REVIEW

The Prevention, Recognition and Treatment of Post-ERCP Pancreatitis

Nison Badalov[1], Scott Tenner[1], John Baillie[2]

[1]Maimonides Medical Center, State University of New York, Health Sciences Center. Brooklyn, NY, USA. [2]Wake Forest Baptist Medical Center. Winston-Salem, NC, USA

Introduction

Acute pancreatitis is the most common and feared complication of endoscopic retrograde cholangio-pancreatography (ERCP). It is associated with substantial morbidity and occasional mortality. The mechanisms that lead to post-ERCP pancreatitis are complex and not fully understood. Rather than having a single pathogenesis, post-ERCP pancreatitis is believed to be multi-factorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, and thermal factors. Although there is some uncertainty in predicting which patients will develop acute pancreatitis following ERCP, a number of risk factors acting independently or in concert have been proposed as predictors of post-ERCP pancreatitis [1, 2, 3, 4]. These include patient and procedure related factors. In patients at high risk for developing post-ERCP pancreatitis, numerous studies have attempted to identify endoscopic or pharmacologic interventions that might reduce the risk. The purpose of this review is to describe recent advances in the prevention and amelioration of post-ERCP pancreatitis.

Identification of Post-ERCP Pancreatitis

Regardless of the etiology, the criteria for the diagnosis of acute pancreatitis requires two of the three following criteria [5]: 1) abdominal pain (symptoms) consistent with the diagnosis; 2) a serum amylase and/or lipase greater than 3 times the upper limit of normal; and/or 3) cross-sectional imaging (CT and/or MRI) consistent with the diagnosis. Although using two of the three criteria will accurately lead to a diagnosis of acute pancreatitis in most patients, the criteria are not always accurate in patients following ERCP. Many patients with post-ERCP pancreatitis have two of these criteria in the absence of acute pancreatitis, pain and an elevation of amylase/lipase. The pain of pancreatitis is typically epigastric, persistent and radiating to the back and lasting for hours if not days. Episodic and fleeting pain is not related to pancreatitis. Some patients have pain following ERCP due to the large volume of air insufflated during the procedure. This results in bowel distention and painful spasm. In addition to pain, asymptomatic elevations in the amylase and/or lipase often occur following ERCP, with no clinical sequelae. Inappropriate labeling of patients with abdominal pain and mild, transient elevation of serum amylase and/or lipase as having post ERCP pancreatitis may explain why the reported incidence of post ERCP pancreatitis varies greatly, from 4% to 31% among studies [1, 2, 5, 6].

Due to the lack of specificity of pain and elevations of the amylase/lipase in patients who have undergone ERCP, imaging becomes the most important criterion in determining the diagnosis of post-ERCP pancreatitis. Post-ERCP pancreatitis should be suspected in any patient who develops pain within 6 hours of the procedure. It is much less likely to develop after 12 hours from the procedure. Post-ERCP pain with marked elevation of serum amylase and/or lipase; especially when the values are greater than 1,000 IU/L, it is strongly suggestive of pancreatitis. In cases of diagnostic doubt, especially when severe pancreatitis is predicted, radiologic imaging should confirm the diagnosis.

Early recognition of post-ERCP pancreatitis may be possible by evaluating serum amylase or lipase within a few hours of the procedure [7, 8, 9]. In a study that involved 231 patients, the 2-hour serum amylase or lipase was more accurate than clinical assessment in distinguishing post-ERCP pancreatitis from other causes of abdominal pain. Values greater than 276 IU/L for serum amylase and greater than 1,000 IU/L

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Correspondence Scott Tenner
Medical Education and Research, Maimonides Medical Center, State University of New York, 2211 Emmons Ave, Brooklyn, NY 11235, USA
Phone: +1-718.368.2960; Fax: +1-718.368.2249
E-mail: drtenner@brooklyngi.com
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for serum lipase obtained 2 hours after the procedure had almost 100% positive predictive value (PPV) for post-ERCP pancreatitis [7]. More recently, Ito *et al*. found that if the serum amylase was normal at 3 hours, only 1% of patients developed post-ERCP pancreatitis compared to 39% if the amylase was greater than 5 times the upper limit of reference [8]. A serum amylase and/or lipase alone should not guide a decision regarding the presence or absence of post-ERCP pancreatitis. However, these tests can assist clinicians in their assessment of patients with post-ERCP pain.

Risk Factors for Developing Post-ERCP Pancreatitis

Awareness of the risk factors for post-ERCP pancreatitis is essential for the recognition of high-risk cases in which ERCP should be avoided if possible, or in which protective endoscopic or pharmacologic interventions should be considered. Risk factors for developing post-ERCP pancreatitis have been assessed in various studies and include patient, procedure, and operator-related factors (Table 1).

On reviewing the literature, the general consensus of the patient related-factors include: young age, female gender, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, prior history of post-ERCP pancreatitis, and patients with normal serum bilirubin. The procedure related factors include: pancreatic duct injection, difficult cannulation, pancreatic sphincterotomy, precut access, - and balloon dilatation. The operator dependant and technical factors are controversial. Although endoscopists who have a high volume of cases might be expected to have intuitively lower rates post-ERCP pancreatitis, in general this does not appear to be true [2]. However, trainee (fellow) participation has been shown to be a significant risk factor for the development of post-ERCP pancreatitis [3].

In general, the more likely a patient is to have an abnormal common bile duct and/or pancreatic duct, the less likely the patient will develop post-ERCP pancreatitis. Cheng *et al*. [3] created a 160 variable database that prospectively evaluated over a thousand patients from 15 referral centers in the U.S. Their study emphasized the role of patient factors, including age, sphincter of Oddi dysfunction, prior history of post-ERCP pancreatitis and technical factors, including number of pancreatic duct injections, minor papilla sphincterotomy and operator experience.

Mehta *et al*. [4] showed that the patient most at risk of developing post-ERCP pancreatitis was a woman with suspected choledocholithiasis, non-dilated common bile duct, but normal serum bilirubin, which undergoes a biliary sphincterotomy and no stone was found. In this patient population, more than a quarter of patients (27%) developed post-ERCP pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound, which do not cause pancreatitis, can provide useful information with an accuracy similar to ERCP in high risk/low yield cases and are the preferred imaging modalities in the initial evaluation of such patients.

Pharmacologic Prevention of Post-ERCP Pancreatitis

Although there has been interest in the pharmacologic prevention of post-ERCP pancreatitis, since its introduction, a large number of studies have failed to identify a consistently effective drug. However, a small number have been shown to be worthy of further study (Table 2). Our limited understanding of the pathogenesis of post-ERCP pancreatitis is a major hurdle to developing effective drug prophylaxis. Drugs that have been studied can be divided into five groups: those that 1) decrease pancreatic inflammation; 2) decrease sphincter of Oddi pressure; 3) attenuate systemic inflammation; 4) decrease pancreatic stimulation; and 5) interrupt the activity of proteases.

Drugs that Decrease Inflammation

These include antioxidants, antibiotics, steroids, and non-steroidal anti-inflammatory drugs (NSAIDS). Oxygen-derived free radicals contribute to the pathogenesis of acute pancreatitis by inducing capillary-endothelial injury, which leads to an increase in capillary permeability. Drugs that prevent the generation of, and/or inactivate, free radicals include allopurinol and n-acetylcysteine**,** respectively. Both have been studied in animal and human models. Initial studies in animals demonstrated a decrease in the incidence and severity of acute pancreatitis for both drugs. However, subsequent human trials failed to show any significant benefit. Four clinical trials that evaluated the efficacy of allopurinol in the prevention of post ERCP pancreatitis showed no clear benefit [10, 11, 12, 13]. One study from Greece [12] looked encouraging, but a high rate of post-ERCP pancreatitis in the control group limited interpretation of the results. Two trials have been published evaluating n-acetylcysteine in the prevention of post-ERCP pancreatitis [14, 15]; neither showed a benefit.

As infectious complications contribute to the morbidity and mortality in acute pancreatitis, studies evaluating the potential role of antibiotics in preventing post-ERCP pancreatitis have been performed. Only one study has appeared to show benefit. Räty *et al*. [16]

Table 1. Factors increasing the risk of post-ERCP pancreatitis.

Patient related factors	Young age, female gender, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, prior history of post ERCP pancreatitis, and patients with normal serum bilirubin
Procedure related factors	Multiple pancreatic duct injections, difficult cannulation, pancreatic sphincterotomy, precut access, and balloon dilation
Operator/technical related factors	Inadequate training and/or experience
	Trainee involvement in procedure

showed reduced rates of post-ERCP pancreatitis in patients receiving 2 grams of ceftazidime 30 minutes prior to ERCP when compared to placebo (2.6% *vs*. 9.4%. P=0.009).

There have been seven studies evaluating the effect of corticosteroids in reducing the incidence or severity of post ERCP pancreatitis. Pooling all of these studies, 3,308 patients have been evaluated [11, 17, 18, 19, 20, 21]. An early retrospective trial [17] showed a reduced incidence of post therapeutic ERCP pancreatitis in patients with iodine sensitivity. Subsequently, 5 large trials (one randomized and four double-blind) using a variety of corticosteroids, including oral prednisolone, intravenous hydrocortisone and methyl-prednisolone, showed no benefit in reduction of severity or incidence of post ERCP pancreatitis. Of note, the two trials that showed benefit with use of corticosteroids in the prevention of post-ERCP pancreatitis used lower amylase levels (2 to 2.5 times the upper limit of reference) as the cut-off for the diagnoses of acute pancreatitis [17, 18].

In terms of attenuating the inflammatory response, the most promising results have been seen with NSAIDs. Two clinical trials have been published evaluating the role of diclofenac in reducing the incidence of post ERCP pancreatitis [22, 23]. In both trials patients received 100 mg of diclofenac by rectal suppository. Both showed a reduction in the incidence of acute pancreatitis. In the trial performed by Murray *et al*. [22], pancreatitis occurred in 6.4% of patients in the diclofenac group compared to 15.5% in the placebo group (P=0.049). Interestingly, there appeared to be no benefit in patients with sphincter of Oddi dysfunction.

Satoudehmanesh *et al.* [24] showed similar beneficial results with indomethacin. Although pancreatitis occurred in 3.2% of treated patients compared to 6.8% of control patients, these results were not statistically significant (P=0.06). However, a post-hoc analysis suggested a possible beneficial effect in the patients undergoing pancreatic duct injection.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that has been shown to reduce the severity of acute pancreatitis in animal models. Deviere *et al*. [25] showed a reduction in the incidence and severity of acute pancreatitis with administration of IL-10, 7.5% in treated patients compared to 24% in controls (P<0.05). However, in a separate double blind, prospective trial, Dumot *et al*. [26] found no difference in the incidence of acute pancreatitis in 200 average risk patients randomized to receive 8 μg/kg of IL-10 *versus* placebo (9% *vs*. 11%, P=0.7). A subsequent, larger, multicenter trial, published only in abstract format at present, showed no benefit of IL-10 in patients undergoing ERCP [27].

Drugs that Secrease Sphincter of Oddi Pressure

It has been suggested that relaxation of the sphincter of Oddi following ERCP will promote pancreatic

Table 2. Trials evaluating medications in the prevention of post-ERCP pancreatitis.

Drug	No. of trials	References of trials		No. of patients	References for RCCT	References for RCCT/DBT
		Showing benefit	Showing no benefit			
Allopurinol	4	[12]	[10], [11], [13]	1,342	[11]	[10][a], [12], [13]
Beta-carotine	1	None	[99]	340	None	[99]
Botulinium	1	None	[34]	26	[34]	None
Calcitonin	1	None	[97]	30	None	[97]
Ceftazidime	1	[16]	None	321	[16]	None
Corticosteroids	7	[17][b], [18]	[11], [19], [20], [21], [80]	3,308	[11]	[18], [19], [20], [21], [80]
Diclofenac	2	[20], [23]	None	320	None	[22], [23]
Epinephrine	1	[35][c]	None	173	None	None
Gabexate	13	[44], [54][a], [56], [57][d], [63][b]	[45][a], [54][a], [55], [58][a], [60][c], [61][b], [62]	5,180	[58][a], [62]	[44], [45][a], [53], [55], [56], [59]
Glucagon	1	None	[98]	55	[98]	None
Heparin	2	[36]	[37]	1,273	None	[37]
Indomethacin	1	[24]	None	420	None	[24]
Interleukin-10	3	[25]	[26], [27]	649	None	[25], [26], [27]
Lidocaine	1	None	[33]	294	None	[33]
N-acetylcysteine	2	None	[14], [15]	355	[11]	[15]
Nifedipine	2	None	[31], [32]	321	None	[31], [32]
Nitroglycerin	3	30	[28], [29]	648	None	[28], [29], [30]
Octreotide	15	[88], [95], [96]	[80], [82], [83], [84], [85], [86], [89], [90], [91], [92], [93]	3,495	[89], [90], [93], [96]	[25], [82], [83], [84], [85], [86], [88], [91], [92], [95]
Somatostatin	16	[67], [69], [70], [71], [72]	[53], [55], [58][a], [68], [73], [74], [75], [77], [78], [79][c]	3,100	[58][a], [73], [78]	[53], [55], [67], [68], [69], [70], [71], [72], [74]
Ulinastatin	3	[66]	[60][c], [62]	533	[62]	[66]

[a] Abstract; [b] Retrospective trial; [c] Uncontrolled, prospective trial; [d] Double blind, non-placebo controlled

RCCT: randomized placebo controlled clinical trials; RCCT/DBT: randomized, placebo controlled and double blinded trials

drainage and prevent acute pancreatitis. Several agents have been used in an effort to relax the sphincter of Oddi, as a way to prevent post-ERCP pancreatitis. There have been 3 recent randomized studies evaluating the use of nitroglycerin during ERCP. Sudhindran *et al*. [28] compared the prophylactic administration of 2 mg of sublingual nitroglycerin compared to placebo in patients undergoing ERCP. They found that the incidence of post-procedure pancreatitis was significantly less in treated patients (7.7% *vs*. 17.8%, P<0.05). The short duration of action of sublingual nitroglycerin raises questions about the plausibility of the proposed pharmacologic effect. In a subsequent trial by Moretó *et al*. [29], 144 patients were randomized to a 15 mg transdermal nitroglycerin patch or an identical placebo patch. A significant reduction in pancreatitis in the placebo arm was demonstrated (4% *vs*. 15%, P=0.03). However, both trials had high rate of acute pancreatitis in the control arm. In the latest and the largest of the three studies [30], 318 patients at low risk for post ERCP pancreatitis were randomized to receive either the active agent or placebo by transdermal patch. No difference in post-ERCP pancreatitis was seen between active nitroglycerin and placebo groups.

Other studies evaluating drugs to decrease sphincter of Oddi pressure for post-ERCP pancreatitis prophylaxis include: two trials of oral nifedipine [31, 32], one of sprayed lidocaine [33] and one of injected botulinum toxin [34]. Unfortunately, none of these trials demonstrated any beneficial role in the reduction of severity or incidence of post ERCP pancreatitis. In a prospective, non-placebo-controlled trial of 173 patients undergoing endoscopic balloon sphincteroplasty [35], irrigation of the dilated orifice with epinephrine, resulted in a reduced incidence of acute pancreatitis (1.2% *vs*. 7.6%, P<0.05).

Drug that Interrupt the Activity of Proteases

As the initiation of acute pancreatitis depends on the activation and propagation of proteases, the theoretical advantage of protease inhibitors in decreasing the incidence and severity of post ERCP pancreatitis warrants study. In experimental models, heparin has been shown to inhibit pancreatic proteases, increase microcirculation, and have anti-inflammatory properties. In a non-randomized, prospective trial of 815 patients, heparin administration was associated with a statistically significant reduction of post ERCP pancreatitis (3.4% *vs*. 7.9%, P=0.005) [36]. However, despite these early encouraging results, two years later the same group performed a randomized, double-blind trial that failed to show a reduction of post ERCP pancreatitis in high risk patients randomized to receive heparin [37].

Gabexate maleate (FOY™) is a protease inhibitor with anti-inflammatory properties. Its ability to inhibit circulating trypsin is greater than most other protease inhibitors. In 1995, Messori *et al*. [38] published a meta-analysis of 5 trials [39, 40, 41, 42, 43] showing a statistically significant reduction in the incidence of complications in patients receiving gabexate after the development of acute pancreatitis. However, the trials were small with possibly insufficient numbers of patients. A larger double blind trial by Cavallini *et al*. [44] subsequently demonstrated a significant reduction in the incidence (2.4% *vs*. 7.6%, P=0.03) and severity of acute pancreatitis in the patients receiving gabexate *versus* placebo. An initial meta-analysis of 6 trials [44, 45, 46, 47, 48, 49] by Andriulli *et al*. [50] demonstrated statistically significant reduction rates of post ERCP pancreatitis (OR: 0.27, 95% CI: 0.13-0.57; P=0.001). Second and 3rd meta-analyses published by the same group [51, 52], which included several large prospective trials [53, 54, 55, 56, 57, 58], did not support the prophylactic use of gabexate in the prevention of acute pancreatitis. Recently, following the publication of the meta-analysis by Andriulli *et al*. [52], several additional trials have been published, with conflicting results [59, 60, 61, 62, 63]. Although the data are conflicting, it appears that infusions of the drug would likely need to be started 1-2 hours pre-ERCP, and continued for 12 hours following ERCP, to show a beneficial effect [1, 64]. In patients with a low risk, the costs likely outweigh any benefit.

The protease inhibitor, ulinastatin, has been long used in the management of acute pancreatitis in Japan and China [65]. In an initial, randomized, placebo-controlled trial [66], an ulinastatin bolus prior to ERCP significantly reduced the incidence (2.9% *vs*. 7.4%; P=0.041) but not the severity of acute pancreatitis. Two subsequent, randomized, controlled trials comparing ulinastatin to gabexate, found no difference in the prevention of acute pancreatitis [60, 62]. Further study of protease inhibitors in high-risk patients is warranted.

Inhibitors of Pancreatic Secretion

Theoretically, inhibition of exocrine pancreatic secretion could prevent post-ERCP pancreatitis by "resting" a damaged gland. Although an attractive concept, there is little scientific basis to support this approach. Somatostatin and its synthetic analog, the octapeptide octreotide, are potent inhibitors of pancreatic secretion. Although several trials of somatostatin have demonstrated an efficacy in reducing the rate of post ERCP pancreatitis [67, 68, 69, 70, 71, 72], the majority of the studies do not support the routine use of this medication [73, 74, 75, 76, 77, 78, 79, 80]. In a meta-analysis published in 2007, Andriulli *et al*. [52] evaluated 16 trials of somatostatin [53, 55, 58, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79] and concluded that this drug's only statistically significant effect is reduction of post ERCP hyperamylasemia (OR: 0.67, 95% CI: 0.57-0.81; number needed to treat equal to 12). However, when one excludes small, heterogeneous studies, somatostatin administered as a bolus and or as 12-hour infusion seems to be effective in prevention of post-ERCP pancreatitis with a risk difference of 2.1% (95% CI: 0.7-3.6, P=0.004) [64].

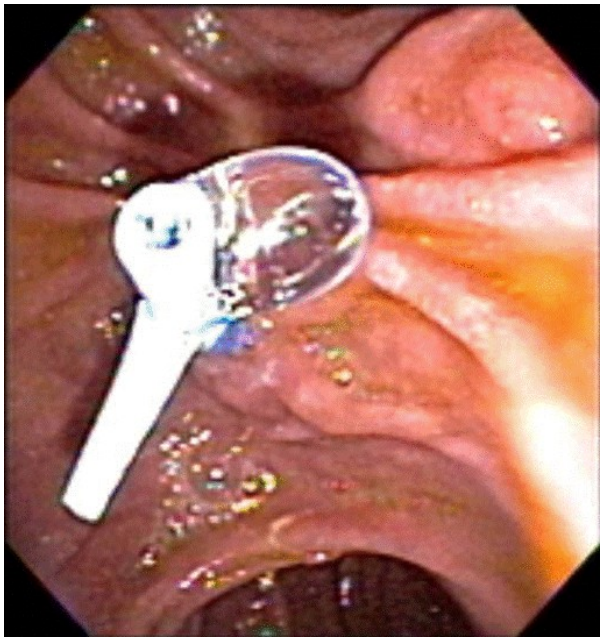

Figure 1. Pancreatic duct stent.

In 2000, Andriulli *et al*. [50] performed a meta-analysis of 10 trials of octreotide [78, 79, 80, 81, 82, 83, 84, 85, 86, 87] in the prevention of post ERCP pancreatitis. They concluded that, similar to somatostatin, octreotide was only effective in reducing post ERCP hyperamylasemia; it did not reduce the incidence of post ERCP pancreatitis. Subsequently, multiple well-designed trials evaluating different doses and scheduling of administration of octreotide [80, 91, 92, 93], and a meta-analysis [94] failed to demonstrate any benefit of octreotide in the prevention of post ERCP pancreatitis. However, two recently published trials [95, 96] reported a beneficial effect of octreotide in reducing the rate of post ERCP pancreatitis, (2% *vs*. 8.9%, P=0.03) and (2.4% *vs*. 5.3%, P=0.046), respectively. Further trials with octreotide are warranted. Drugs such as somatostatin, calcitonin [97], and glucagon [98], have been shown to inhibit pancreatic secretion, however none of them has been shown to have a protective effect. It is worth mentioning that a single trial has shown beneficial effects of beta-carotine administration in the reduction of severity of post ERCP pancreatitis (2.22% *vs*. 0%; P<0.01) [99].

Stents and Guidewires to Prevent Post-ERCP Pancreatitis

Pancreatic stent placement decreases the risk of post-ERCP pancreatitis in high-risk patients [6, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111]. This technique has become a common practice during ERCP in patients who are thought to be at particular risk for post-ERCP pancreatitis (Figure 1). Stenting is thought to prevent obstruction to pancreatic duct outflow that can result from papillary edema following instrumentation. Pancreatic sphincter hypertension is a significant risk factor for post-ERCP pancreatitis, which may explain the high risk of pancreatitis in patients with sphincter of Oddi dysfunction. There is prolonged alleviation of ductal obstruction when pancreatic stents are placed. Typically, 3-5 French (Fr) gauge, unflanged, plastic pancreatic stents are used in the following settings: sphincter of Oddi dysfunction, difficult cannulation, balloon dilation (balloon sphincterotomy), and precut sphincterotomy. Thirteen trials (6 prospective, randomized, controlled trials and 7 case-control trials) have been published evaluating the role of pancreatic stent placement in the prevention of post-ERCP pancreatitis (Table 3) [6, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111]. In all of the reported studies, which cumulatively include 1,500 high-risk patients undergoing ERCP, only one patient developed severe pancreatitis after a pancreatic duct stent had been placed [1]. A meta-analysis published in 2004 by Singh *et al.* [112], evaluating 5 prospective

Table 3. Trials evaluating the role of pancreatic stent placement in the prevention of post-ERCP pancreatitis.

First Author/year	Study design	Patient characteristics	No. of patients	Pancreatitis rate		P
				Without stent	With stent	
Smithline, 1993 [100]	RCT	Pre-cut biliary ES, sphincter of Oddi dysfunction	93	18%	14%	0.299
Sherman, 1996 [101]	RCT[a]	Pre-cut biliary ES - come back	93	21%	2%	0.036
Tarnansky, 1998 [102]	RCT	Biliary ES for sphincter of Oddi dysfunction	80	26%	7%	0.03
Elton, 1998 [103]	RCC	Pancreatic ES for all indications	164	12.5%	0.7%	<0.003
Patel, 1999 [104]	RCT[a]	Biliary ES for sphincter of Oddi dysfunction	36	33%	11%	>0.05
Vandervoort, 1999 [105]	PCC	Pancreatic brush cytology for suspected malignancy	42	28.1%	0	0.08
Aizawa, 2001 [106]	RCC	Biliary balloon dilatation for stone	40	6%	0	011
Fogel, 2002 [107]	RCC	Biliary plus/minus pancreas ES for sphincter of Oddi dysfunction	436	28.3%	13.5%	<0.05
Norton, 2002 [108]	RCC	Endoscopic ampullectomy	28	11.1%	20%	>0.05
Fazel, 2003 [109]	RCT	Difficult cannulation, biliary ES, sphincter of Oddi dysfunction	76	28%	5%	<0.05
Freeman, 2004 [110]	PCC	All attempted major papilla PD stent in high risk therapeutic ERCP	225	66.7%	14.4%	0.06
Catalano, 2004 [111]	RCC	Endoscopic ampullectomy	103	16.7%	3.3%	0.10
Harewood, 2005 [112]	RCT	Endoscopic ampullectomy	19	33%	0	0.02

[a] Abstract

ES: endoscopic sphincterotomy; PCC: prospective case control trial; PD: pancreatic duct; RCC: retrospective, case control trial; RCT: randomized controlled trial

trials including 483 patients, showed a three-fold reduction in the incidence of post-ERCP pancreatitis in patients with pancreatic duct stents *versus* no stent (15.5% *vs*. 5.8%; P=0.001; OR: 3.2, 95% CI: 1.6-6.4). Similarly, a 2007 meta-analysis published by Andriulli *et al.* [113], that evaluated 4 randomized, prospective trials including 268 patients, showed a two-fold drop in the incidence of post-ERCP pancreatitis (24.1% *vs*. 12%; P=0.009; OR: 0.44, 95% CI: 0.24-0.81). In a large, retrospective review of 2,283 patients having a total of 2,447 ERCPs, 3 Fr unflanged stents were more effective in reducing the incidence of post ERCP pancreatitis (P=0.0043), more likely to pass spontaneously (P=0.0001), and less likely to cause ductal changes (24% *vs*. 80%) when compared to larger 4 Fr, 5 Fr or 6 Fr stents [114]. Although prophylactic pancreatic duct stenting is a cost-effective strategy for the prevention of post-ERCP pancreatitis for high-risk patients [115], higher incidence of severe pancreatitis has been reported in patients with failed pancreatic duct stenting [116]. Also, pancreatic duct stenting is not always technically feasible with reported failure rate ranging from 4 to 10% [116].

The potential for pancreatic ductal and or parenchymal injury, risk of inward stent migration and fracture following stent placement is of a concern. In order to minimize pancreatic ductal and or parenchymal changes it is recommended that long 3 Fr (8-12 cm) or short 4 or 5 Fr (2-3 cm) single pigtail unflanged stents should be used, followed by removal within two to four weeks after placement [116].

Guidewire cannulation, in which the bile duct and pancreatic duct are cannulated by a guide-wire inserted through a catheter (e.g. a sphincterotome), has been shown to decrease the risk of pancreatitis [117]. By avoiding cannulation with radiocontrast agents, thus minimizing the risk of hydrostatic injury to the pancreas, the incidence of acute pancreatitis appears to be dramatically decreased. In a study of 400 consecutive patients who underwent ERCP by a single endoscopist, randomized to initial cannulation with contrast *versus* initial cannulation by guide-wire under fluoroscopic control, pancreatitis rates were markedly different. No case of acute pancreatitis was seen in the guidewire group compared to 8 cases in the standard contrast group (P<0.001). Cannulation success rates between the standard contrast and guide-wire techniques were comparable, 98.5% *versus* 97.5%. A more recent study [118] confirmed a decrease in post-ERCP pancreatitis in 300 patients prospectively randomized to guide-wire cannulation compared to conventional contrast injection. However, the reduction in post-ERCP pancreatitis appears to have been related to less need for precut sphincterotomy in patients undergoing guide-wire cannulation.

Treatment of Post-ERCP Pancreatitis

As not all patients with pain and hyperamylasemia following ERCP have acute pancreatitis, clinicians may be having difficulty in establishing the diagnosis. As a result, some patients with severe post-ERCP pancreatitis may not be identified in the early stages of their illness, when aggressive hydration is most important. Some endoscopists may have difficulty acknowledging that post-ERCP pancreatitis has occurred, as this requires accepting that there has been a complication. A sense of guilt on the part of the clinician performing the procedure is understandable. However, delay in both the diagnosis and treatment of post-ERCP pancreatitis may lead to adverse consequences.

Post-ERCP pancreatitis should be managed like other causes of acute pancreatitis. This is sometimes complicated by difficulty distinguishing mild from severe disease during the early stages. The degree of elevation of serum amylase and lipase do not always correlate with severity. Prospective systems using clinical criteria have been developed to predict severity in patients with acute pancreatitis, such as the Ranson, Imrie (Glasgow) and, APACHE scores [5]. The Ranson and Imrie scoring systems are effectively obsolete. They are cumbersome, requiring serial measurements of numerous physiologic, hematologic and biochemical indices. Additionally, it may take up to 48 hours to develop the predictive score. Although improved, the APACHE III is even more complex. In acute pancreatitis, close monitoring for signs of organ dysfunction is paramount. An apparently mild post-ERCP pancreatitis can sometimes progress to life threatening necrotizing disease. CT-based scoring systems, such as the Balthazar CT score may be helpful but also may be inaccurate within the first 24 hours of the disease process [119].

Aggressive intensive care to prevent complications of acute pancreatitis requires the early identification of patients with severe disease, and those at risk of developing severe disease. An advanced age (more than 55 years), obesity (BMI greater than 30 kg/m^2), organ failure at admission, and pleural effusion and/or infiltrates are risk factors for severity that should be noted early [5]. Patients with these characteristics may require treatment in a highly supervised area, such as a step-down or intensive care unit.

Hematocrit is the best laboratory marker to follow in monitoring patients with acute pancreatitis. The role of hematocrit in determining severity is related to hemoconcentration. As the inflammatory process progresses early in the course of the disease, there is an extravasation of protein-rich intravascular fluid into the peritoneal cavity resulting in hemoconcentration. The decreased perfusion pressure into the pancreas leads to microcirculatory changes that lead to pancreatic necrosis. An admission hematocrit equal to, or greater than, 47 % and/or a failure of the admission hematocrit to decrease at 24 hours have been shown to be predictors of necrotizing pancreatitis [120].

The relationship of hematocrit to severity implies that the opposite is also true: i.e. that maintaining the hematocrit in the normal range protects against pancreatic necrosis. Early, vigorous intravenous

hydration to expand the intravascular volume (hemodilution) is imperative. Too often patients with acute pancreatitis are given inadequate intravenous hydration. Acute pancreatitis typically results in significant intravascular losses. Intravenous hydration should be at least 250-300 mL per hour and titrated to the hematocrit [121]. Pain control, monitoring infection and attention to nutrition are important for all patients with acute pancreatitis. Detailed review of these topics is beyond the scope of this article, but they are extensively discussed elsewhere [5, 121, 122].

Conclusions

Multiple studies have shown that patient-related factors are as important as technical factors in predicting the risk of acute pancreatitis following ERCP. Risk stratification will allow endoscopists to better identify patients who are at risk. ERCP should be avoided in patients with a low likelihood of pathology (e.g. stones, strictures) as complications are especially likely to occur in the setting of normal anatomy. No drug has been identified that consistently prevents post-ERCP pancreatitis. However, until effective, safe and low-cost prophylactic drugs are identified and made available, selective use of a few agents in high-risk groups may be warranted. The best strategies for prevention of post-ERCP pancreatitis appear to be avoiding unnecessary and low-yield procedures, guide-wire rather than contrast-guided cannulation and judicious placement of pancreatic duct stents in high-risk patients.

Conflict of interest The authors have no potential conflicts of interest

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