Post-ERCP Pancreatitis:
Patient and Technique-Related Risk Factors

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Introduction

Reported rates of pancreatitis after ERCP and sphincterotomy range from less than one percent to 40 percent, but rates of 5 percent or more are typical [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]. Variations in reported rates of pancreatitis relate to many factors including the definition used, the thoroughness of follow up [24], and to patient and technique-related risk factors. In the consensus classification [1], pancreatitis is defined as clinical syndrome consistent with pancreatitis (i.e. new or worsened abdominal pain) with an amylase at least three times normal at more than 24 hours after the procedure, and requiring more than one night of hospitalization (Table 1). Some events are difficult to classify in the consensus definition, such as for patients with post-procedural abdominal pain and elevation of amylase to just under 3 times normal, or those with dramatic amylase elevations but minimal symptoms that are not clearly suggestive of clinical pancreatitis. There are many potential mechanisms of injury to the pancreas during ERCP and endoscopic sphincterotomy: mechanical, chemical, hydrostatic, enzymatic, microbiologic, and thermal. Although the relative contribution of these mechanisms to post-ERCP is not known, recent studies have used multivariate analyses to identify the clinical patient and procedure-related factors that are independently associated with pancreatitis [3, 16, 18, 19, 20, 21, 22]. However, even multivariate analyses can sometimes be misleading if key variables are not assessed, thereby making surrogate associated markers appear significant instead [25].

Patient-Related Risk Factors for Post-ERCP Pancreatitis

Risk of post-ERCP pancreatitis is determined at least as much by the characteristics of the patient as by endoscopic techniques or maneuvers (Table 2). Patient-related predictors found to be significant in one or more major studies include younger age, indication of suspected sphincter of Oddi dysfunction, history of previous post-ERCP pancreatitis, and absence of elevated serum bilirubin [3, 16, 18, 19, 20, 21, 22]. Women

Table 1. Consensus definitions for the major complications of ERCP [1].

<table>
<thead>
<tr>
<th>Type of pancreatitis</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mild pancreatitis</td>
<td>Clinical pancreatitis, amylase at least three times normal at more than 24 h after the procedure, requiring admission or prolongation of planned admission to 2-3 days</td>
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<tr>
<td>Moderate pancreatitis</td>
<td>Pancreatitis requiring hospitalization of 4-10 days</td>
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<tr>
<td>Severe pancreatitis</td>
<td>Hospitalization for more than 10 days, pseudocyst, or intervention (percutaneous drainage or surgery)</td>
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</table>

Any intensive care unit admission after a procedure grades the complication as severe.
may have increased risk [18], but it is difficult to sort out the contribution of sphincter of Oddi dysfunction, a condition that almost exclusively occurs in women. Patients with multiple risk factors have dramatically enhanced risk [18, 21].

Suspicion of sphincter of Oddi dysfunction, most often suspected in women with post-cholecystectomy abdominal pain [26, 27, 28], poses a formidable risk for pancreatitis after any kind of ERCP whether diagnostic, manometric or therapeutic [4, 5, 6, 7, 14, 16, 18]. Suspicion of sphincter of Oddi dysfunction independently increases the risk of post-ERCP pancreatitis by as much as five-fold to about 10-30% (Figure 1). The reason for heightened susceptibility in these patients remains unknown. Contrary to the widely held opinion that sphincter of Oddi manometry is the culprit [29, 30], recent multivariate analyses have shown that empirical biliary sphincterotomy or even diagnostic ERCP has a similarly high risk [16, 18, 31]. In a large multicenter study, biliary sphincterotomy after manometry was associated with an 18% risk of pancreatitis, but empirical biliary manometry was associated with a similarly high pancreatitis rate of 20% [16]. With the widespread use of aspirating instead of conventional perfusion catheters, the risk of manometry has probably been reduced to that of cannulation with any other ERCP accessory [31]. The perception that manometry is high risk results in the past from use of perfusion catheters in the pancreatic duct, and more recently from the fact that in centers where it is performed, manometry is always performed in patients with suspected sphincter of Oddi dysfunction, thus losing the ability to separate the contribution of risk from the procedure from that of the patient. Absence of a stone in patients with suspected choledocholithiasis was found to be the most potent single risk factor for post-ERCP pancreatitis in a prior study in which the diagnosis of sphincter of Oddi dysfunction was not considered [21]. These observations point out the danger of performing diagnostic ERCP to look for bile duct stones in women with recurrent post-cholecystectomy pain and minor or no liver chemistry abnormalities, as there is generally a low probability of finding stones in such patients.

Figure 1. Frequency of complications of 2,347 biliary sphincterotomies by indication [16].

Table 2. Risk factors for post-ERCP pancreatitis in multivariate analyses.

<table>
<thead>
<tr>
<th>Definite *</th>
<th>Maybe **</th>
<th>No ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected sphincter of Oddi dysfunction</td>
<td>Female sex</td>
<td>Small CBD diameter</td>
</tr>
<tr>
<td>Young age</td>
<td>Acinarization</td>
<td>Sphincter of Oddi manometry</td>
</tr>
<tr>
<td>Normal bilirubin</td>
<td>Absence of CBD stone</td>
<td>Biliary sphincterotomy</td>
</tr>
<tr>
<td>History of post-ERCP pancreatitis</td>
<td>Lower ERCP case volume</td>
<td></td>
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<tr>
<td>Difficult cannulation</td>
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<tr>
<td>Pancreatic duct contrast injection</td>
<td></td>
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<tr>
<td>Pancreatic sphincterotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precut sphincterotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon dilation of biliary sphincter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significant by multivariate analysis in most studies
** Significant by univariate analysis only in most studies
*** Not significant by multivariate analysis in any study

CBD: common bile duct
patients, and a high risk of causing pancreatitis. It is an erroneous and potentially dangerous assumption that merely avoiding sphincter of Oddi manometry will significantly reduce risk. History of previous post-ERCP pancreatitis was found to be a potent risk factor (OR 5.4) in the only study to evaluate it [18], and warrants special caution. Advanced chronic pancreatitis, on the other hand, confers some immunity against ERCP-pancreatitis, perhaps because of atrophy and decreased enzymatic activity [18]. Pancreas divisum is only a risk factor if minor papilla cannulation is attempted [18].

Technique-Related Risk Factors for post-ERCP Pancreatitis

Technical factors have long been recognized to be important in causing post-ERCP pancreatitis. Papillary trauma induced by difficult cannulation has a negative effect that is independent of the number of pancreatic duct contrast injections [16, 18]. Pancreatitis occurred in one study after 2.5% of ERCP in which there was no pancreatic duct contrast injection at all [18]. Pancreatic contrast injection itself is independently associated with pancreatitis risk, and increases with number of injections [16, 18]. Acinarization of the pancreas, although undesirable, is probably less important than generally thought [3, 16, 18, 20]. Overall, risk of pancreatitis is generally similar for diagnostic and therapeutic ERCP [4, 18, 20] (Figure 2). Performance of biliary sphincterotomy does not appear to add significant independent risk of pancreatitis to ERCP [18, 20], a finding that is contrary to widely held opinion [1]. This points not to the safety of sphincterotomy, but rather to the risk of diagnostic ERCP. Pancreatic sphincterotomy was found to be a significant risk factor for pancreatitis in the only large multivariate study in which it was evaluated [18], although the risk of severe pancreatitis was very small (less than one percent), perhaps because nearly all of these patients had pancreatic drainage via a pancreatic stent. Precut, or access papillotomy to gain access to the common bile duct has uniformly been associated with a higher risk of pancreatitis in multicenter studies involving endoscopists with varied experience [3, 16, 18, 20]. This elevated risk emerges even after adjusting for difficulty of cannulation [3, 15, 16, 18, 20, 23]. In contrast, many series from tertiary referral centers have found complication rates no different than for standard sphincterotomy [32, 33, 34, 35, 36, 37, 38, 39, 40, 41], suggesting that risk of precut sphincterotomy is highly operator-dependent. However, a single expert endoscopist reported that with increasing experience, although his success rate improved, the complication rate remained quite high at nearly 15%; this author did not use pancreatic stents [42]. Use of pancreatic stents prior to needle-knife precut [41], different technique, or different case mix may account in part for lower rates of precut-induced pancreatitis by other advanced endoscopists. Complications of precut sphincterotomy probably vary with the indication for the procedure (most risky with sphincter of Oddi dysfunction in the absence of pancreatic stenting) [16] and probably with other anatomic factors such as small papillas. Balloon-dilation of the biliary sphincter has been introduced as an alternative to sphincterotomy for the extraction of bile duct stones [43, 44]. Although two randomized trials from overseas have shown complications to be equivalent to or less than for sphincterotomy [45, 46], balloon dilation has been associated with a markedly
increased in risk of pancreatitis in the U.S., resulting in two deaths in one study [18, 47]. It is not clear why results of balloon dilation are so different between the United States and other regions of the world. In general, we do not recommend balloon dilation for extraction of bile duct stones unless there is a relative contraindication to sphincterotomy such as coagulopathy or need for early anticoagulation. Balloon dilation should especially be avoided in higher-risk patients such as younger patients who are anicteric – the very patients in whom one might otherwise be most interested in sphincter preservation.

Use of a papillotome for biliary cannulation has been prospectively compared to a standard catheter in two randomized trials [48, 49]. Although both showed significantly higher success with the sphincterotome, there was no difference in rates of pancreatitis or other complications. It stands to reason, however, that the most expeditious method of cannulation will likely be the safest.

Thermal injury is thought to play some role in causing pancreatitis after biliary sphincterotomy. Two studies have evaluated different current generators for electrocautery [50, 51]. Bipolar cautery, which is seldom used, was shown in one study to result in significantly lower rates of pancreatitis than conventional monopolar cautery (0% vs. 6%) [50]. A more recent study showed that pure cutting current significantly reduced pancreatitis rates when compared with the more conventional blended current (3% vs. 11%) [51]. Automated current delivery systems such as ERBE (Surgical Technology Group, Hampshire, England, UK) are increasingly used, but their effect on pancreatitis is unclear. Preliminary data suggest no difference in pancreatitis rates compared with conventional blended current [52].

Most multicenter studies have failed to show a significant correlation between ERCP case volumes and pancreatitis rates [13, 16, 18]. In one study, endoscopists averaging more than 100 ERCP per year did not have significantly lower pancreatitis rates, but did have substantially higher rates of success at bile duct access (96.5% versus 91.5% for lower volume endoscopists) [18]. It is possible that none of the participating endoscopists in those studies reached the threshold volume of ERCP above which pancreatitis rates would diminish (perhaps greater than 250-500 cases per year). However, most American endoscopists average less than 2 ERCPs per week [18], and the reported rates of pancreatitis from the highest volume tertiary referral centers in the U.S. are often relatively higher than those in private practices [16, 18]. All of these observations suggest that case mix is at least as important as expertise in determining risk of post-ERCP pancreatitis.

### Pancreatic Stenting to Reduce Risk of Post-ERCP Pancreatitis

Pancreatic stent placement can reduce risk of post-ERCP pancreatitis in a number of settings (Table 3), and is widely performed at many advanced centers for this purpose (Figure 3). Specific situations where placement of a pancreatic stent has been shown to reduce risk include after biliary sphincterotomy for sphincter of Oddi dysfunction (Figure 3) [53], after pancreatic sphincterotomy [54], prior to precut sphincterotomy (Figure 3) [41] and after balloon-dilation of the biliary sphincter [55]. A randomized trial suggested equivocal benefit of pancreatic stenting for difficult

<table>
<thead>
<tr>
<th>Setting</th>
<th>Benefit</th>
<th>Evidence</th>
</tr>
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<tbody>
<tr>
<td>Biliary sphincterotomy for SOD</td>
<td>Yes</td>
<td>RCT</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy for SOD</td>
<td>Yes</td>
<td>RCT (abstract)</td>
</tr>
<tr>
<td>Biliary balloon dilation for stone</td>
<td>Yes</td>
<td>RCT</td>
</tr>
<tr>
<td>Precut (access) biliary sphincterotomy</td>
<td>Yes</td>
<td>RCT</td>
</tr>
<tr>
<td>“High risk” including difficult cannulation</td>
<td>Equivocal</td>
<td>RCT</td>
</tr>
</tbody>
</table>

SOD: sphincter of Oddi dysfunction  
RCT: randomized controlled trial

**Table 3.** Pancreatic stents to reduce risk of post-ERCP pancreatitis.

Pancreatic stenting is an effective method to reduce the risk of post-ERCP pancreatitis. The use of pancreatic stents is particularly beneficial in patients with high-risk conditions such as biliary sphincterotomy for sphincter of Oddi dysfunction, precut sphincterotomy, and after balloon-dilation of the biliary sphincter.

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cannulation and other high-risk situations; however, the stents were placed relatively late in the procedure, perhaps after the damage was done. There was elimination of severe pancreatitis, however, in the group receiving pancreatic stents [56]. Liberal use of pancreatic stents for high-risk procedures at advanced centers has resulted in substantially reduced rates of pancreatitis, and with virtual elimination of any pancreatitis for routine obstructive biliary disease, and of severe pancreatitis for the highest risk cases [18, 41, 56]. One large study showed that in patients with sphincter of Oddi dysfunction, combined pancreatic and biliary therapy including a pancreatic stent was significantly safer than conventional biliary sphincterotomy alone [57]. After conventional biliary sphincterotomy, pancreatitis occurred in 26%, and 5% were severe, rates consistent with other prospective studies. In contrast, the rate of pancreatitis after combined pancreatic and biliary therapy including a pancreatic stent was under 15% with no episodes of severe pancreatitis in over 100 cases. It is difficult for many endoscopists who do not utilize pancreatic stents on a regular basis to accept the concept that invasive manipulation of the pancreas with a stent and even pancreatic sphincterotomy may be safer than ERCP that is diagnostic or involves primarily biliary instrumentation.

For prevention of pancreatitis, we recommend placement of small caliber (3 to 5 French) stents relatively early in the procedure in all high risk circumstances for which stents have proven effective as listed above, and also for difficult cannulation in patients who are younger, female, and have a normal pancreas. In this setting we generally use short (2-3 cm) flanged stents as premature dislodgement and resultant delayed pancreatitis is problematic with short unflanged stents. Some centers are using very long (8 cm or longer) small caliber (3-4 French) unflanged stents, and allowing them to pass spontaneously within a few weeks. Placement of pancreatic stents is usually unnecessary regardless of cannulation difficulty in older, jaundiced patients especially if they have a pancreatic duct obstructed by cancer.

Pancreatic stenting has limitations as a strategy to reduce risk. Many endoscopists and their assistants are unfamiliar with their placement and may have a substantial failure rate, leaving the patient worse off than if no attempt was made. Once placed, pancreatic stents have potential to cause ductal injury or perforation, especially if placed in a normal duct, or if the size or shape are mismatched to the duct [58, 59]. Whatever stent is used, it should be documented to have passed by pain abdominal X-ray or be removed via endoscopy within two weeks of placement in a normal duct.

Cumulative Effect of Multiple Risk Factors on Post-ERCP Pancreatitis

Risk of post-ERCP pancreatitis escalates in patients with multiple risk factors [40]. For the same difficulty of cannulation, one multivariate analysis showed that addition of normal serum bilirubin, female gender, and possible sphincter dysfunction increased the risk of pancreatitis by more than 10-fold [18]. The interactive effect of multiple risk factors is reflected in the profile of patients developing severe post-ERCP pancreatitis. In two different studies, nearly all of the patients
who developed severe or fatal pancreatitis were young to middle-aged women with recurrent abdominal pain, a normal serum bilirubin, and with no biliary obstructive pathology - therefore consistent with the syndrome of possible sphincter of Oddi dysfunction, whether or not it was suspected by the endoscopist [18, 60]. Nearly half were purely diagnostic procedures. Some involved relatively easy cannulation. None involved placement of a pancreatic stent in the major papilla. Few if any of these patients had much probability of harboring obstructive biliary pathology or of benefiting from conventional therapeutic ERCP such as empirical biliary sphincterotomy.

Keywords
Acute Disease; Cholangiopancreatography, Endoscopic Retrograde; Pancreatitis/complications; Sphincterotomy, Endoscopic

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