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Prophecy about post-endoscopic retrograde cholangiopancreatography pancreatitis: From divination to science

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Abstract

One unresolved issue of endoscopic retrograde cholangiopancreatography (ERCP) is post-ERCP pancreatitis (PEP), which occurs in up to 40% of patients. Identification of risk factors for PEP is especially important in the field of ERCP practice because it may assist physicians in taking protective measures in situations with high risk. A decade ago, Freeman *et al* meticulously evaluated a large number of potentially relevant risk factors for PEP, which can be divided into patient-related and procedure-related issues. In this commentary, we summarize this classic article and reevaluate the risk factors for PEP from the current point of view. This is followed by assessment of strategies for prevention of PEP that can be divided into mechanical and pharmacologic methods.

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Key words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Risk factor; Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis; Pancreatic stents; Nonsteroidal antiinflammatory drugs

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COMMENTARY ON HOT TOPICS

One unresolved issue of endoscopic retrograde cholangiopancreatography (ERCP) is post-ERCP pancreatitis (PEP), which occurs after 1% to 40% of procedures[1-4]. This variable frequency of PEP is due to a number of factors, including the definition used, the patient population, the type of maneuvers, the type and duration of patient follow-up, and the personnel performing the ERCP[2,3,5]. Postulated mechanisms for pancreatitis after ERCP include mechanical, chemical, hydrostatic, enzymatic, microbiologic, and thermal disruptions[1,2]. A widely used consensus definition for PEP is: (1) new or worsened abdominal pain; (2) new or prolongation of hospitalization for at least 2 d; and (3) serum amylase three-fold or more above the upper limit of normal, measured more than 24 h after the procedure[6,7].

Prediction of PEP is of utmost importance in the field of ERCP practice. Although PEP is sometimes inevitable and can occur in the best of hands, identification of its risk factors may assist physicians in taking protective measures in situations with high a priori risk[8,9]. This article is intended as a commentary on the classic article "Risk factors for post-ERCP pancreatitis: a prospective, multicenter study" by Freeman *et al*[1] published in *Gastro-*

intestinal Endoscopy, a landmark study in the field of PEP, and it also provides strategies for the prevention of PEP.

In the classic article[1], comprehensive evaluation of the risk factors for PEP were performed by 26 endoscopists from 11 centers in the United States (6 private practices and 5 university-affiliated teaching hospitals), who collaborated in a painstaking prospective study of almost 2000 procedures[10]. The authors of the classic article meticulously determined eye-opening numbers (n = 32) of potentially relevant risk factors for PEP and provided vigilant analysis.

Risk factors for PEP

In the classic article[1], the authors classified risk factors into clearly demarcated patient-related and procedure-related factors. This allowed them to demonstrate that the risk of PEP is determined as much by patient characteristics as by endoscopic technique or maneuvers. Stratification of patients into low-risk or high-risk categories for PEP is important in order to ensure that gastroenterologists remove borderline indications of ERCP in high-risk patients and that adequate pre-procedure information is provided to the patient[5].

Patient-related risk factors: Of the 16 patient-related risk factors identified, in the classic article, 5 variables were statistically significant by multivariate analysis: history of PEP, suspected sphincter of Oddi dysfunction, female gender, normal serum bilirubin, and absence of chronic pancreatitis. Although a few other factors, such as young age and absence of common bile duct stones, were only significant in univariate analysis, subsequent multivariate studies by other groups or further meta-analysis showed that young age, non-dilated extrahepatic ducts, and absence of common bile duct stones are factors that may increase the risk for PEP (Table 1)[3,5,6,11,12]. A recent multivariate study, published in abstract form, suggested that obesity and hyperlipidemia were independent risk factors for PEP based on a nationwide database analysis[13]. Interestingly, some of the patient-related risk factors, such as normal serum bilirubin, non-dilated extrahepatic ducts, and absence of common bile duct stones, are poor indicators of ERCP. This may attest to the statement by Cotton[10,14] that "ERCP is most dangerous for those who need it least".

Procedure-related risk factors: Of the 16 procedure-related risk factors identified, in the classic article, 4 variables were significant by multivariate analysis: biliary balloon sphincter dilation, moderate-to-difficult cannulation, pancreatic sphincterotomy, and pancreatic contrast injections. Subsequent multivariate studies by other groups or further meta-analysis showed that precut sphincterotomy, ampullectomy, pancreatic brush cytology, failure to clear bile duct stones, and involvement of trainees are all factors that may increase the risk for PEP (Table 2)[3,5,6,11,12].

Although pancreatic stent placement was associated with risk of pancreatitis by univariate analysis, no independent contribution of pancreatic stent placement was evident in the multivariate analysis because pancreatic stents were primarily placed in patients with multiple other independent risk factors for PEP. Actually, pancreatic stent placement can reduce the risk of PEP in a number of settings, so that prophylactic pancreatic stent placement has become a standard of care for reducing PEP in high-risk cases[15-17].

The classic article also indicated the importance of the general similarity of the overall risk of pancreatitis for diagnostic and therapeutic ERCP and showed that the performance of biliary sphincterotomy did not appear to add significant independent risk of pancreatitis to ERCP[1]. The article emphasized that these observations point not to the safety of sphincterotomy, but rather to the risk of diagnostic ERCP[1]. Despite the general similarity of the overall risk of PEP for diagnostic and therapeutic ERCP, certain high risk procedures such as pancreatic sphincterotomy, pancreatic brush cytology, and ampullectomy may increase the risk for PEP. Therefore, we should pay attention to the type and complexity of maneuvers when comparing the incidence of PEP between studies.

Interactive effect of patient-related and procedure-related risk factors: The striking message of the classic article was that patient-related and procedure-related risk factors are cumulative and perhaps even synergistic[1,10]. Subsequent studies confirmed that patients with multiple factors had an extremely high chance (up to 40%) of developing PEP[5,17-20]. The typical very high risk patient is a young to middle-aged woman with recurrent abdominal pain, normal serum bilirubin, no biliary obstruction, and difficult cannulation. The combinations of patient-related and procedure-related risk factors allow reliable prediction of the possibility that an individual patient will develop PEP[17]. Furthermore, this cumulative effect may influence the severity as well as the incidence of PEP. According to the literature[1,21-23], nearly all patients who developed severe or fatal pancreatitis after ERCP had multiple risk factors. Gastroenterologists are now more able to predict PEP.

Field of vision after a decade from the classic article: Even from the current point of view, the classic article investigated most of the potentially relevant risk factors for PEP, dividing these into patient-related and procedure-related issues. Over the past decade, subsequent studies have usually confirmed or just slightly altered the significance of these risk factors. The confirmation of the risk of diagnostic ERCP has focused the role of ERCP into an exclusively therapeutic modality with the advent of other diagnostic modalities[22]. Confirmed risk factors for PEP have also enabled the conception of several strategies for the prevention of PEP in actual practice[3,5,17,22,24,25].

Strategy for prevention of PEP

The most important goal of recognizing the risk factors for PEP is the development of a strategy for prevention

Table 1 Comparison of patient-related risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis by multivariate analysis in the classic article and current knowledge by meta-analysis or multivariate studies

Risk factors in the classic article	Current knowledge[1]
Significant in multivariate analysis	High risk factors
Suspected sphincter of Oddi dysfunction	Suspected sphincter of Oddi dysfunction
Female gender	Female gender
History of post-ERCP pancreatitis	Previous pancreatitis
Normal serum bilirubin	Normal serum bilirubin
Absence of chronic pancreatitis	Young age
Significant only in univariate analysis	Possible risk factors
Pancreas divisum	Non-dilated extrahepatic ducts
Recurrent abdominal pain	Absence of chronic pancreatitis
History of acute pancreatitis of any etiology	Absence of definite common bile duct stone
Cholangiogram normal	Obesity[2]
Pancreatogram normal	
Age < 55 yr	
Prior cholecystectomy	
Absence of definite common bile duct stone	
Not significant	Not related
Previous sphincterotomy	Pancreas divisum
Distal common bile duct diameter ≤ 5 mm	Allergy to contrast media
Prior failed ERCP	Prior failed ERCP

[1]Current knowledge is based on recent guidelines by American Society for Gastrointestinal Endoscopy[6] and European Society of Gastrointestinal Endoscopy[5], and relevant articles[3,22]; [2]Based on recent multivariate analysis in abstract form[13]. ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Comparison of procedure-related risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis by multivariate analysis in the classic article and current knowledge by meta-analysis or multivariate studies

Risk factors in the classic article	Current knowledge[1]
Significant in multivariate analysis	High risk factors
Difficult cannulation	Difficult or failed cannulation
Balloon dilation of biliary sphincter	Balloon dilation of biliary sphincter
Pancreatic sphincterotomy	Pancreatic sphincterotomy
≥ 1 pancreatic contrast injections	Pancreatic duct injection
	Precut sphincterotomy
	Failed attempts at placing pancreatic duct stent
Significant only in univariate analysis	Possible risk factors
Sphincter of Oddi manometry	Ampullectomy
Pancreatic stent placement	Pancreatic acinarization
Minor papilla cannulation	Pancreatic brush cytology
Precut (access) papillotomy	Failure to clear bile duct stones
≥ 1 pancreatic deep wire pass/cannulation	Involvement of trainee during ERCP
Endoscopist performing > 2 ERCP/wk	
Not significant	Not related
Acinarization of pancreas	Sphincter of Oddi manometry (using aspirated catheter)
Biliary sphincterotomy	Biliary sphincterotomy
Intramural contrast injection	Intramural contrast injection
Pancreatic stricture dilation by any method	Prior failed ERCP
Pancreatic duct tissue sampling by any method	Therapeutic *vs* diagnostic
Training fellow involved	

[1]Current knowledge is based on recent guidelines by American Society for Gastrointestinal Endoscopy[6] and European Society of Gastrointestinal Endoscopy[5], and relevant articles[3,22]. ERCP: Endoscopic retrograde cholangiopancreatography.

of PEP. A practical strategy appears to be the combination of careful patient selection - which means avoiding inappropriate ERCP in high-risk patients - and selection of appropriate preventive measures (Table 3)[2,6].

Patient selection: Gastroenterologists should take much more care in the selection of patients for ERCP. The clinical role of ERCP has diminished substantially with the advance of relevant diagnostic and therapeutic modalities[6,9,26,27]. For diagnostic purposes, a plethora of relevant diagnostic procedures now are available, such as magnetic resonance cholangiopancreatography and endoscopic ultrasonography (EUS), which may obviate the need for ERCP or better focus its application[9]. For therapeutic purposes, minimally invasive surgeries now show considerable improvements in safety and outcomes[9]. Thus, balancing the benefit with risk is a prerequisite for determining the indication for ERCP. If the potential risk

Table 3 Clinical pearls to help avoid post-endoscopic retrograde cholangiopancreatography pancreatitis

Remember that ERCP is the most dangerous endoscopic procedure that can be associated with bad outcomes
Instead of diagnostic ERCP, use alternative imaging techniques such as magnetic resonance cholangiopancreatography or EUS, especially in high-risk patients
Rectal NSAIDs before or after ERCP procedure can be a simple measure to prevent PEP
Tailor a variety of cannulation techniques to the individual risk profile and the papillary anatomy of the patient
In cases of difficult cannulation, early precut or fistulotomy technique with a pancreatic stent (performed by an expert endoscopist) can decrease the risk of PEP
Quit the ERCP procedure earlier in high-risk patients if success is not achieved quickly. After a failed ERCP, alternative therapeutic methods such as percutaneous or EUS-guided approaches can be considered
In high risk patients, make sure that a prophylactic pancreatic stent is placed. In cases with equivocal risk at the end of the procedure, a prophylactic pancreatic stent can eliminate the fear of PEP

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; EUS: Endoscopic ultrasonography; NSAIDs: Non-steroidal anti-inflammatory drugs.

is much greater than the possible benefit, gastroenterologists should seek other diagnostic and/or therapeutic modalities or refer their high-risk patients to tertiary centers that have more experience and other tools.

Once a decision for ERCP is made, the gastroenterologist should reassess the risk profile of the patient and apply several mechanical and pharmacological interventions in order to reduce the likelihood of PEP[2]. In addition, an adequate consent process is very important to ensure that patients and their relatives understand that ERCP is potentially dangerous[14].

Mechanical prevention: Careful endoscopic techniques in cannulation and therapy are naturally important, but these are not sufficient to prevent PEP in high-risk patients[17]. Several modifications in endoscopic technique have been identified that can reduce the risk of PEP. (1) Prophylactic placement of pancreatic duct stents**:** The prophylactic placement of pancreatic duct stents improves the drainage of the manipulated pancreatic duct. Otherwise, this might be impaired by mechanical injury to the pancreatic sphincter from catheter and guidewire manipulation, and from thermal injury caused by biliary and pancreatic sphincterotomy[17]. The general consensus in the literature is that prophylactic pancreatic stents can reduce the risk of PEP in high-risk populations, such as those undergoing ampullectomy, pancreatic sphincterotomy, sphincter of Oddi manometry, precut sphincterotomy, pancreatic brush cytology, difficult cannulation, and pancreatic duct injection[3,8,17,28,29]. Recent meta-analyses of high-risk populations demonstrated that prophylactic pancreatic stents reduced the incidence of PEP from 18.6% to 5.6%[28,29]. An elegant cost-effectiveness analysis also suggested that prophylactic pancreatic stents in high-risk patients were a cost-effective strategy[30]. Actually, the routine use of pancreatic stents in high-risk cases has reduced the incidence and severity of PEP to a more acceptable level in advanced centers, allaying the fear of ERCP in high risk settings[17,31]; (2) Wire-guided cannulation: Compared with conventional use of contrast injection, wire-guided cannulation may avoid inadvertent injection of contrast into the pancreatic duct and decrease the risk of PEP[3,8]. Several meta-analyses have demonstrated a greater success of biliary cannulation and a lowered risk of PEP[21,32], but recent studies have shown that guidewire manipulation of the pancreatic duct for guidewire biliary cannulation is an another independent risk factor for PEP[33-35]. Prophylactic pancreatic stents might be recommended after pancreatic-guidewire assisted biliary cannulation to reduce the incidence of PEP[33]; and (3) Early precut biliary sphincterotomy and fistulotomy in cases of difficult cannulation: Although precut biliary sphincterotomy is an independent risk factor for PEP, prolonged cannulation attempts using standard techniques may also impart a higher risk for PEP than does the precut biliary sphincterotomy itself[5,36-39]. Early precut technique can be considered in cases of difficult biliary cannulation by advanced endoscopists with expertise in various cannulation techniques[5]. Fistulotomy is a variation of the precut needle-knife techniques that creates a direct bilio-enteric fistula by making an incision at the upper end of the ampullary region of the major papilla[40,41]. This technique has a potential advantage in that it evades the pancreatic orifice, which is the probable site of initiation of the cascade of PEP. Several studies have reported a lower incidence of PEP (up to 0%) in patients who underwent fistulotomy, with or without the prophylactic pancreatic stent[40-43]. Fistulotomy, however, may be more feasible in patients with bulging papillae and clear landmarks than in patients with tiny or diminutive papillae[40, 44]. For sparing the pancreatic orifice, reported investigational techniques include suprapapillary puncture with a needle-tip catheter, blunt dissection using a cotton swab, and EUS-guided suprapapillary puncture[39,45-47].

Pharmacologic prevention: Numerous trials have been attempted with many kinds of pharmacologic agents in order to reduce the risk of PEP. Pharmacologic agents, based on various theoretical benefits, have included nitroglycerin, ceftazidime, somatostatin, octreotide, gabexate, ulinastatin, nafamostat, antioxidants, allopurinol, glucocorticoid, non-steroidal anti-inflammatory drugs (NSAIDs), and *etc.*[5,24,48-52]. Early studies suggested that protease inhibitors such as gabexate or nafamostat may decrease the incidence of PEP[53,54]. At present, the dismally universal finding is that a strategy of pharmacologic prevention that proves effective in a few trials ultimately yields largely disappointing results over the long term

Table 4 Unresolved issues with prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

The ideal design of a prophylactic pancreatic stent
Cannulation technique to lower incidence of PEP, tailored to the shape of the major papilla
The ideal pharmacologic agent
Comparison of rectal NSAIDs *vs* pancreatic stent placement *vs* combination in high risk patients
The route (rectal or intravenous) and the timing (before or after ERCP) of NSAIDs administration

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post-ERCP pancreatitis; NSAIDs: Non-steroidal anti-inflammatory drugs.

when adopted in routine clinical practice[55,56]. Endoscopists in the ERCP field appear to believe that mechanical techniques such as pancreatic stents, much more than pharmacologic prophylaxis, play a key role in the prevention of PEP[55].

Despite a current climate of skepticism regarding the efficacy of any prophylactic medication for PEP, evidence for the efficacy of rectal NSAIDs in reducing PEP continues to accumulate[15,57-60]. Rectal NSAIDs are particularly attractive because of their low cost, easy administration, and known favorable risk profiles.[15] In addition to several meta-analyses[15,58,59], a recent well-designed randomized controlled trial beautifully showed the effect of rectal indomethacin in preventing PEP in 602 high risk patients (9.2% in the indomethacin group *vs* 16.9% in the placebo group, $P = 0.005$)[57]. However, only time will tell whether rectal NSAIDs can significantly reduce PEP.

Selection of preventive measures: According to the European Society of Gastrointestinal Endoscopy guidelines, periprocedural rectal administration of NSAIDs is recommended for low-risk ERCPs, whereas prophylactic pancreatic stent placement should be strongly considered for high-risk ERCPs[5]. However, the combined use of NSAIDs and prophylactic pancreatic stent placement might further reduce the rate of PEP in high-risk patients[61]. Therefore, rectal administration of NSAIDs for all ERCPs and prophylactic pancreatic stent placement for high-risk ERCPs might be more practical. A further practical strategy might be rectal administration of NSAIDs for patient-related high risk and prophylactic pancreatic stent placement for procedure-related high risk. However, the possibility remains that rectal NSAIDs may obviate the need for prophylactic pancreatic stent placement[61]. Studies to compare the effectiveness of rectal NSAIDs and pancreatic stent placement in high risk patients are warranted.

Future prospects for research

Although PEP has benefited from evolved understanding, there is still room for continuing research. In the future, the individual incidence of PEP should be accurately calculated according to the previously listed patient-related and procedure-related risk factors for PEP. In addition, the complexity of ERCP procedures[62,63] should be incorporated into the calculation of the individual incidence of PEP. Regarding the prevention of PEP, many issues still remain to be resolved (Table 4).

In conclusion, more than a decade has passed since the publication of the classic article that revealed the risk factors for PEP. Subsequent multivariate analyses have confirmed a number of risk factors for PEP that can be divided into patient-related and procedure-related issues. Prophylactic pancreatic stent placement has become a standard of care in high-risk patients and rectal NSAIDs have become a potential candidate as an ideal pharmacologic agent for preventing PEP. However, PEP is still the most frequent and most feared complication of ERCP. In the past decade, indications of ERCP have become more stringent owing to the development of other diagnostic and therapeutic modalities. To minimize PEP and maximize benefits[9], ERCP should be done for the best indications, while recognizing accurate risks to the individual and using meticulous endoscopic techniques with optimal preventive measures.

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