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TOPIC HIGHLIGHT

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Endoscopic prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is not an uncommon adverse event but may be an avoidable complication. Although pancreatitis of severe grade is reported in 0.1%-0.5% of ERCP patients, a serious clinical course may be lethal. For prevention of severe PEP, patient risk stratification, appropriate selection of patients using noninvasive diagnostic imaging methods such as magnetic resonance cholangiopancreatography or endoscopic ultrasonography (EUS), and avoidance of unnecessary invasive procedures, are important measures to be taken before any procedure. Pharmacological prevention is also commonly attempted but is usually ineffective. No ideal agent has not yet been found and the available data conflict. Currently, rectal non-steroidal anti-inflammatory drugs are used to prevent PEP in high-risk patients, but additional studies using larger numbers of subjects are necessary to confirm any prophylactic effect. In this review, we focus on endoscopic procedures seeking to prevent or decrease the severity of PEP. Among various cannulation methods, wire-guided cannulation, precut fistulotomy, and transpancreatic septostomy are reviewed. Prophylactic pancreatic stent placement, which is the best-known prophylactic method, is reviewed with reference to the ideal stent type, adequate duration of stent placement, and stent-related complications. Finally, we comment on other treatment alternatives, and make the point that further advances in EUS-guided techniques may afford useful PEP prophylaxis.

Key words: Endoscopic retrograde cholangiopancreatography; Prevention; Pancreatitis; Pancreas stent; Cannulation; Fistulotomy

Core tip: Endoscopic prevention and/or reduction in the severity of pancreatitis (PEP) are considered to be an essential component of appropriate therapy for Post-endoscopic retrograde cholangiopancreatography patients, especially those at high risk. Numerous techniques and drugs have been developed. However, their proven benefits in terms of reducing the severity of pancreatitis are limited. Currently, one popular endoscopic method is prophylactic placement of a pancreatic stent. In this review, we focus primarily on the ideal type of stent, the timing of stent insertion, and the duration of stent placement adequate to prevent PEP. Also, we describe initial cannulation methods including wire-guided cannulation and precut fistulotomy (infundibulotomy), and the alternative techniques of percutaneous biliary drainage and recently emerging endoscopic ultrasonography-guided methodology.

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INTRODUCTION

Among complications of endoscopic retrograde cholangiopancreatography (ERCP), post-ERCP pancreatitis (PEP) is the most common, and the clinical course may be downhill. The prevalence of PEP depends on several factors, including the case mix, the thoroughness of follow-up evaluation, the PEP definition used, patient susceptibility factors, the type of instrumentation used, and the skill of the endoscopist[1-4]. PEP occurrence is variable, developing after 1%-40% of all procedures, but typical PEP rates have been reported to range from 5%-15% in most prospective studies with unselected patients. Moreover, pancreatitis of severe grade is very rare, occurring after 0.1%-0.5% of ERCPs[1-6].

Currently, the well-known risk factors for PEP include endoscopic papillectomy, sphincterotomy (including precut or pancreatic sphincterotomy), sphincter of Oddi dysfunction (SOD), younger age, female sex, balloon dilation of an intact biliary sphincter, a previous history of PEP, difficult cannulation or prolonged attempts to cannulate, repeated injection of pancreatic contrast medium, and acinarization[1-11]. These risk factors can be divided into patient-related factors, procedural factors, and operator-related factors.

Although, ideally, PEP should be prevented, complete prevention may be impossible, and decreasing the severity of PEP may be a more realistic goal. Patient risk stratification prior to ERCP, adequate selection of patients using noninvasive diagnostic imaging methods such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography (EUS), avoiding unnecessary procedures, pharmacological prevention and treatment, and the use of various endoscopic techniques to minimize complications, should all be considered. The presence of patient- or procedure-related risk factors allows possible complications to be predicted with reasonable accuracy. Thus, careful patient selection for high-risk and endoscopic procedures, conducted by experienced endoscopists, may reduce procedure-related complications. Pharmacotherapy has also been used widely in efforts to prevent PEP, but the results are inconclusive. Several pharmacological prophylactic treatments have been suggested; these include rectal diclofenac, octreotide, prednisone, and allopurinol[12-17]. Effective prophylaxis of PEP has been demonstrated only using rectal diclofenac or indomethacin[12,15]. However, larger-scale multicenter studies of non-steroidal anti-inflammatory drugs (NSAIDs), with consideration of racial and/or geographical differences, are necessary to confirm any prophylactic effect of PEP. Also, it remains unclear whether NASIDs act synergistically with other prophylactic interventions including pancreatic stenting; this topic requires further work.

In this literature review, we focus on endoscopic aspects of PEP prevention or reduction in severity. We describe primary cannulation techniques including initial wire-guided cannulation, the use of precut fistulotomy (infundibulotomy) and transpancreatic septostomy when cannulation is difficult or as early rescue cannulation techniques, and prophylactic pancreatic stent (PS) placement during the procedure. Also, we mention alternatives, including percutaneous transhepatic biliary drainage (PTBD), and the possibilities afforded by further advances in EUS-guided biliary drainage techniques.

DEFINITION AND MECHANISMS OF POST-ERCP PANCREATITIS

Cotton *et al*[8] reported a consensus classification of ERCP-related complications. In the cited report, PEP was defined as a clinical syndrome, consistent with acute pancreatitis, associated with a serum amylase level at least three times the normal value, measured more than 24 h after the procedure, and requiring hospital admission or prolongation of planned admission. The severity of PEP is based primarily on the length of hospitalization. Mild PEP is defined as the need for hospital admission or prolongation of planned admission for up to 3 d; moderate PEP is defined by the need for hospitalization for 3-to-10 d; and severe PEP is defined by hospitalization for more than 10 d, or development of significant complications.

The underlying pathogenesis of PEP is thought to be multifactorial, and remains unclear, but numerous mechanisms of PEP induction have been proposed. These include difficult biliary access caused by biliary sphincter hypertension, repeated inadvertent pancreatic duct cannulation and contrast injection, secondary prolonged papillary edema caused by mechanical injury attributable to difficult papillary manipulations, and thermal injury caused by sphincterotomy[18,19]. Thermal injury may be caused by the electrocautery current applied during biliary or pancreatic sphincterotomy, endoscopic papillectomy, or ablation of neoplastic lesions in the region of the ampulla of Vater. Obstructions in the outflow of pancreatic juice may be caused by mechanical injury to the papilla and pancreatic sphincter attributable to use of instrumentation to manipulate the papilla. Chemical or allergic injury may be caused by instillation of contrast medium into the pancreas. Hydrostatic injury may occur after contrast injection into the pancreatic duct or infusion of water or saline through manometry catheters. Enzymatic injury may result from intraluminal activation of proteolytic enzymes as a result of introduction of foreign substances into the pancreatic duct. Infection may also play a role, after pancreatic instillation of flora from the intestine or from contaminated endoscopes or accessories. The results of all of these problems are varied, and include mechanical, chemical, and hydrostatic injury; and infection, triggering premature intracellular activation of proteolytic enzymes, which in turn causes further damage and stimulates local inflammation, as indicated by increased cytokine levels (those of interleukins 1, 6, and 8). If inflammation is severe, a systemic inflammatory response with multi-organ involvement may be activated[1,20,21].

Most strategies for preventing PEP, or decreasing the severity of this condition, have sought to interrupt a step of the inflammatory cascade before, during, or after

ERCP. Endoscopic prevention of PEP seeks to remedy the obstruction of pancreatic outflow caused by the various factors described above.

WIRE-GUIDED CANNULATION

Basic catheterization accompanied by contrast injection was the first cannulation technique developed in the era of ERCP cannulae, and probably remains the most widely used initial cannulation method for ERCP. However, when the first attempts at contrast injection fail, a guidewire may be used as a crossover method to facilitate selective biliary access and to reduce complications caused by prolonged cannula manipulation or contrast injection into the pancreatic duct. Of procedure-related factors, selective cannulation of the common bile duct (CBD) *via* insertion of a guidewire may cause fewer complications than do conventional methods (which use contrast injection to access the bile duct). Ideally, accessing the bile duct with the aid of a guidewire may reduce traumatic injury to the pancreatic duct and papilla, and avoid the buildup of hydrostatic pressure associated with contrast injection, thereby reducing development of ERCP-related pancreatitis[22-26].

Endoscopic technique

Technically, wire-guided cannulation is simple. Usually, a guidewire tipped with a hydrophilic substance, 0.035 or 0.025 inch in diameter, is preloaded into a pull-type papillotome. Next, the papillotome is oriented in the 11-to-12 o'clock position on the papilla, and bent to ensure correct alignment with the axis of the bile duct. In the direct contact method, after minimal insertion (2-3 mm) of the pull-type papillotome into the ampulla, the guidewire is carefully advanced through the CBD under fluoroscopic guidance until it is seen to enter the bile duct. It is also possible to attempt selective cannulation using the slightly (2-3 mm) protruding guidewire on the papillotome to make gentle contact with the papillary orifice. This non-contact method may seek to avoid direct injury caused by contact with the cannula or papillotome. If the pancreatic duct is entered, the guidewire is simply withdrawn and attempts are made to redirect it toward the CBD[22]. However, neither an adequate extent of guideline insertion nor the time that should be permitted for pancreatic duct insertion of the guidewire including retrials, has yet been defined. If unintentional pancreatic duct insertion occurs three-to-five times, it is appropriate to consider switching to another method, such as double-guidewire-induced cannulation, prophylactic PS insertion followed by a precut, transpancreatic septostomy, or early precut fistulotomy, to minimize complications. A precut following prophylactic PS placement may optimally decrease the frequency or severity of PEP, in contrast to use of early precut fistulotomy or double-guidewire-induced cannulation only although these techniques may improve the success rate of selective biliary cannulation.

Clinical outcomes

The PEP-protective effects of wire-guided cannulation remain controversial. In the study by Lella *et al*[25], no patient in a cohort of 200 randomly selected for bile duct cannulation using a soft polytetrafluoroethylene-tipped guidewire (tipped with Teflon; DuPont, Wilmington, DE) developed pancreatitis (0% in the guidewire group *vs* 4.1% in the control group, $P < 0.01$). The cited authors concluded that wire-guided cannulation reduced the frequencies of pancreatic injuries by preventing unintentional injection of contrast media into the main pancreatic duct or the papilla *per se*. However, the authors did not assess PEP frequency with respect to the difficulty of CBD cannulation (the number of cannulation attempts made). Artifon *et al*[23] also showed that use of the guidewire technique for bile duct cannulation lowered the frequency of PEP (8.6% in the guidewire group *vs* 16.6% in the conventional group, $P = 0.02$). The cited authors assessed the difficulty of CBD cannulation, and the numbers of unintentional pancreatic duct cannulations, and concluded that the reduction in PEP was mainly attributable to prevention of injection of contrast media into the pancreatic ducts. The guidewire technique reduced the risk of pancreatitis by facilitating cannulation, by potentially limiting papillary trauma, and by reducing the need to conduct precut sphincterotomies. Although the ranges of cannulation attempts were given as 0 to 3, 4 to 6, and 7 to 10, the investigators did not report the frequencies of PEP development in these subgroups (thus by number of attempts). Even when soft wires tipped with hydrophilic material are used in cannulations, difficult wire passage or frequent pancreatic manipulations may cause injury to the papilla, increasing the risk of PEP. Another randomized study by Lee *et al*[22] showed that wire-guided cannulation reduced PEP development. Totals of 3 patients [2%; 1 mild, 1 moderate, 1 severe (in terms of disease)] in the wire-guided cannulation group and 17 (11.3%; 14 mild, 2 moderate, 1 severe) in the conventional group developed PEP ($P = 0.001$). However, the study population may have been a low-risk cohort. Only seven patients with suspected SOD were included. Among patients with SOD, PEP is a well-recognized complication, occurring at frequencies of 10%-20%[8,19]. SOD independently increases the risk of PEP because of hypersensitivity of the papilla to trauma or an increase in hydrostatic pressure on the main pancreatic duct[3,8,27]. On the contrary, in the study by Vandervoort *et al*[5] guidewire- or sphincterotome-mediated cannulation seem to have been used as rescue methods in high-risk patients who failed conventional cannulation. This explains why the PEP rate was higher when guidewire cannulation was used. Thus, in the cited work, PEP was more frequent in the wire-guided cannulation group (10.2% after wire-guided cannulation *vs* 6.1% after conventional cannulation, $P = 0.04$). However, a recent meta-analysis of the data of five randomized controlled trials showed that the wire-guided technique increased the primary cannulation

Table 1 Prospective randomized trials of wire-guided cannulation to reduce the incidence of post- endoscopic retrograde cholangiopancreatography pancreatitis

	n	Design	Pancreatitis (*n*)/accidental PD (*n*) (WGC *vs* CC)[1]	Post-ERCP pancreatitis *n*/*n* (%)		*P* value
				WGC	CC	
Lella *et al*[25]	200/200	Prospective/Randomized	0/82, 5/113	0/197 (0)	8/195 (4.1)	< 0.01
Artifon *et al*[23]	150/150	Prospective/Randomized	0/27, 4/21	13/150 (8.6)	25/150 (16.6)	0.02
Bailey *et al*[24]	202/211	Prospective/Randomized	NA	16/202 (7.9)	13/211 (6.2)	0.48
Katsinelos *et al*[26]	167/165	Prospective/Comparative	NA	9/167 (5.4)	13/165 (7.9)	0.37
Lee *et al*[22]	150/150	Prospective/Randomized	2/39, 8/44	3/150 (2)	17/150 (11.3)	0.001
Mariani *et al*[28]	678/571	Prospective/Comparative	15/99, 8/95	35/678 (5.2)	25/ 571 (4.4)	0.60
Kawakami *et al*[29]	199/201	Prospective/Randomized[2]	NA	8/199 (4.0)	6/201 (2.9)	NS

[1]The number of post-ERCP pancreatitis following accidental PD injection or cannulation in CC and WGC group; [2]Multicenter RCT with a 2 × 2 factorial design. 0/82 *vs* 5/113, $P = 0.08$; 0/27 *vs* 4/21, $P = 0.05$; 2/39 *vs* 8/44, $P = 0.09$ by Fisher's exact test. PD: Pancreatic duct cannulation or contrast injection; WGC: Wire-guided cannulation; CC: Conventional cannulation; NS: Not significant; NA: Not available.

rate and reduced the risk of PEP compared to use of the standard contrast-injection method. Pooled analysis of PEP rates in wire-guided cannulation groups compared to those in groups treated using standard methods yielded an OR of 0.23 (95%CI: 0.13-0.41). Also, use of the wire-guided technique was associated with a significantly higher primary cannulation rate (OR = 2.05; 95%CI: 1.27-3.31). Although the meta-analysis included a relatively small number of studies, each work employed different cannulation difficulty criteria (involving cannulation times or numbers of attempts made), and, indeed, some studies did not define their criteria. Three well-designed studies using wire-guided cannulation techniques showed that use of such cannulation could reduce the development of PEP[22,23,25]. However, other recent reported studies have yielded contrary results. Mariani *et al*[28] found that the PEP rates in high- and low-risk patients did not differ between wire-guided cannulation and contrast injection groups (5.2% *vs* 4.4%). In a multicenter randomized study performed by Kawakami *et al*[29], it was also shown that wire-guided cannulation did not reduce the incidence of PEP compared with use of a conventional method (Table 1). In both studies, trainees conducted (some) procedures. When used as an initial cannulation method, wire-guided cannulation seems to shorten cannulation times, as revealed in numerous studies, but any benefit in terms of reducing PEP development is now controversial.

The mechanisms by which guidewire cannulation reduces PEP risk remain uncertain. In the meta-analysis of Masci *et al*[30], several technical issues, including multiple contrast injections into the pancreatic duct, difficult cannulation, precutting, pancreatic sphincterotomy, and balloon dilatation of the sphincter of Oddi, were identified as risk factors for PEP. Notably, the definition of "difficult" cannulation is imprecise, being both subjective and varying among studies. In the report on wire-guided cannulation by Lee *et al*[22], the definition used was failure to achieve biliary access after attempting to do so for 10 min, or after more than five unintentional pancreatic cannulations. Artifon *et al*[23] defined cannulation as difficult when 7-10 attempts were required to ultimately achieve cannulation. Recent studies suggest that the guidelines for difficult cannulation should be stricter. Large, well-performed, randomized controlled studies aiming to establish cannulation difficulty criteria are needed to resolve these controversies. Also, wire-guided cannulation may not prevent PEP in patients with suspected SOD and who are subjected to unintentional pancreatic duct guidewire cannulation. In high-risk patients, such as those with SOD, repeated unintentional pancreatic duct guidewire cannulation may trigger PEP caused by mechanical trauma or increases in hydrostatic pressure attributable to repeated introduction of a guidewire into the main pancreatic duct. In instances of unintentional pancreatic duct guidewire cannulation, therefore, wire-guided cannulation followed by temporary placement of a PS may be preferred over wire-guided cannulation alone to prevent increases in pancreatic enzyme levels and to reduce the frequency or severity of PEP in high-risk patients[5,22,31,32].

In summary, primary wire-guided cannulation in experienced hands can reduce cannulation time and facilitate successful biliary access, and may reduce the frequency and/or severity of PEP. However, more large-scale comparative studies that consider race, high-risk status, and operator experience, are required to confirm the existence of any prophylactic effect.

PRECUT SPHINCTEROTOMY

Pros and Cons

Precut sphincterotomy is an essential rescue technique in instances of difficult biliary cannulation. Irrespective of the technique used, the initial success rates of precut sphincterotomy have previously been reported to be as high as 90% during the first attempt, with success rates of 95%-99% following second attempts conducted 48-72 h later after edema and inflammation had subsided. In precut methods, various techniques including needle-knife sphincterotomy with or without PS guidance, fistulotomy (infundibulotomy), and transpancreatic sphincterotomy, are used, although few data are available to aid in the selection of a procedure[33-40]. The overall complication rates after precut sphincterotomy have been reported to vary from 1.9% to 34%, compared to rates of 7%-14%

with conventional sphincterotomy. PEP is the most common and serious complication; the rates range from 2.1% to 14.9%, compared to the 1%-10% associated with conventional sphincterotomy[3,33-46].

Although precut sphincterotomy may be an effective rescue technique, such sphincterotomy using a needle-knife has been directly implicated as a primary cause of PEP. Therefore, this technique has been considered potentially dangerous, especially when performed by less-experienced endoscopists. Most authorities recommend that only experts perform a precut. However, recent studies have shown that the complications of precut sphincterotomy are similar to those associated with conventional sphincterotomy, namely bleeding, PEP, perforation, and cholangitis[33,43,46-49]. In terms of the endoscopist learning curve ensuring the safety and success of precut sphincterotomy, Akaraviputh *et al*[47] reported that the rate of procedure-related complications decreased significantly after the first 100 procedures were performed. Also, among all complications, the rate of immediate bleeding varied significantly, but the success of cannulation or the rate of PEP development did not differ with endoscopist experience. Lee *et al*[33] obtained similar results. The frequency of PEP in 159 patients who underwent precut fistulotomy did not differ by time interval. In the cited study, the risks associated with use of precut fistulotomy under circumstances where biliary cannulation was employed were not influenced by experience. Thus, the overall complication and PEP rates were similar; *i.e.*, not differing significantly, from those reported previously, at 10.7% and 5.7%, respectively, and the overall success rates were also similar, at 93.7%. No other serious complications were noted.

Consequently, most criticisms of the (supposedly) higher complication rates associated with precut sphincterotomy may be unwarranted. The high frequencies of post-procedural complications after such sphincterotomy may be associated with excessively edematous major papillae and extensive injuries caused by multiple or prolonged attempts to cannulate the CBD by standard methods before precut sphincterotomy. Huibregtse *et al*[49] showed that early implementation of precut increased successful biliary access on the first attempt, as well as the overall success rate, while reducing the rate of complications to 11.8% (pancreatitis: 0.5%). Previous repeat cannulation attempts, prolonged cannulation time, or numerous insertions of a guidewire into the pancreatic duct, may increase the risk of PEP. Freeman *et al*[3] reported that moderate numbers of cannulation trials (6-15), or more-than-moderate numbers (> 15), and use of more than one pancreatic contrast injection, were important in terms of the development of pancreatitis; multivariate analysis was used to arrive at these conclusions. Lee *et al*[33] showed that more than 15 attempts at cannulating the major papilla prior to precut fistulotomy was a risk factor for PEP development upon multivariate analysis (OR = 4.8, 95%CI: 1.178-19.580, P = 0.029). Bailey *et al*[41] also found that the number of attempts at cannulating the papilla played a key role in guiding decision-making to minimize the risk of PEP. Thus, if precut fistulotomy is indeed a treatment candidate, early implementation of this approach may aid in successful selective biliary cannulation as well as reducing the severity of PEP. On the contrary, Cennamo *et al*[50] reported that the timing of precutting did not influence the operative success rate or the rate of complications associated with ERCPs. The cited authors showed that the rates of PEP did not differ between subgroups treated with early precutting (no more than 5 min of attempts at biliary cannulation using the standard approach, and three cannulations of the pancreatic duct) and delayed precutting (cannulation attempts lasting 25 min). However, the cited study had a small sample size and, thus, a low statistical power. A recent meta-analysis of early precut studies (although including precuts performed at different times and the use of various techniques including needle-knife precutting starting at the orifice, and fistulotomy) showed that early precut implementation reduced the PEP risk (to 2.5% *vs* 5.3%, OR = 0.47, 95%CI: 0.24-0.91) but not the overall complication rate[51].

Theoretically, the greater number of complications could have resulted from direct thermal injury caused by the needle-knife *per se*, especially during precut sphincterotomy, in which incisions commenced at the papillary orifice. Avoidance of thermal injury to the pancreatic duct, by making incisions above the papillary orifice during precut fistulotomy, minimizes the risk of pancreatitis[35,36,46]. However, too small a papilla, a short papillary roof, distortion caused by invasion of a tumor or a mass, or location of the ampulla of Vater on the inner center or ridge of a huge periampullary diverticulum, may preclude use of precut fistulotomy[33].

In summary, although some aspects of the timing and optimal type of precut sphincterotomy remain controversial, as does the need for endoscopist experience, use of early precut fistulotomy in patients for whom cannulation is difficult may not exacerbate PEP to an extent greater than conventional methods. In instances of persisting papillary contact or prolonged cannulation time, early precut fistulotomy may minimize the severity of PEP by decreasing mechanical trauma. However, a definition of a "difficult" cannulation, and adequate training in precut sphincterotomy are required, as are data from more large-scale multicenter studies.

Transpancreatic sphincterotomy/septostomy

Transpancreatic sphincterotomy or septostomy is a technique involving cutting of the septum that separates the pancreatic duct from the bile duct, through the pancreatic orifice[52]. Unlike a freehand technique such as use of a needle-knife, transpancreatic papillary septostomy in patients for whom cannulation is difficult, or who experience unintentional pancreatic duct cannulation, can be performed using a papillotome, without exchange of devices, after guidewire introduction into the pancreatic duct; or indeed without a guidewire. When unintentional

Table 2 Studies for the use of pancreatic stents to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis

Study	Design	Indications	PEP rate		
			n	Non-stent/stent (%)	*P* value
Smithline *et al*[63]	RCT	Biliary ES for SOD, small ducts, or precut	93	18/14	0.229
Aizawa and Ueno[31]	Retrospective case-control	Biliary balloon dilatation for stone	40	6/0	0.110
Fogel *et al*[18]	Retrospective case-control	Biliary ± pancreatic ES for SOD	436	28.2/13.5	< 0.05
Fazel *et al*[32]	RCT	Difficult cannulation, biliary ES, SOD	76	28/5	< 0.05
Freeman *et al*[19]	Prospective case-control	Consecutive high-risk ERCP in which a major papilla PD stent was attempted	225	66.7/14.4	0.060
Harewood *et al*[58]	RCT	Endoscopic ampullectomy	19	33/0	0.020
Sofuni *et al*[64]	RCT	All consecutive ERCP (excluding pancreatic cancer, pancreas divisum, PD therapy cases)	201	13.6/3.2	0.020
Tsuchiya *et al*[66]	RCT	All consecutive ERCP irrespective of risk factors	64	12.5/3.1	> 0.05
Saad *et al*[70]	Retrospective nonrandomized	Suspected SOD and normal manometry	403	9/2.4	0.006
Lee *et al*[59]	RCT	Difficult biliary cannulation	101	29.4/12	0.031

ES: Endoscopic sphincterotomy; SOD: Sphincter of Oddi dysfunction; RCT: Randomize controlled study; PD: Pancreatic duct; PEP: Post-ERCP pancreatitis.

pancreatic duct cannulation has occurred, the procedure is relatively easy. Wire-guided septostomy is performed after introducing a soft guidewire into the pancreatic duct, and sphincterotomy follows, maintaining the bile duct orientation at 11 o'clock. If the septum between the pancreatic and bile ducts is incised, the biliary and pancreatic orifices become separately visible[52-54]. Another useful option for septostomy is a precut following placement of a prophylactic PS along the stent. This may primarily prevent PEP and also facilitates selective biliary access. This means that the second procedure, the precut from the orifice, is relatively easy; the operator is more comfortable in such circumstances than is the case when a freehand technique such as fistulotomy is to be performed. Either a precut from the orifice or fistulotomy is possible, but precutting from the orifice in the biliary direction along a supporting stent may be more feasible than use of the freehand technique. The prophylactic effects of PSs are described below.

PROPHYLACTIC PLACEMENT OF PANCREATIC STENTS

Pancreatic stents were originally introduced to treat pancreatic ductal pathology such as benign or malignant strictures and ductal leaks after trauma or surgery. The exact mechanism by which PSs may reduce the risk of PEP is but poorly understood. The stents probably preserve pancreatic drainage that otherwise might be impaired by mechanical injury to the pancreatic sphincter caused by prolonged or repeated manipulations of catheters and guidewires and thermal injury caused by biliary and pancreatic sphincterotomy or snare papillectomy. Many clinical trials and a meta-analysis have shown that placement of PSs in high-risk patients effectively reduces the incidence and/or severity of PEP. Recent studies have found that prophylactic placement of a PS reduces the frequency and severity of PEP in particular high-risk groups, including those with known or suspected SOD; those who have undergone papillectomy, precut sphincterotomy, or pancreatic sphincterotomy; those with a history of PEP; or those for whom cannulation is difficult (Table 2)[18,31,32,55-70]. Prophylactic placement of PSs is now increasingly adopted to reduce the risk of PEP. PS placement also reduces the frequency of severe PEP[18-21,31,32,55-68].

Presently, the routine use of PSs in high-risk patients and in procedures conducted at advanced centers has changed attitudes toward ERCP; the incidence and severity of PEP have been reduced to more acceptable levels. However, few data are available on the effects of prophylactic PSs, especially in terms of technical difficulties in the context of cannulation time or the frequency of papillary contact[56,61,69]. Also, the sizes and lengths of the stents employed have been variable, and no guideline or consensus yet exists on the optimal type, diameter, or length of a PS.

Ideal types of pancreatic stents

PSs vary in terms of diameter, length, and shape. An ideal PS should completely prevent development of PEP, be easily deployed, spontaneously dislodge after exerting an adequate preventative effect, and not cause ductal or parenchymal pancreatic changes[71]. In terms of such changes, a retrospective analysis of 34 patients with 38 PSs placed to deal with disrupted ducts, isolated strictures, pancreas divisum, and hypertensive pancreatic sphincters, found that 36% of all patients exhibited subsequent ductal changes[72]. Also, a study on the dog pancreas showed that polyethylene PSs caused histopathological changes in normal tissues attributable to stent occlusion or local stent-induced trauma[73]. These results suggest that PSs may cause permanent changes to the pancreatic duct or parenchyme. If the placement time is too short, a smaller and shorter stent may not sufficiently protect against PEP development. Short stents (less than 3 cm long) are generally preferred to longer stents to avoid stenting across the neck of the pancreatic duct. However, longer stents should be considered when the pancreatic duct is angulated in the head of the pancreas. Stents may be straight, or may have a single pigtail or partial curl in the

Table 3 Efficacy of 3- *vs* 5-F pancreatic stents in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

	Technical success	Spontaneous migration	PEP	Stents
Rashdan *et al*[61] (3 F *vs* 4, 5, 6 F)	NA	86%/73%/67%/65%[1] ($P < 0.01$)	7.5%/10.6%/9.8%/14.6% ($P = 0.047$)	COOK, 4-12 cm
Chahal *et al*[56] (3 F *vs* 5 F)	91%/100% ($P = 0.0003$)	88%/98% ($P = 0.0001$)[2]	14%/9% ($P = 0.3$)	3 F, 8 and 10 cm/5 F, 3 cm
Zolotarevsky *et al*[69] (3 F *vs* 5 F)	97.5%/100%	75%/68.4% ($P = 0.617$)[2]	17.5%/10.5% ($P = 0.519$)	COOK, Zimmon 3 F, 3 cm/ 5 F, 5 cm

[1]10-14 d; [2]2 wk. PEP: Post-ERCP pancreatitis; NA: Not available.

duodenum, to prevent proximal migration. Short stents without proximal flaps facilitate early spontaneous migration (within 1 wk). Thus, establishment of drainage may be not assured when stents without proximal flaps are used because of the potential for very early stent migration. However, stents with flaps require endoscopic removal at a later date. Another option is to place longer (> 7 cm) stents of small diameter (3 or 4 F) that have no proximal flaps. This practice has the potential advantages of less ductal trauma and spontaneous distal migration; repeat endoscopy is not necessary[74]. A large retrospective study suggested that unflanged longer-length (8-10 cm) 3 F polyethylene stents with single duodenal pigtails were associated with significantly higher spontaneous dislodgement rates compared to larger-caliber, shorter unflanged 4 or 5 F stents. The cited study also reported a somewhat lower incidence of PEP in patients who received 3 F compared with 5 F stents, although the difference was not statistically significant[61]. Another study by Chahal *et al*[56] compared use of long 3 F and short 5 F stents and showed that the spontaneous dislodgement rate of unflanged, short 5 F PSs (98%) was significantly higher than that of unflanged, long 3 F stents (88%) after 14 days in patients at high risk for PEP development ($P < 0.01$). Placement of short stents reduced the need for later endoscopic stent removal. Higher rates of PS placement failure (0% in the 5 F group but 8.3% in the 3 F group, $P = 0.0003$) and PEP (14% in the 3 F group and 9% in the 5 F group, $P = 0.3$) were observed in patients with 3 F stents. Recently, Zolotarevsky *et al*[69] reported that placement of 5 F compared to 3 F PSs for PEP prophylaxis was easier, more rapid, and required fewer wires. However, no statistically significant differences in spontaneous passage rates (68.4% in the 5 F group; 75.0% in the 3 F group; $P = 0.617$) or PEP rates ($P = 0.519$) were evident (Table 3).

The prophylactic utility of placing smaller 3 F stents during difficult biliary cannulations has undergone little evaluation. Technically, the failure rates in previous studies involving placement of 3 F PSs after therapeutic ERCP have been rather high (9%-10%)[56,63]. The main problem is that a guidewire of smaller diameter than the standard 0.035-inch wire must be used. Deployment of long 3 F PSs is technically more difficult because of the need to use smaller caliber (0.018- or 0.021-inch) guidewires, which can be difficult to maneuver around tortuous pancreatic ducts compared to a hydrophilically tipped 0.035-inch guidewire. Placement of long stents also requires deeper guidewire access into the main pancreatic duct, which may not be possible in patients with highly angulated or tortuous ducts. Thus, usually, placement of a 5 F PS using a 0.035-inch guidewire may be valuable to allow easy negotiation of the pancreatic duct and stent deployment. However, one recent randomized controlled trial evaluating the feasibility and utility of smaller and shorter (4-8 cm) 3 F stents showed that placement of a 3 F PS was technically feasible, significantly reduced the rate of PEP developing after difficult biliary cannulations, and that a higher rate of distal spontaneous dislodgement (94%) was evident within 7 d. The technical failure rate when experts operated was low (4%), and no complications resulted from PS placement[59]. The use of smaller-sized guidewires may require extensive endoscopic experience and skilled assistance.

Timing of pancreatic stent placement

It is unclear whether stents should be placed before or after therapeutic procedures such as sphincterotomy, stone extraction, and biliary stent placement, but early placement of a PS may be beneficial because various procedure-related factors may contribute to development of PEP. A retrospective study by Fogel *et al*[18] found that pancreaticobiliary sphincterotomy with PS placement was associated with a lower rate of pancreatitis than was biliary sphincterotomy alone. The cited authors noted a tendency for pancreatitis rates to be lower when a PS was placed before major papillar pancreatic or biliary sphincterotomy (10.7%), than after sphincterotomy (19.2%). Another retrospective study reported similar complication rates upon traction minor papillotomy followed by PS placement, compared with needle-knife surgery after PS placement (8.3% *vs* 7.8%)[75]. A recent randomized trial comparing use of the needle knife and pull-sphincterotome techniques for pancreatic sphincterotomy in high-risk patients showed that PEP was significantly more frequent among patients undergoing pancreatic sphincterotomy with a pull sphincterotome followed by placement of a PS than in those treated with needle-knife pancreatic sphincterotomy performed after placement of a PS [7 of 24 (29%) *vs* 0 of 24 (0%), $P < 0.01$]. Forty patients undergoing major papillar pancreatic sphincterotomy for manometrically documented SOD were randomized to traction sphincterotomy using a blended current followed by placement of a PS *vs* needle-knife sphincterotomy after placement of a stent; all patients received long, unflanged 3 F stents[76].

Access to the pancreatic duct after biliary sphincterotomy or other biliary therapy such as balloon dilatation or stone extraction is sometimes very difficult. Failure usually occurs either because the pancreatic orifice cannot be identified or a guidewire cannot be deeply advanced into the pancreatic duct. Also, deep pancreatic cannulation can be difficult or impossible when, anatomically, looping or tight angulations are evident in the distal pancreatic duct. For such reasons, it is recommended to access the pancreatic duct with a guidewire early in the procedure and to maintain wire access until a stent has been placed in high-risk cases in which PS placement is believed to be warranted[19,74]. However, sometimes, repeat procedures such as stone extraction using a retrieval balloon, or mechanical lithotripsy, may dislodge the guidewire or preloaded stent even though the stent was placed using a guidewire.

Usually, prophylactic PS placement, rather than only maintaining a guidewire, may be reasonable before any therapeutic procedure. This suggestion is based on the data of the studies reported above, but further large-scale, prospective studies are warranted.

Duration of pancreatic stent placement

Few data are available to indicate the duration for which a PS should remain in place to effectively prevent PEP. Cha *et al*[55] reported that the rates of pancreatitis were significantly higher in patients from whom PSs were removed immediately after needle-knife precut sphincterotomy compared to those in whom the stents were left in place for 7-10 d (21.3% *vs* 4.3%, $P = 0.027$). These data suggest that placement and maintenance of a PS when needle-knife precut sphincterotomy is performed reduces the frequency and severity of PEP. The cited study also showed that excessively early removal of a PS might not effectively prevent development of pancreatitis. However, no data regarding the adequacy of the duration of stenting that is needed to consistently prevent PEP are available. This may be anywhere from a few hours to a week or more. The precise duration of PS placement required to effectively reduce the risk of PEP is not well known.

In general, stent removal at the end of ERCP is not recommended. Excessively early removal of a PS may increase the risk of pancreatitis. However, removing a stent too late may increase the risk of ductal or parenchymal change. Ideally, the PS should be in place for a minimum of 24 h or more, and then dislodge spontaneously[2].

Pancreatic stent-related complications

Relapsing acute and chronic (painful) pancreatitis can develop in patients with pancreatic stent-induced injuries. However, the long-term outcomes of PS placement have not yet been thoroughly investigated although it is assumed that most ductal injuries are transient, eventually resolving spontaneously, without clinical symptoms. A large-scale retrospective study suggested that unflanged longer (8- to 10-cm), 3 F polyethylene stents with single duodenal pigtails were associated with a substantially reduced frequency of ductal change (24% for 3 and 4 F stents compared to 80% for 5 and 6 F polyethylene stents)[61]. This may indicate that use of smaller-caliber stents is associated with a reduced risk of ductal injury. Ductal and parenchymal changes may be most prominent in patients with traditional 5 or 7 F stents, because which may be of similar caliber to the native main pancreatic duct. The stent diameter should be less than that of the pancreatic duct.

Summary of use of prophylactic pancreatic stents

In prophylactic PS placement, a long PS of smaller diameter (3 F) may dislodge spontaneously within a few weeks without any ductal change, but small guidewires (0.018 or 0.021 inch) are required, and such small guidewires may be difficult to handle and to insert deeply into the tail portion. On the other hand, placement of short (2-3 cm) 5 F unflanged stents can commonly be achieved using 0.035-inch guidewires that can be handled relatively easily by endoscopists. Also, over 90% of such stents dislodge spontaneously. However, a stent that is too short may migrate soon after insertion, thus failing to prevent PEP and (perhaps) causing injury to the duct genu because of the short length. To effectively prevent PEP, the duration of stent placement that is adequate, without causing ductal or parenchymal change, should be determined. Finally, careful study of an ideal stent design, and the material used, is warranted. All of easy stent insertion, risk reduction, and spontaneous dislodgement in a timely fashion without ductal injury, are required. We suggest that short 5 F, or long 3 F, stents without inner flanges should be used to stent a normal pancreatic duct. The stent diameter should be less than that of the targeted pancreatic duct. However, endoscopists should remember that technical failure of PS insertion might aggravate the severity of pancreatitis, so that the procedure *per se* unfortunately becomes a risk factor.

OTHER ALTERNATIVES

Repeat or delayed ERCP

Repeat or continuing attempts at cannulation increase the risk of PEP, as explained above. When primary cannulation fails, the alternatives include PTBD, repeat ERCP conducted by same or another endoscopist (perhaps in a more advanced institution) after 2-3 d of delay, or surgical exploration[77,78]. Of these approaches, delayed ERCP performed 2-3 d later by the same endoscopist may increase the success rate of selective cannulation and also reduce the complication risk to within an acceptable range by avoiding excessive papillary manipulation or unintentional ductal injury. Delayed ERCP may afford a good visual field, without papillary edema or bleeding, and reduce the rapid bowel movement that develops with longer procedure times, in turn reducing the need for additional procedures and enhancing successful biliary cannulation. However, excessively prolonged manipulations during primary cannulation attempts are inevitably

associated with complications. A decision to interrupt a procedure should be considered as early as possible.

Percutaneous transhepatic biliary drainage

Percutaneous transhepatic biliary drainage (PTBD) is the most common salvage procedure used to access the biliary tract after failure of ERCP. Especially in patients with advanced malignant hilar biliary strictures, percutaneous drainage may be more feasible than endoscopic drainage. To palliate jaundice in patients with non-resectable malignant hilar biliary strictures, the biliary obstruction pattern (particularly the Bismuth type) should be considered before selection of an optimal drainage method. Endoscopic biliary drainage and stenting is recommended as the first-line drainage procedure in Bismuth type Ⅱ patients, considering that this approach is efficacious and relatively noninvasive. However, internal stent insertion and drainage through the PTBD tract may be the best option for Bismuth type Ⅳ[79] patients. One retrospective study found that the success of biliary drainage was significantly higher when drainage was percutaneous rather than endoscopic (93% *vs* 77%, $P = 0.049$)[80]; no between-group differences in overall complication rates or the median survival time of successfully drained patients were evident. The goal of palliative drainage of hilar cholangiocarcinoma patients is drainage of an adequate liver volume (50% or more), irrespective of unilateral, bilateral, or multisegmental stenting. In patients of Bismuth types Ⅲ or Ⅳ, the percutaneous approach was preferred over the endoscopic approach in a document detailing Asia-Pacific consensus recommendations[81]. However, PTBD-related adverse event rates of 9%-33%, and mortality rates of 2%-15%, have been reported[82-85]. Furthermore, in terms of quality of life, long-term placement of external catheters is very uncomfortable for patients. Also, recent studies on bilateral metallic stenting have enjoyed high levels of technical success, and a reduced revision rate, even in patients with advanced hilar cholangiocarcinoma[86-88].

The choice of an endoscopic approach or PTBD may depend on endoscopist experience and institutional guidelines. In the near future, advanced endoscopic techniques and newly developed devices may improve endoscopic methods. However, in terms of complications, in particular PEP, primary PTBD does not irritate the ampulla of Vater. Accordingly, in difficult cases, and in advanced hilar cholangiocarcinoma patients requiring adequate drainage, PTBD can be both an alternative option and a rescue method.

FUTURE ADVANCES IN ENDOSCOPIC PROCEDURES

Repeated cannulation attempts and pancreatic duct manipulations on the ampulla of Vater are associated with PEP development, caused by inevitable contact with the papilla. Thus, theoretically, PTBD, or EUS-guided biliary drainage (EUS-BD), may serve as alternatives to ERCP when it is performed to inhibit development of pancreatitis by avoiding direct contact with the ampulla of Vater. Recent studies have shown that EUS-BD is an effective alternative to PTBD after failure of ERCP. Also, a potential benefit of EUS-BD is internal drainage, thereby avoiding long-term external drainage in patients who are expected to enjoy longer survival and in those for whom external PTBD drainage catheters cannot be internalized. However, EUS-BD with transluminal stenting is inherently complex in procedural terms, requiring several multi-step processes, thus prolonging procedure times, in turn associated with the possible development of several adverse events, including stent migration and bile peritonitis[89-93]. Also, EUS-guided drainage techniques have been but recently developed and no dedicated devices or guidelines are yet available. Procedure-related complications including bile peritonitis or pneumoperitoneum are not uncommon. To date, the procedure has been performed by only experienced endoscopists in advanced endoscopy centers, usually as a salvage method rather than as a form of primary biliary drainage. Further development of technical devices and establishment of standard techniques minimizing complications are needed. Also, further long-term follow-up in the context of large-scale studies (including primary intervention to ensure biliary drainage) are required before the technique can be recommended for primary use.

SUGGESTED ALGORITHM FOR ENDOSCOPIC PREVENTION OF POST-ERCP PANCREATITIS

Prior to ERCP, patient selection considering risk stratification, operator-related factors, and hospital circumstances, should be considered, and efforts should be made to avoid unnecessary ERCP by diagnostic replacement with EUS or MRCP, if possible. Trainee involvement must be taken into account. If possible, pharmacological prophylaxis - such as rectal NSAIDs - should also be considered. We recommend wire-guided rather than conventional cannulation as the initial cannulation method. If unintentional pancreatic duct cannulation occurs more than three times, it may be wise to consider changing to double-guidewire cannulation or transpancreatic septostomy to enhance biliary access. However, in such instances, precutting from the orifice following early prophylactic PS placement may be more effective to reduce the severity of PEP. If attempts at double-guidewire cannulation persist for some time or a technical difficulty is encountered, an early switch to a precut following prophylactic PS placement should be considered. Also, the use of a double-guidewire cannulation technique may increase the risk of complications caused by additional frequent papillary contact, or pancreatic duct cannulation, even though use of the method may facilitate selective biliary cannulation. Transpancreatic sphincterotomy may be also a risk factor for PEP if pancreatic juice passage is disturbed.

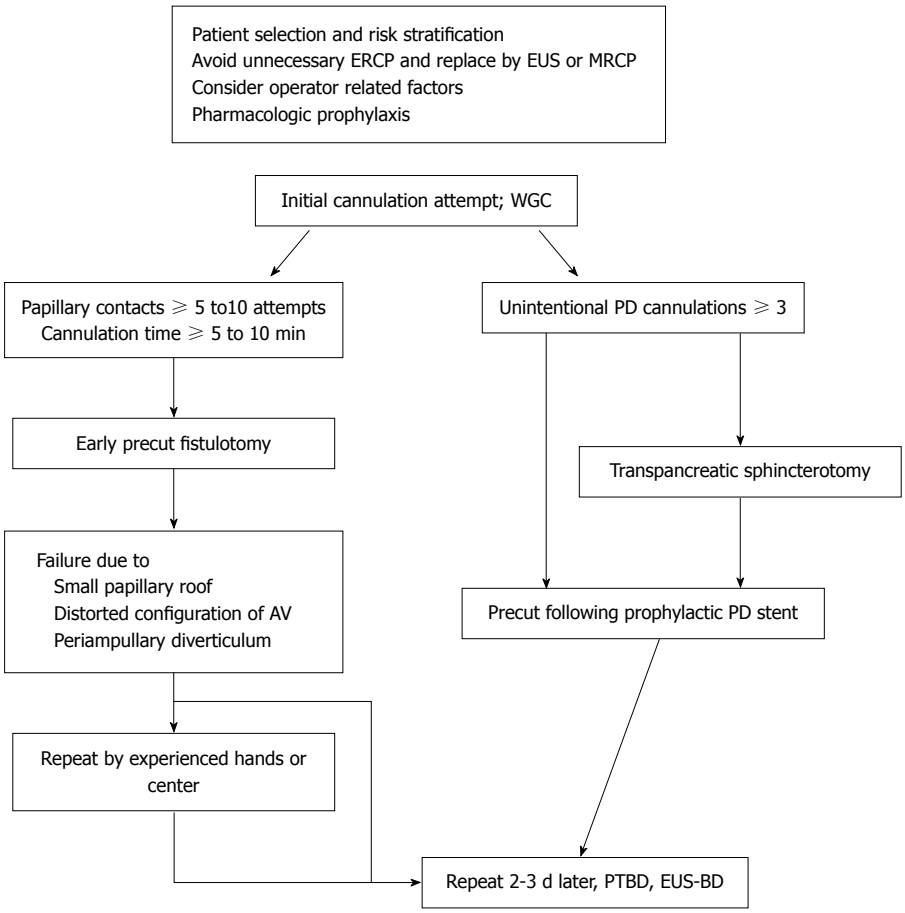

Figure 1 Suggested endoscopic algorithm for decreasing the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis and facilitating biliary access. WGC: Wire-guided cannulation; AV: Ampulla of Vater; PD: Pancreatic duct; PTBD: Percutaneous transhepatic biliary drainage; EUS-BD: EUS-guided biliary drainage.

Thus, risky operative conditions, such as a prolonged procedure time (more than 5-10 min), or technical failure of selective cannulation, should trigger consideration of prophylactic pancreatic stenting. Otherwise, if frequent papillary contacts persist (if more than 10 cannulation attempts, or at the very most up to 15 attempts, are made), or the cannulation time is more than 5-to-10 min without unintentional pancreatic cannulation, early precut fistulotomy can be considered. However, if the papilla is too small, the segment of the papillary roof short, a periampullary diverticulum present, or the ampulla is located in the center of the ridge of the diverticulum, a precut may be disturbed. In those cases, PTBD, EUS-BD, the rendezvous technique, repeat ERCP performed by a senior experienced endoscopist, or delay in ERCP for 2 or 3 d, should be considered. Use of such a step-wise algorithm may enhance successful biliary access and avoid unnecessary prolongation of procedure time (Figure 1). However, such options should be considered against a background of hospital circumstances and the availability of endoscopists.

CONCLUSION

Various endoscopic or interventional techniques including primary wire-guided cannulation, precut fistulotomy, transpancreatic septostomy, prophylactic PS placement, or alternatives such as PTBD or EUS-BD, have been described above as prophylactic methods for the decreasing severity or frequency of PEP. Till now, prophylactic PS placement in high-risk patients or those treated with certain procedures may be the single most effective method to reduce the severity and/or frequency of PEP. Improvements in stent design and the materials used in stent construction are to be expected. Also, the optimal timing of stent placement and its duration require study. Wire-guided cannulation and precut fistulotomy should be compared using strict definitions of "difficult" cannulation, endoscopist experience, and racial or regional characteristics. Furthermore, as either alternative or primary methods, PTBD or more advanced EUS-guided techniques may be available in difficult or failed cannulation. Finally, recently emerging pharmacological prophylaxis, such as rectal NSAIDs, should be considered either in combination, or alone, in large-scale comparative studies.

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