines that produce both local and systemic effects.[2,12,17–19]

Among pathogenic factors of PEP, cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm and/or edema of the papilla. It creates an obstacle to the flow of pancreatic juice, and subsequently determines an acute pancreatic inflammation.[20]

Another important factor is the contrast media used with its osmolarity and ionic nature believed to be the major factors responsible.[21,22]

Injection pressure during contrast media injection into the pancreatic duct contributes to ductal epithelial or acinar injury. This injury is believed to happen from the disruption of cellular membranes or tight junctions between the cells and the backflow of the intraductal contents, especially into the interstitial space.[22] The role of intestinal enzymes refluxed into the pancreatic ductal system by ERCP maneuvers has been suggested as another possible trigger.[23]

It has also been suggested that bacteria may play a role in the induction of PEP, where bacterial-specific enzymes, toxins or activators of bacterial origin may initiate cytokine release from immune cells which will subsequently initiate pancreatic cell damage.[24,25]

Finally, genetic abnormalities should be noted as a risk factors as well. Homozygous alpha-1-anti trypsin deficiency causing increased rates of hemorrhagic PEP compared to the general cohort is a known example.[26]

Definition of post-ERCP pancreatitis

The consensus definition of PEP consists of the following criteria: serum amylase at least 3 times above the upper limit of normal 24 h post-procedure level accompanied by new abdominal pain consistent with pancreatitis and symptoms severe enough to require a hospital stay or to extend the length of stay of already hospitalized patients, and/or abdominal computer tomography scan (CT) consistent with the diagnosis of acute pancreatitis.[9] The classification has been widely accepted as it allows standardized reporting of the incidence and severity of PEP.

The severity of attack was graded by the proposed classification of mild, moderate and severe based on needed duration of hospital stay, presence of local or systemic complications, which may be also estimated using the revised Atlanta classification consensus.[27]

Various alternative diagnostic criteria for PEP were proposed since the first encounter with ERCP complications has happened. Testoni et al. concluded that the level of serum amylase measured 4 h after endoscopic sphincterotomy was a sufficiently reliable indicator of PEP, as more than two-thirds of the cases involving pancreatitis occurred among the patients whose 4-h amylase level was higher than 5 times the normal upper limit.[28]

The subsequent study conducted by Testoni et al. indicated that serum amylase levels at 24 h after the procedure appear to be more sensitive than those at 4 h.[10] Authors declared that pain at 24 h associated with amylase levels greater than 5 times the normal upper limit is the most reliable indicator of PEP.

Ito et al. has stressed the importance of a dynamic rise of serum amylase between 3 and 6 h post procedure in the diagnosis of PEP.[29] He suggested that when hyperamylasemia (higher than 2 times the normal upper limit) is observed at 3 h after ERCP, serum amylase concentration should be measured at 6 h after the procedure. A decrease in serum amylase level at 6 h after ERCP indicates the absence of PEP. Gottlieb et al. proposed ruling out the diagnosis of PEP

in accordance with 2-h serum amylase and lipase values.[30] Monitoring the intensity of patients' pain in the first 6 h after the ERCP procedure using visual analog scales (VAS) was also proposed as one of the early independent PEP's diagnosis criteria by a single center case control study.[31]

Both Cotton's and the revised Atlanta classification consensuses are agreed by the Revised European Society of Gastrointestinal Endoscopy Guidelines 2014 (ESGE) as PEP's definition statements and severity assessors, although notice is given that 2 definition statements poorly correlate with each other.[9,27,32]

With regards to post-procedural prediction of PEP, ESGE suggest testing serum amylase or lipase 2–6 h after ERCP in patients presenting with pain and those who are to be discharged on the day of ERCP. It is reported that patients with amylase or lipase values less than 1.5 and 4 times the upper normal limit, respectively, can be discharged without concern about the risk of PEP.[32]

Efforts have been made by other authors trying to identify alternative biochemical markers for PEP diagnosis. Among markers which were proven to be associated with PEP by a small observational series were: trypsinogen, trypsinogen activation peptide, C-reactive protein (CRP), serum elastase-1, erythrocyte sedimentation rate (ESR), chemerin, and various interleukins such as IL-6 and IL-10.[11,33–38]

Yet, the distinction between hyperamylasemia with transient abdominal discomfort (TAD) due to post-procedural intestinal distension and PEP remains difficult to establish during the first 24 h after the procedure.

Is ERCP an outpatient procedure?

There is a lack of randomized comparative trials to compare ERCP as an outpatient or inpatient procedure in terms of safety, efficacy, cost-effectiveness. ERCP as an outpatient procedure is widely utilized and relatively safe, but results in a significant number of readmissions due to complications. The main factor in favor of same-day discharge ERCP is that it is cost-effective as it avoids unnecessary hospital admissions. The main advantage of in-patient ERCP care is that it eliminates the risks related to ERCP complications, which may develop under unsupervised non-clinical setting and late readmission. A selective policy for early discharge and identification of those who possess a high risk of PEP, based on 2–6 h post-ERCP monitoring and assessment of risk factors, has been proposed to address the existing disadvantages of ERCP as an outpatient procedure.[39–41]

Risk stratification

Early and accurate post-procedural PEP diagnosis is aided by a pre-procedural risk stratification that would allow us to clearly establish low-risk, while identifying patients with a higher risk.

There is a lack of uniformity between different observational studies in defying risk factors for PEP. Where some risk factors have been widely accepted by the majority of observational studies, some factors continue to show conflicting evidence between different studies as to whether they are related to increased incidence of PEP. Among the recent studies, a retrospective cohort study by Cheng et al., which included a total of 1,115 patients, revealed a suspected dysfunction of the sphincter of Oddi (SOD), a history of post-ERCP pancreatitis and the age of 60 years and above to be risk factors of PEP.[8] A retrospective cohort study by Katsinelos et al., which included a total of 2,715 patients, revealed by both univariate and multivariate analysis that the history of acute pancreatitis is the only significant risk factor, thus denying the role of age and gender in the development of PEP.[42]

ESGE indicates SOD, female gender, younger age, and previous history of pancreatitis as risk factors for PEP, based on data from the meta-analysis, plus those from 7 prospective, multicenter studies that analyzed potential risk factors for PEP using multivariate analysis.[2,4–6,32,43–45]

A different age cutoff was used to investigate the correlation between age and the occurrence of PEP. The most common cutoff adopted is 60 years, with 70 years holding the 2nd place in the literature references.[5–8,45–47]

Risk factors for PEP were shown to be independent by a multivariate analysis and are reported to increase PEP's rate synergistically, hence they might have a cumulative effect. Freeman et al. calculated the adjusted odds ratio (OR) for various combinations of risk factors by using data prospectively collected from about 2,000 ERCPs: the highest risk of PEP (42%) was found in female patients with a normal serum bilirubin level, SOD, and difficult biliary cannulation.[2]

The list of recognized risk factors is not exhaustive, because not all potential risk factors have been analyzed. For example, the underlying presence of cirrhosis, primary sclerosing cholangitis (PSC), chronic (autoimmune) hepatitis, Crohn's disease, and obesity were found to be independent predictors of post-ERCP complications, including PEP on the basis of small prospective studies.[48–50]

Individual singularities of the anatomy of the pancreatic duct and second part of duodenum have been shown to affect the risks of PEP. Where SOD has been widely agreed as a risk factor, and the presence of a peripapillary diverticulum was reported to be a risk factor by a few observational studies, pancreas divisum has been found, in contrast, to be a protective factor.[51–54]

One study has shown the predictive quality of pre-ERCP blood urine nitrogen (BUN) and hematocrit (HCT) level as potential predictors of PEP.[55] Higher pre-procedure BUN and HCT level were found to be associated with a higher incidence of PEP.

Another case-control study enrolling 6,505 patients found that smoking, former drinking and diabetes are independent risk factors.[56]

Study by Freeman et al. showed that the presence of at least 1 of the independent risk factors (suspected sphincter of Oddi dysfunction, cirrhosis, difficult bile duct cannulation, precut sphincterotomy, or combined percutaneous endoscopic procedure) significantly increases the risk of overall complications, including PEP. This has lead to justifying overnight stays for post ERCP patients who exhibited one of the listed risk factors.[57]

Based on the retrospective case control study involving 1,372 ERCPs, where predictors of PEP were evaluated in a multivariable analysis, and supported by existed evidence of risk factors from the literature review, a prognostic model offering eligibility criteria for early discharge was proposed by Jeurnink et al.[47] The prognostic model based on patient- and procedure-related factors that are associated with PEP is reported to be able to identify patients who can be safely discharged within 6 h after ERCP.

Risk factors included are (precut) sphincterotomy, suspected SOD, younger age (<60 years), PSC, female gender, history of pancreatitis, pancreas divisum, and difficult cannulation (>10 min attempting to cannulate). Each of the included factors is worth 1 point and PSC is worth 2 points. The sum score for each of the risk factors allows us to allocate patients to the high-risk group (overall sum score >3) or a low to intermediate risk group (overall sum score ≤3). Based on that, a 6 h post procedure discharge plan can be executed.

Procedural risk factors and prophylaxis of PEP

Procedure-related risk factors are similarly important as patient-related factors in determining the incidence and severity of post-ERCP pancreatitis. However, technical factors, as well as those dependent on the surgeon, are controversial. The obvious fact is that a minimized number of cannulation and injections and a minimal amount of contrast medium cause less papillary trauma and are therefore important in preventing PEP. ESGE have defined definitive procedural risk factors: cannulation attempts whose duration exceeds 10 min, pancreatic guidewire passages more than 1 time, pancreatic injection. Those considered to be likely risk factors are: precut sphincterotomy, pancreatic sphincterotomy, biliary balloon sphincter dilation, failure to clear bile duct stones, intraductal ultrasound.[32] At the same time, it is agreed that temporary stenting with 5-Fr stent of the pancreatic duct is a protective measure which can reduce the risk of pancreatitis after ERCP in high-risk patients.[32,58,59]

Several agents have been tested experimentally and in clinical trials for potential efficacy in the prevention of PEP, including antibiotics, heparin, corticosteroids, nifedipine, octreotide and somatostatin derivatives, trinitrin, lidocaine spray, gabexate, secretin, topical epinephrine, and cytokine inhibitors. Among all these, sufficient evidence of the efficiency was reached only for nonsteroidal anti-inflammatory drugs (NSAIDs). ESGE recommend routine rectal administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication. Sublingually administered glyceryl trinitrate or 250 µg somatostatin given in bolus injection are considered optional in high-risk cases if NSAIDs are contraindicated.[32]

Recent observational studies have revealed a protective role of aggressive hydration in the development of PEP.[60–62] Large-scale randomized controlled trials to establish an evidence-based approach to intensive hydration are needed before the strategy is applied in clinical practice. Once the new strategy has emerged, it may backshift the trend towards the prioritization of inpatient management of ERCP patients.

Conclusions

The etiology of PEP is multi-factorial. The pathophysiology has not yet been studied entirely. Patient physiological characteristics and co-morbidities, procedural features, post-procedural factors are influential in the pathogenesis of PEP and may be used to determine the risk of its appearance. The prediction and early identification of PEP is challenging. Despite various diagnostic techniques and different attempts at establishing scoring models of early PEP recognition, they are all flawed and the task of improving risk stratification and early diagnosis is still relevant. Various diagnostic approaches and scoring systems have been devised that aim to stratify those at high risk of developing PEP. Recently, PEP's risk stratification and early identification strategies have been proposed as being based on grouping clinical and procedural factors and generating single integral diagnostic model. It is anticipated that next guidelines on the prognosis, diagnosis, prophylaxis, and management of PEP will include a complex prognostic model for early discharge post-ERCP, which will be able to distinguish event-free cases early and with the highest level of sensitivity and specificity.

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