

Risk Factors for Post-ERCP Pancreatitis: A Prospective Multicenter Study

Chi-Liang Cheng, M.D.,¹ Stuart Sherman, M.D.,¹ James L. Watkins, M.D.,² Jeffrey Barnett, M.D.,³ Martin Freeman, M.D.,⁴ Joseph Geenen, M.D.,⁵ Michael Ryan, M.D.,⁶ Harrison Parker, M.D.,⁷ James T. Frakes, M.D.,⁸ Evan L. Fogel, M.D.,¹ William B. Silverman, M.D.,⁹ Kulwinder S. Dua, M.D.,¹⁰ Giuseppe Aliperti, M.D.,¹¹ Paul Yakshe, M.D.,¹² Michael Uzer, M.D.,¹³ Whitney Jones, M.D.,¹⁴ John Goff, M.D.,¹⁵ Laura Lazzell-Pannell, RN,¹ Abdullah Rashdan, M.D.,¹ M'hamed Temkit, MS,¹ and Glen A. Lehman, M.D.¹

¹Indiana University Medical Center, Indianapolis, Indiana; ²University of Wisconsin, Madison, Wisconsin;

³University of Michigan, Ann Arbor, Michigan; ⁴Hennepin County Medical Center, Minneapolis, Minnesota;

⁵GI Consultants Ltd., Milwaukee, Wisconsin; ⁶The Marshfield Clinic, Marshfield, Wisconsin; ⁷Milwaukee GI

Specialists, Milwaukee, Wisconsin; ⁸Rockford Gastroenterology Associates, Ltd., Rockford, Illinois; ⁹University

of Pittsburgh, Pittsburgh, Pennsylvania; ¹⁰Medical College of Wisconsin, Milwaukee, Wisconsin; ¹¹Washington

University, St. Louis, Missouri; ¹²University of Minnesota Hospital, Minneapolis, Minnesota; ¹³Rush

Presbyterian, Chicago, Illinois; ¹⁴University of Louisville, Louisville, Kentucky; ¹⁵Gastroenterology Associates,

P.C., Arvada, Colorado

OBJECTIVES: Pancreatitis is the most common and serious complication of diagnostic and therapeutic ERCP. The aim of this study is to examine the potential patient- and procedure-related risk factors for post-ERCP pancreatitis in a prospective multicenter study.

METHODS: A 160-variable database was prospectively collected by a defined protocol on patients undergoing diagnostic or therapeutic ERCP at 15 centers in the Midwest Pancreaticobiliary Group and participating in a randomized controlled study evaluating whether prophylactic corticosteroids will reduce the incidence of post-ERCP pancreatitis. Data were collected prior to the procedure, at the time of procedure, and 24–72 h after discharge. Post-ERCP pancreatitis was diagnosed and its severity graded according to consensus criteria.

RESULTS: Of the 1,115 patients enrolled, diagnostic ERCP with or without sphincter of Oddi manometry (SOM) was performed in 536 (48.1%) and therapeutic ERCP in 579 (51.9%). Suspected sphincter of Oddi dysfunction (SOD) was the indication for the ERCP in 378 patients (33.9%). Pancreatitis developed in 168 patients (15.1%) and was graded mild in 112 (10%), moderate in 45 (4%), and severe in 11 (1%). There was no difference in the incidence of pancreatitis or the frequency of investigated potential pancreatitis risk factors between the corticosteroid and placebo groups. By univariate analysis, the incidence of post-ERCP pancreatitis was significantly higher in 19 of 30 investigated variables. In the multivariate risk model, significant risk factors with adjusted odds ratios (OR) were: minor papilla sphincterotomy (OR: 3.8), suspected SOD (OR: 2.6), history of post-ERCP pancreatitis (OR: 2.0), age <60 yr (OR: 1.6), ≥ 2 contrast injections into the pancreatic duct (OR: 1.5), and trainee involvement (OR: 1.5). Female gender, history of recurrent idiopathic pancreatitis, pancreas divisum, SOM, difficult cannulation, and major papilla sphincterotomy (either biliary or pancreatic) were not multivariate risk factors for post-ERCP pancreatitis.

CONCLUSION: This study emphasizes the role of patient factors (age, SOD, prior history of post-ERCP pancreatitis) and technical factors (number of PD injections, minor papilla sphincterotomy, and operator experience) as the determining high-risk predictors for post-ERCP pancreatitis.

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INTRODUCTION

Pancreatitis is the most common and feared complication of ERCP, occurring in up to 30–40% of high-risk patients (1–3). It is associated with substantial morbidity and occasional mortality. There have been ongoing efforts to minimize

the incidence and severity of post-ERCP pancreatitis. Precise identification of risk factors for post-ERCP pancreatitis is essential to recognize high-risk cases in which ERCP should be avoided if possible, or in which protective endoscopic or pharmacologic interventions should be considered (2, 4). The mechanisms that lead to post-ERCP pancreatitis are not

fully understood but believed to be multifactorial (mechanical, chemical, hydrostatic, enzymatic, microbiologic, and thermal), and the triggering event is thought to cause premature intracellular activation of proteolytic enzymes within acinar cells resulting in cellular injury and autodigestion of pancreatic tissue (1, 5).

A number of specific risk factors, acting independently or in concert, have been proposed as predictors of post-ERCP pancreatitis. These include both patient- and procedure-related factors. However, the reported risk factors vary widely from study to study. These discrepancies may be attributable to heterogeneous patient populations, differing levels of endoscopic expertise, varying cannulation techniques, and disparate definition of post-ERCP pancreatitis. More important, the use of univariate analysis to identify risk factors for post-ERCP pancreatitis may produce misleading results because of inability to sort out confounding variables (6–10). Recent studies have used multivariate analysis as a tool to identify and quantify the effect of multiple potentially confounding risk factors (11–20).

The aim of this study was to use multivariate analysis and examine the independent risk factors for post-ERCP pancreatitis in a group of patients who were prospectively randomized to receive prophylactic corticosteroids or placebo in a double-blinded, multicenter, controlled clinical trial.

MATERIALS AND METHODS

Physicians from 15 participating endoscopic centers affiliated with the Midwest Pancreaticobiliary Group conducted a randomized, prospective, placebo-controlled study to evaluate whether prophylactic administration of corticosteroids reduces the risk and severity of post-ERCP pancreatitis. Data were prospectively collected to determine the patient- and procedure-related risk factors for post-ERCP pancreatitis. The research proposal was approved by the institutional review boards at all participating centers.

Patients

Patients were recruited serially as they presented for diagnostic or therapeutic ERCP. Patients were excluded from the study for any of the following reasons: (1) age less than 18 yr, (2) pregnancy, (3) mental disability, (4) incarceration, (5) active pancreatitis before procedure, (6) allergy to corticosteroids, (7) actual treatment with corticosteroids, (8) active tuberculosis, (9) uncontrolled diabetes, (10) contrast allergy, (11) known hepatitis B, (12) active bacteremia or septicemia, (13) planned biliary stent removal or exchange without planned pancreatogram, or (14) need for emergent ERCP within 12 h.

Study Protocol

After obtaining informed consent, enrolled patients were randomized to receive either prednisone, 40 mg by mouth, 15

h (± 3 h) and 3 h (± 1 h) before ERCP, or a placebo (similar pill without the active drug) given at similar time intervals. Randomization was accomplished in a blinded fashion by pharmacy staff. In sequence, concealed envelopes with active drug or placebo were dispensed. Baseline values for biochemical tests of liver function, amylase and lipase, and a complete blood count (CBC) were determined before the procedure. ERCP was performed by using the standard high-osmolality ionic-contrast agent diatrizoate meglumine (Hypaque, Winthrop Pharmaceuticals, New York, NY). A CBC and serum amylase and lipase levels were obtained at 2–4 h after the ERCP was completed. Patients were prospectively evaluated for the development of post-ERCP pancreatitis. Admission of an outpatient or prolongation of current hospitalization was at the discretion of the managing physician. Patients discharged on the day the ERCP was performed were contacted by telephone during the 24–72 h following the procedure to assess their clinical condition and evaluate for the development of postprocedure pancreatitis.

Definitions

Suspected sphincter of Oddi dysfunction (SOD) referred to the pre-ERCP suspicion of a functional or structural abnormality of the sphincter of Oddi, independent of any manometric findings, thought to be the cause of recurrent abdominal pain or pancreatitis. Cannulation difficulty was determined on the basis of the number of attempts on the papilla with a cannulation instrument (both common bile duct and pancreatic duct). Cannulation was judged easy when one to eight attempts took place and moderate/difficult when more than eight occurred. The number of pancreatic duct injections was the total number of times any volume of contrast was injected into the pancreatic duct. Acinarization was defined as any fluoroscopically observed focal or diffuse pancreatic parenchymal blush of contrast. Bile duct diameter was the measured maximal duct diameter within 2 cm of the papilla adjusted for radiographic magnification. Chronic pancreatitis was defined as the presence of mild, moderate, or severe pancreatographic abnormalities according to Cambridge criteria (21).

The definition of pancreatitis and the grading of its severity were based on consensus criteria (3). Post-ERCP pancreatitis was diagnosed when new-onset or increased abdominal pain lasted for more than 24 h, caused an unplanned admission of an outpatient for more than one night or prolonged a planned hospitalization of an inpatient, and was associated with an increase in serum amylase level of at least three times greater than the normal upper limit at approximately 18 h (the next morning) after the procedure. The severity of the pancreatitis was graded mild when hospitalization lasted 2–3 days, moderate when 4–10 days, and severe when hospitalization was prolonged for more than 10 days or any of the following occurred: hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or a need for percutaneous drainage or surgery.

Data Management

Demographic, procedure, and follow-up data were prospectively collected at the time of the procedure, before, and 24–72 h after discharge, and entered into a 160-variable database. The database was developed using specific software (Foxpro, Microsoft Corp., Seattle, WA) with screen entry and built-in edit checks to maintain the quality of the data. The clinical centers were asked to send copies of the data form to the coordinating center. The data were then entered by a nurse coordinator and checked by a second coordinator.

Statistical Analysis

The primary outcome analyzed was development of post-ERCP pancreatitis. Risk factors for pancreatitis were assessed using univariate analysis with χ^2 test for categorical variables and simple logistic regression for continuous variables. Variables with a *p* value less than 0.2 in the univariate analysis were all included in a forward stepwise multiple logistic regression model to identify the independent risk factors for pancreatitis. Goodness-of-fit for the final multivariate model was assessed by the 2-log likelihood criterion. Statistical analyses were performed using the statistical software package SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

A total of 1,115 patients (396 men, 719 women; mean age 51.2 [16.7] yr) were enrolled into the study (Table 1). Five hundred fifty-five patients were randomized to the prednisone group and 560 to the placebo group. The rates of post-ERCP pancreatitis in those patients receiving oral prednisone and those receiving placebo have been reported previously (22). Because the frequency of post-ERCP pancreatitis (16.6% receiving prednisone vs 13.6% in the placebo group, *p* = 0.19) and the risk factors for pancreatitis were similar for both groups, the data presented here will be combined treatment and placebo groups unless otherwise stated.

Three hundred and seventy-eight patients (33.9%) were evaluated for suspected SOD. A prior history of post-ERCP pancreatitis was noted in 81 patients (7.3%). Diagnostic ERCP with or without sphincter of Oddi manometry (SOM) was performed in 536 patients (48.1%), while 579 patients (51.9%) underwent therapeutic procedures. Endoscopic sphincterotomies were performed in 577 patients

(51.7%); sphincterotomies were biliary alone in 381 patients (34.2%), pancreatic alone (major and/or minor papilla) in 126 patients (11.3%), and dual pancreaticobiliary in 70 patients (6.3%). Manometry was performed in 395 patients (35.4%); SOM was biliary alone in 98 patients (8.8%), pancreatic alone in 47 (4.2%), and both biliary and pancreatic in 250 (22.4%). Precut sphincterotomy was performed in 103 patients (9.2%). Pancreas divisum was found in 123 patients (11.0%) and minor papilla sphincterotomy was performed in 50 (4.5%). Chronic pancreatitis was found in 192 patients (17.2%).

Post-ERCP pancreatitis occurred in 168 patients (15.1%). It was graded as mild in 112 patients (10%), moderate in 45 (4%), and severe in 11 (1%). Pancreatitis occurred after 63 (11.8%) of 536 ERCPs that were diagnostic alone and 105 (18.1%) of 579 procedures that were therapeutic.

Univariate Analysis

In the univariate analysis, 11 of 15 patient-related factors and 8 of 15 procedure-related factors were found to be statistically significantly associated with an increased risk of post-ERCP pancreatitis (Table 2). Technical factors that significantly influenced the risk of pancreatitis included: minor papilla sphincterotomy, major papilla pancreatic sphincterotomy, moderate/difficult cannulation, performance of SOM, pancreatic stent placement, minor papilla cannulation, and therapeutic ERCP procedure. Trainee involvement and ≥ 2 pancreatic duct injection with contrast were almost significant in the univariate analysis. Acinarization, precut sphincterotomy, biliary sphincterotomy, biliary orifice balloon dilation, and prior failed ERCP were not significant risk factors.

Significant patient-related risk factors by univariate analysis included: history of post-ERCP pancreatitis, pancreas divisum, suspected SOD, recurrent idiopathic pancreatitis, prior cholecystectomy, recurrent abdominal pain, age <60 yr, female sex, periampullary diverticulum, presence of common bile duct stone, and obstructive jaundice. Body mass index, distal bile duct diameter, absence of chronic pancreatitis, and prednisone premedication were not significant risk factors.

Multivariate Analysis

Only those risk factors that reached a *p* value cutoff 0.20 or less were used to create the multivariate model. Table 3 shows the results of the stepwise multiple logistic regression from the pool of 21 potential risk factors in the univariate analysis. Six risk factors were significant by multivariate analysis, three were characteristics of the patients (suspected SOD, younger age, prior history of post-ERCP pancreatitis), and three were procedure-related (≥ 2 pancreatic duct injections, minor papilla sphincterotomy, trainee involvement). There was no evidence of multicollinearity issues or lack of fit. The Hosmer-Lemeshow goodness of fit test was not significant at the 0.05 significance level and the C-statistic was 0.692 (which nears 0.70, the value of acceptable predictive power).

Of the 11 cases with severe post-ERCP pancreatitis, the risk factors are shown in Table 4. One patient had four

Table 1. Patient Characteristics

Number of patients	1115
% female	64.5%
Mean age	51.2
Number older than 60 yr old	362 (32.5%)
Mean BMI	26.8 kg/m ²
Prior pancreatitis	433 (38.8%)
Suspected SOD	378 (33.9%)
Chronic pancreatitis	192 (16.1%)

BMI = body mass index; SOD = sphincter of Oddi dysfunction.

Table 2. Univariate Analysis of Risk Factors for Post-ERCP Pancreatitis

Variables	Post-ERCP Pancreatitis Incidence (%)		<i>p</i> Value
	With Variable	Without Variable	
Patient-related variables			
Significant			
History of previous post-ERCP pancreatitis	23/81 (28.4)	145/1034 (14.0)	0.0005
Pancreas divisum	30/123 (24.4)	138/992 (13.9)	0.002
Suspected sphincter of Oddi dysfunction	92/378 (24.3)	76/737 (10.3)	<0.0001
Recurrent idiopathic pancreatitis	46/221 (20.8)	122/894 (13.6)	0.008
Prior cholecystectomy	64/327 (19.6)	104/788 (13.2)	0.007
Recurrent abdominal pain	120/656 (18.3)	48/459 (10.5)	0.0003
Age <60 yr	134/753 (17.8)	34/362 (9.4)	0.0002
Female sex	120/719 (16.7)	48/396 (12.0)	0.042
Periampullary diverticulum	10/119 (8.4)	158/994 (15.9)	0.03
Common bile duct stones	18/232 (7.8)	150/883 (17.0)	0.0005
Obstructive jaundice	10/145 (6.9)	158/970 (16.3)	0.003
Not significant			
Body mass index <30 kg/m ²	133/702 (18.9)	54/413 (13.1)	0.10
Prednisone premedication	92/555 (16.6)	76/560 (13.6)	0.19
Distal bile duct diameter <5 mm	47/302 (15.6)	99/688 (14.4)	0.63
Absence of chronic pancreatitis	137/923 (14.8)	31/192 (16.1)	0.28
Procedure-related variables			
Significant			
Minor papilla sphincterotomy	17/50 (34.0)	151/1065 (14.2)	0.0001
Major papilla pancreatic sphincterotomy	30/146 (20.6)	138/969 (14.2)	0.0485
Pancreatic sphincterotomy (major + minor)	47/196 (24.0)	121/919 (13.2)	0.002
Moderate/difficult cannulation	36/137 (26.3)	132/978 (13.5)	<0.0001
Sphincter of Oddi manometry	94/395 (23.8)	74/720 (10.3)	<0.0001
Pancreatic stent placement	49/218 (22.5)	119/897 (13.3)	0.0007
Minor papilla cannulation	31/146 (21.2)	137/969 (14.1)	0.03
Therapeutic ERCP procedure	105/579 (18.1)	63/536 (11.8)	0.003
Not significant			
Acinarization	11/59 (18.6)	157/1056 (14.9)	0.43
Precut sphincterotomy	19/103 (18.4)	149/1012 (14.7)	0.31
Biliary sphincterotomy	74/451 (16.4)	94/664 (14.1)	0.30
Trainee involvement	100/588 (17.0)	68/524 (13.0)	0.06
≥2 pancreatic duct injections	103/613 (16.8)	65/502 (13.0)	0.07
Prior failed ERCP	22/156 (14.1)	146/959 (15.2)	0.72
Biliary orifice balloon dilatation	3/23 (13.0)	165/1092 (15.1)	0.78

independent risk factors for pancreatitis, four patients had three, five patients had two, and one patient had one. Four of these patients had successful pancreatic stent placement. The average days of hospitalization were 18 days and one patient died from the post-ERCP pancreatitis.

Table 3. Significant Risk Factors for Post-ERCP Pancreatitis by Multivariate Analysis

Risk Factors	Odds Ratio	95% Confidence Interval	<i>p</i> Value
Minor papilla sphincterotomy	3.8	2.003–7.106	<0.0001
Suspected sphincter of Oddi dysfunction	2.6	1.828–3.717	<0.0001
History of post-ERCP pancreatitis	2.0	1.186–3.448	0.01
Age <60 yr	1.6	1.033–2.402	0.04
≥2 pancreatic duct injections	1.5	1.046–2.103	0.03
Trainee involvement	1.5	1.029–2.057	0.03

DISCUSSION

The primary aim of this multicenter, randomized controlled study was to evaluate the effect of corticosteroid on the incidence of post-ERCP pancreatitis. Unfortunately, this study and others found that prednisone did not reduce the incidence or severity of post-ERCP pancreatitis (22). Identification of patient- and procedure-related risk factors for post-ERCP pancreatitis was prospectively evaluated as a secondary goal of this study. This study suggests that the risk of pancreatitis

Table 4. Risk Factors of the 11 Cases with Severe Post-ERCP Pancreatitis

Risk Factors	No. (Percentage)
Age <60 yr	8 (73%)
Trainee involvement	8 (73%)
Suspected sphincter of Oddi dysfunction	7 (63%)
≥2 pancreatic duct injections	7 (63%)
Minor papilla sphincterotomy	1 (9%)
History of post-ERCP pancreatitis	1 (9%)

is determined as much by patient characteristics as by endoscopic techniques or maneuvers. The overall post-ERCP pancreatitis rate is 15.1%, which is higher than previous reports and perhaps can be explained by a higher proportion of patients with suspected SOD (33.9%) in our study population. In previous prospective large-scale risk factor studies, the reported pancreatitis rates ranged from 1.3% to 8.6%, and the proportion of SOD patients was usually less than 10% (11–18).

The results of our study are in agreement with prior prospective multivariate analysis studies with regard to suspected SOD (11, 12, 19), younger age (11, 16, 18, 19), history of post-ERCP pancreatitis (12–14), and pancreatic duct contrast injections (11, 12, 15, 18, 19) as independent predictors for post-ERCP pancreatitis. Minor papilla sphincterotomy was shown in the current study to be a significant risk factor by univariate and multivariate analysis, which was not evaluated in the previous reports. Freeman *et al.* evaluated pancreatic sphincterotomy and considered it as an independent risk factor for pancreatitis, but they did not separate out minor and major pancreatic sphincterotomy in that study (12). There are conflicting data for the effect of endoscopic experience as a significant risk factor for post-ERCP pancreatitis (11, 12, 17). Our results showed that trainee participation was a significant risk factor by multivariate analysis.

One recent meta-analysis assessing risk factors for post-ERCP pancreatitis revealed that suspected SOD, history of post-ERCP pancreatitis, female sex, precut sphincterotomy, and pancreatic contrast injections were independent predictors for this complication (23). In a review that selectively included full-length English language reports with multivariable analysis of the relationship between patient, procedure, or operator factors and post-ERCP pancreatitis found younger age, SOD, multiple pancreatic duct contrast injections, difficulty in cannulation, and precut sphincterotomy as significant risk factors in more than one study (24). The following factors were analyzed but were not found to be significant for pancreatitis in any study: cholangitis, coagulopathy, previous gastrectomy, history of jaundice, emergency procedure, intramural injection, SOM, biliary drainage, length of sphincterotomy, and bleeding during sphincterotomy.

The multivariate method has become the desired form of data analysis, particularly for quantifying the independent risk of an individual variable on the outcome. However, the multivariate method is limited by the structure of the mathematical model and the coding of variables (25). Moreover, adequate number of outcome events is needed to ensure accurate *p* values and risk estimate. Therefore, some variables may have minimal impact on the outcome despite achieving statistical significance, whereas other variables that fail to achieve the threshold of $p < 0.05$ may still have substantial effect on the outcome (25). Because of the complex nature of post-ERCP pancreatitis, there are numerous variables to adjust for, many of which are closely interrelated and often simultaneously present in the same case; it may be difficult to precisely define risk factors with high degree of certainty.

For example, a young female with suspected SOD, who undergoes ERCP and SOM with or without endoscopic sphincterotomy that could involve a difficult cannulation along with multiple pancreatic duct contrast injections is at high-risk for post-ERCP pancreatitis. But what is the relative contribution of each of these factors to pancreatitis may not be clear yet since this scenario is very common among high-risk cases for post-ERCP pancreatitis. It is also likely that other unknown factors, for instance, at the cellular level (*e.g.*, genetic susceptibility, hormonal or inflammatory mediators) may have a significant role in such individuals indicating further consideration.

Patients with suspected SOD carry a substantial risk for pancreatitis after any type of ERCP, whether diagnostic, manometric, or therapeutic (26). Our data show that a suspicion of SOD independently, nearly tripled the risk of post-ERCP pancreatitis to a frequency (24%) that is comparable with that found in other studies (9, 11, 12, 23). Contrary to the widely held opinion that SOM is the cause for such a high risk (27, 28), recent multivariate analyses show that empirical biliary sphincterotomy or even diagnostic ERCP in suspected SOD cases has similarly high risk, so that the manometry appears to have been erroneously blamed by association rather than being the cause (11, 12). Furthermore, the widespread use of aspiration catheters for pancreatic duct manometry is likely to have nearly eliminated any additional risk of manometry from other ERCP instrumentation (29).

Placement of a prophylactic pancreatic stent in SOD patients has been shown to reduce the risk of post-ERCP pancreatitis (30, 31). The reason for the high susceptibility to post-ERCP pancreatitis among patients with suspected SOD remains unclear.

Mehta *et al.* conducted a study evaluating predictors of post-ERCP complications in patients with suspected choledocholithiasis and found that absence of common bile duct stones was an independent risk factor for post-ERCP pancreatitis (19). In this study, a younger patient (age <59 yr) undergoing biliary sphincterotomy for suspected choledocholithiasis without a stone in the bile duct had a 27% risk of developing post-ERCP pancreatitis. Although the diagnosis of SOD was not considered in this study, the results clearly showed the danger of performing ERCP to look for bile duct stones in patients with recurrent postcholecystectomy pain (in the absence of objective evidence for stones) because there is generally a low probability of finding stones in such patients and a high risk of causing pancreatitis. Magnetic resonance cholangiopancreatography and endoscopic ultrasound can provide useful information in many of these cases and are becoming widely available. These techniques may be preferable to ERCP for patients with equivocal evidence of biliary obstruction, especially those at high risk for post-ERCP pancreatitis (12).

A history of previous post-ERCP pancreatitis was another clinical risk factor for post-ERCP pancreatitis, and our findings are consistent with several recent multivariate risk factor studies (12–14). Our analysis showed that the risk in such

patients was increased twofold (OR: 2.0). In the study by Freeman *et al.*, a history of previous post-ERCP pancreatitis was found to be the most potent risk factor (OR: 5.4) (12). Like other reports, a history of previous noniatrogenic pancreatitis is only a risk factor by univariate analysis, but not by multivariate analysis (11, 12, 14).

Younger age was significant risk factor for pancreatitis in our study and four other reports using multivariable analysis (11, 16, 18, 19). However, a different age cutoff was used in these studies with 60 yr in 3 and 70 yr in two studies, respectively. The progressive decline in pancreatic exocrine function with aging may protect older patients from pancreatic injury (32). Similarly, chronic pancreatitis was found to provide some protection against ERCP-induced pancreatitis, perhaps explained by atrophy and decreased enzymatic activity (12). However, absence of chronic pancreatitis was not a significant factor in the present study.

The finding of pancreatic contrast injections as an independent risk factor for post-ERCP pancreatitis is consistent with previous reports (11, 12, 14, 15, 18, 19). However, somewhat different from other studies, our results showed that pancreatic contrast injections was barely significant (OR: 1.5), and a difficult cannulation was not significant. A possible explanation for these findings is that, unlike other similar studies, prophylactic pancreatic stents were frequently used in our patient group (about 20% of all ERCP) to reduce post-ERCP pancreatitis. There have been several prospective studies showing that successful pancreatic stent placement might mitigate the risk of post-ERCP pancreatitis (30, 31, 33). The higher post-ERCP pancreatitis rates in this series (by univariate analysis) in patients undergoing prophylactic pancreatic duct stenting is almost certainly related to the fact that the stents were placed in high-risk cases. Thus, the frequent use of prophylactic pancreatic stents may somewhat modify the apparent risk factors found in this study compared to traditional studies.

The mechanism of how contrast injection induces pancreatic ductal and acinar cell injury is not clear. Current evidence does not support the notion that nonionic contrast is more effective than conventional ionic contrast in preventing post-ERCP pancreatitis (1). The widely held concept is that hydrostatic injury from overfilling of the pancreatic duct with contrast material is a major cause of pancreatitis. Previous studies have demonstrated a ducto-interstitial-venous pathway, and if enough radiographic contrast is injected into the pancreatic duct, the collecting system of the kidney can be seen during ERCP (34). Roszler *et al.* reported an inadvertent urogram during ERCP was followed by pancreatitis in 45% of patients (35). The pathophysiologic basis for these observations is related to the occurrence of ductal epithelial or acinar injury, with resultant backflow of intraductal contents into the interstitial space and venous circulation. However, acinarization of the pancreas is probably less important than has been previously believed. Most studies showed acinarization of the pancreas was significant by univariate analysis only (11, 16, 18). Like other recent studies, acinarization was

not a significant risk factor by univariate analysis in our series (12, 14).

Difficult cannulation has been shown to be an independent risk factor for pancreatitis and may occur without any apparent pancreatic duct instrumentation (11–14). This suggests that trauma to the papilla and pancreatic sphincter with impaired pancreatic drainage may be important in the pathogenesis of pancreatitis. Although there is an association with the number of times the papilla was manipulated, the cutoff numbers vary widely, with six attempts in two studies (11, 12) and 20 attempts in one study (13). In the current study, however, moderate to difficult cannulation (>8 attempts) was only significant in the univariate analysis and this was possibly due to frequent placement of pancreatic stents mitigating this risk factor as described above. The difficulty of cannulation is not easily quantifiable and interactions with time for cannulation, method of cannulating, and number of pancreatic duct injections may occur. Balloon dilation of the biliary sphincter to extract bile duct stone was an independent factor for pancreatitis in a large multicenter study with a fourfold increase in risk (12). Likewise, trauma to the pancreatic sphincter is suspected to be the cause of pancreatitis. In our report, however, biliary orifice balloon dilatation was not found to be a risk factor for post-ERCP pancreatitis. This may be due to the infrequent performance of biliary orifice dilation in this study.

Thermal injury of the papilla is exclusive to endoscopic sphincterotomy. Edema produced by electrocautery is a well-recognized consequence (36). It is hypothesized that swelling around the pancreatic orifice may hinder the flow of pancreatic juice. Overall, performance of a standard biliary sphincterotomy does not appear to add significant independent risk of pancreatitis (12, 17, 20). On the contrary, pancreatic sphincterotomy was found to be a significant risk of pancreatitis in a large multivariate analysis (12). Pancreatic duct stenting appears to be beneficial in reducing the incidence of pancreatitis after pancreatic sphincterotomy. Patel *et al.* conducted a prospective, randomized, controlled study, and the preliminary results showed that pancreatic duct stenting after pancreatic sphincterotomy was associated with a lower rate of pancreatitis but had not reached statistical significance (37). Coagulation current causes more tissue injury and edema than cutting current, and the use of pure cut current has been shown to cause less pancreatitis than with blended current sphincterotomy (38). In our series, we evaluated all types of endoscopic sphincterotomy and found only minor papilla sphincterotomy was an independent risk factor for post-ERCP pancreatitis (OR: 3.8). Biliary sphincterotomy was not a significant risk factor by univariate analysis. Pancreatic sphincterotomy of major papilla was significant only by univariate but not by multivariate analysis. According to our findings, pancreas divisum is not a risk factor unless minor papilla therapy is performed.

Pre-cut papillotomy to gain access to the common bile duct was not a risk factor in this study. However, like another similar report (12), most of these procedures were performed by

a few highly experienced endoscopists and often followed or preceded by placement of a pancreatic stent, which has been shown to reduce the risk of precutting (39). Increasing numbers of reports from tertiary referral centers also confirmed that complication rates were not different from standard sphincterotomy (40). However, precutting was associated with a higher risk of pancreatitis in two other multicenter studies involving endoscopists with varied experience in ERCP (11, 16), and in the meta-analysis study (23). These observations suggest that the risk of precut papillotomy is highly operator dependent. Our data support the concept that early use of precut by expert endoscopists might be preferable to prolonged attempts at cannulation in patients at high risk for pancreatitis (12, 17).

Trainee participation has been previously evaluated in one large multicenter study and the result showed it was not a significant risk factor (12). In another report by Vandervoort *et al.*, the complications of ERCP performed solely by attending physician were not significantly different from those performed by fellows under the supervision of attending endoscopists, but detailed statistical data were not provided (13). In our series, trainee participation did increase the risk by multivariate analysis (OR: 1.5). The reason for this disagreement was not clear. A similar discrepancy was also noted in the evaluation of endoscopists' case volume as a risk factor for post-ERCP pancreatitis. Some series reported low case volume was not significant in the multivariate analysis (12, 15), while others considered it as independent risk factor of pancreatitis (17, 18). Low case volume was also an independent risk factor for postsphincterotomy bleeding in two large multicenter series (11, 12). In the prospective multicenter study by Freeman *et al.*, sphincterotomy-induced complications were noted more frequently at university-affiliated referral centers than private practices, which the authors attributed to different case mix (11). All of these observations suggest that case mix is at least as important as expertise in determining risk of post-ERCP pancreatitis.

There is an escalating risk of post-ERCP pancreatitis in patients with multiple risk factors (12, 14). In the report by Freeman *et al.*, a woman with normal serum bilirubin, easy cannulation, and a bile duct stone had about a 5% chance of post-ERCP pancreatitis. If an even moderately difficult cannulation was encountered, the risk rose to more than 16%. If such a patient also had suspected SOD and had a difficult cannulation, the risk of pancreatitis rose to more than 40% (12). Friedland *et al.* designed a bedside scoring system for the risk of post-ERCP pancreatitis based on the results of multivariate analysis (14). Independent risk factors included in the scoring system were new pain during ERCP, pancreatic ductal contrast injection, a prior history of post-ERCP pancreatitis, and difficult cannulation. The results showed that cases scoring 4 or fewer points (the low-risk group) had a 2% risk of post-ERCP pancreatitis, cases scoring between 5 and 8 points (the medium-risk group) had a 7% risk, and cases scoring more than 8 (the high-risk group) had a 28% risk.

Pharmacological methods to prevent post-ERCP pancreatitis have been studied for many years. Most drugs appear promising in initial randomized single-center trials; however, conflicting results are often obtained from larger, multicenter studies. Octreotide, steroids, and interleukin-10 are typical examples. From the meta-analysis report by Andriulli *et al.*, somatostatin (an antisecretory agent) and gabexate mesilate (a protease inhibitor) are two effective prophylactic drugs for preventing post-ERCP pancreatitis (41). Neither drug is available in the United States. The number of patients that need to be treated with both drugs to prevent a single case of pancreatitis is 13–27. One recent report showed that a single dose of diclofenac (a nonsteroidal antiinflammatory agent, NSAID) suppository helped to reduce the incidence of post-ERCP pancreatitis (42). NSAIDs can inhibit the early inflammatory cascade involving phospholipase-A2, prostaglandins, or endothelial neutrophil attachment during acute pancreatitis. It should be appreciated that this is only a single-center study and diclofenac was not effective in the subgroup of patients with SOD, the very group of patients that are at greatest risk. A larger multicenter study is needed to confirm the protective role of NSAIDs.

In conclusion, multivariate analysis indicates that patient-related risk factors are as important as technical ones. Until effective, safe, and low-cost prophylactic drugs are definitively identified and made available, selective use in high-risk groups may be warranted. Unfortunately, such a drug is not available in the United States. Risk stratification will allow endoscopists to better identify patients who are at significant risk and permit detailed informed consent as well as possibly defer examinations in the highest-risk groups. Appropriate technical "prophylaxis" during ERCP, such as pancreatic ductal stenting, should also be carefully considered in high-risk patients to prevent the development of pancreatitis.

Appendix

Other contributing authors: Klaus Gottlieb, MD, Indiana University Medical Center, Indianapolis, Indiana; Kevin Block, MD, Mark Reichelderfer, MD, University of Wisconsin, Madison, Wisconsin; Grace Elta, MD, William D. Chey, MD, University of Michigan, Ann Arbor, Michigan; Oliver Cass, MD, Hennepin County Medical Center, Minneapolis, Minnesota; Marc Catalano, MD, Michael Schmalz, MD, Daniel Geenen, MD, GI Consultants Ltd., Milwaukee, Wisconsin; Christopher Rall, MD, Marshfield Clinic, Marshfield, Wisconsin; David Carron, MD, Milwaukee GI Specialists, Milwaukee, Wisconsin; John Johanson, MD, Roger Greenlaw, MD, Mark Shiels, MD, Rockford Gastroenterology Associates, Ltd., Rockford, Illinois; Adam Slivka, MD, University of Pittsburgh, Pittsburgh, Pennsylvania; Anthony Bohorfoush, MD, Reza Shaker, MD, Medical College of Wisconsin, Milwaukee, Wisconsin; Hitesh Chokshi, MD, David Walden, MD, Washington University, St. Louis, Missouri; Raja Kaikous, MD, University of Louisville, Louisville, Kentucky.

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Reprint requests and correspondence: Stuart Sherman, M.D., Professor of Medicine and Radiology, Indiana University Medical Center, 550 N University Blvd, Suite 4100, Indianapolis, IN 46202.
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