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Preventing Post-ERCP Pancreatitis

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INTRODUCTION

Since the introduction of endoscopic biliary sphincterotomy during endoscopic retrograde cholangiopancreatography (ERCP) for the management of retained or recurrent bile duct stones in 1974,[1,2] the procedure has become a widely employed treatment modality for a variety of clinical indications. Pancreatitis remains the most common severe complication of ERCP, the incidence of which has been estimated to range from 1.6 to 15 percent, with most studies demonstrating rates of 3 to 9 percent.[3-7] The severity of post-ERCP pancreatitis (PEP) can range from minor, with post procedure abdominal pain resulting in one or two days added hospitalization followed by a full recovery, to a devastating illness with pancreatic necrosis, multi-organ failure, permanent disability, and, rarely, death. The reported incidence of severe PEP is estimated to be 0.3% to 0.6%.[8,9] Therefore, precise identification of risk factors for PEP is essential to the recognition of high-risk cases in which ERCP should be avoided if possible, or in which protective endoscopic or pharmacologic measures should be considered.

The general consensus is that risk factors for PEP can be classified as operator-, patient-, or procedure-related. Operator-related risk factors include inadequate training, lack of experience, poor patient selection, and poor technique. Patient-related risk factors include young age, female sex, history of recurrent pancreatitis, normal serum bilirubin, prior history of PEP and sphincter of Oddi dysfunction. Procedure-related risk factors include difficult cannulation, repeated pancreatic injection, pancreatic sphincterotomy and endoscopic papillary large-balloon dilation of an intact sphincter.[10] Several prophylactic pharmacological and procedural strategies have been deployed to prevent the occurrence of PEP in selected

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patients. Administration of pharmacological agents including non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and indomethacin, protease inhibitors such as gabexate mesilate and ulinastatin, as well as other agents including somatostatin and glucocorticoids, prior to the procedure has been studied for the prevention of PEP.[11] Other strategies including the use of periprocedural intravenous fluid administration as well as use of pancreatic stents have also been extensively studied. This article will describe each of these management strategies and summarize the quality of evidence for each of them.

1. PHARMACOLOGICAL PROPHYLAXIS STRATEGIES

A. Non-Steroidal Anti-Inflammatory Drugs

It is believed that the local and systemic inflammatory response induced by ERCP is the pathophysiological event that triggers PEP.[12,13] It has been proposed that phospholipase A2 (PLA2) plays an important role in the pathogenesis of this inflammatory response. In vitro assays have shown that NSAIDs are potent inhibitors of PLA2 activity, resulting in the suppression of several important classes of pro-inflammatory lipids (prostaglandins, leukotrienes and platelet activating factor), thereby reducing the occurrence of PEP.[14] Given that indomethacin, followed by diclofenac, are the most effective PLA2 inhibitors, their use has been proposed, and widely adopted, at many centers, for reducing the risk of PEP, and reducing the severity of PEP among those who develop it. (Figure 1)

Preliminary studies from early 2000s evaluating the protective effects of single-dose rectal indomethacin or diclofenac among patients undergoing ERCP have suggested a benefit.[15-17] Elmunzer et al. conducted a meta-analysis including four randomized controlled trials (RCTs), with a total of 912 patients, and found that the pooled relative risk (RR) for PEP after prophylactic administration of NSAIDs was 0.36 (95% Confidence Interval (CI) 0.22-0.60). Patients who received NSAIDs in the periprocedural period were 64% less likely to develop pancreatitis and 90% less likely to develop moderate to severe pancreatitis.[18] This was followed by a landmark multicenter, randomized, placebo-controlled, double-blind clinical trial specifically including patients at elevated risk for PEP. Patients received a single 100 mg dose of rectal indomethacin or placebo immediately after their ERCP. Among 602 patients, majority of whom had a clinical suspicion of sphincter of Oddi dysfunction, PEP developed in 9.2% patients in the indomethacin group and 16.9% patients in the placebo group (P=0.005).[19]

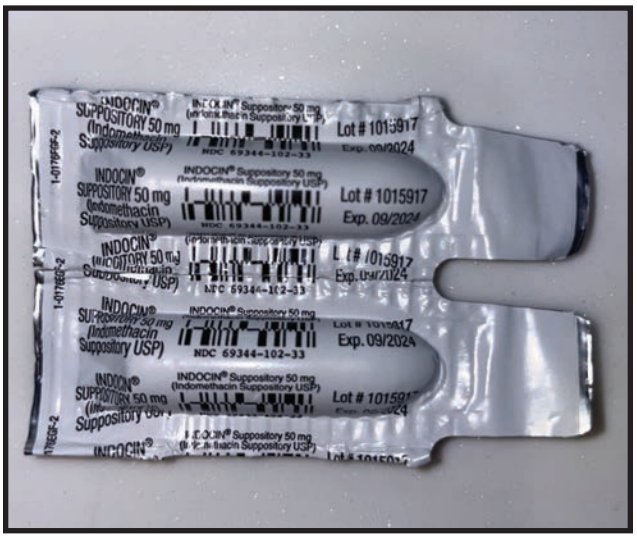

Figure 1. Indomethacin suppositories as commonly used in patients undergoing ERCP.

While several subsequent RCTs have reported similar results, favoring the use of rectal indomethacin,[20,21] Levenick et al. conducted a prospective, double-blind, placebo-controlled trial of 449 consecutive patients in which patients were assigned randomly to groups given either a single 100 mg dose of rectal indomethacin (n = 223) or a placebo suppository (n = 226) during the procedure. They found that giving a single 100 mg dose of rectal indomethacin in consecutive, unselected individuals undergoing ERCP did not prevent PEP. Interestingly, the authors did not exclude patients based on indications or interventions and the study was designed to mirror the unenhanced patient population that is encountered in general gastroenterology practice. Additionally, these authors did not categorize patients into high and low risk for PEP, to maintain appropriate randomization. Inamdar et al. conducted a systematic review and meta-analysis of 8 randomized controlled trials and concluded that while rectal indomethacin given before or after ERCP was protective against PEP

in high-risk patients versus placebo, it did not offer the same protection in average-risk patients.[22] The reasons for this result are unclear.

Another meta-analysis of 10 RCTs by He et al. concluded that rectal indomethacin was protective against PEP in both high- and average-risks patients, and also reduced the severity of PEP. Additionally, pre-ERCP administration of indomethacin seemed to be better than post-ERCP administration.[23] Yaghoobi et al. conducted their meta-analysis of eight trials published between 2007 and 2016 and reported that administering rectal indomethacin before rather than during or after ERCP significantly reduced PEP rates [odds ratio (OR): 0.56; 95% CI (0.40–0.79)] and this strategy also significantly decreased the rate of moderate to severe PEP and death amongst all patients [OR: 0.53; (0.31–0.89) and 0.10; (0.02–0.65)], respectively.[24]

Backed by moderate quality of evidence from several cohort studies as well as randomized controlled trials, the European Society of Gastrointestinal Endoscopy (ESGE) in 2020 recommended routine rectal administration of 100 mg of diclofenac or indomethacin immediately prior to ERCP in all patients without contraindications to NSAIDs administration.[25] The American Society of Gastrointestinal Endoscopy (ASGE) in 2017 recommended that rectal indomethacin may reduce the risk and severity of PEP in average risk individuals, however this recommendation was backed by low quality of evidence.[10] To assess whether a higher than 100 mg dose was more effective, a recent randomized, double-blind, multicenter, comparative effectiveness trial concluded that dose escalation to 200 mg did not confer any advantage compared with the standard 100 mg regimen, with pancreatitis incidence remaining elevated in high-risk patients.[26]

Numerous studies have also evaluated the use of rectal diclofenac for preventing PEP. While several of these have assessed the use of standard dose (100 mg) rectal diclofenac either 30-60 minutes prior to or during ERCP,[27-29] data regarding the efficacy of low dose (25 mg) diclofenac remains controversial. Furthermore, while in western countries, a 100 mg suppository and a 100 mg tablet of both diclofenac and indomethacin are on the market, with the maximum dosage per administration being 100 mg, in Japan, only a maximum dose of 50 mg is on the market.[30] For assessing the efficacy of low dose diclofenac, a prospective randomized controlled study of 104 patients was carried out, in which 3.9% patients in the diclofenac group and 18.9% patients in the control group developed PEP (p=0.017).[31] Another recent retrospective single center study concluded that the incidence rate of PEP in the low dose (25 mg) rectal diclofenac group was significantly lower than that in the non-diclofenac group (4% vs. 14%, p = .01). Further analysis revealed that this dose was an independent protective factor against PEP in elderly patients aged over 75 years.[32]

Despite small center experiences highlighting the use of low dose diclofenac, several additional studies have reported contradictory evidence. Tomoda et al. conducted a retrospective analysis of 301 patients with native papilla and a body weight of <50 kg who underwent ERCP, 72 of whom were administered a 25 mg dose of rectal diclofenac 15 min before the procedure and 229 of whom did not receive the treatment. The authors concluded that prophylactic administration of a 25 mg dose of rectal diclofenac did not reduce the incidence of PEP.[33] Similar findings were reported in another prospective, single-center, single-blinded, two-arm parallel group, randomized controlled trial in which PEP occurred in 13 of 297 patients (4.4%), including eight (5.4%) in the 50 mg diclofenac group and five (3.3%) in the control group (P = 0.286).[34] Another single center study assessing the effectiveness of a 50 mg vs. a 25 mg dosage, also concluded that the proportion of PEP was significantly lower in the 50 mg group than in the 25 mg group, 15.5% (11/71) vs. 33.3% (28/84), P=0.018.[35] Similar results were also reported by a recent retrospective study in which authors included 246 patients who were rectally administered 50 mg of diclofenac approximately 30 minutes before the start of ERCP. Additionally, for patients older than 85 years or under 50 kg of body weight, the dose of diclofenac was reduced to 25 mg. Outcomes were compared to control group of patients, who were not administered therapy, based on the similarity of propensity scores in a 1:1 ratio. The authors concluded that the incidence rate of PEP in each group was comparable (2.4% in the diclofenac group vs. 3.3% in the control group, P = 0.608).[36]

A 2009 practice survey of 141 endoscopists performing ERCP in 29 countries reported that a majority of survey respondents (83.7%) did not routinely use NSAIDs for PEP prophylaxis, with most citing a lack of adequate high quality evidence, whereas others stated that they performed few ERCPs in high-risk patients or used other drugs.[37] Contrary to a large body of supportive evidence, a few small studies have also been published showing the lack of efficacy of NSAIDs in preventing PEP. Among the reasons for conflicting results are the varying NSAID agents used, exclusion of high-risk patients, as well as timing, dosage and route of drug administration. Dobronte et al. conducted a prospective, randomized, placebo-controlled multicenter trial in five endoscopic units in which a total of 686 patients were randomized to receive a 100 mg indomethacin suppository or an inert placebo 10-15 min before ERCP. Post-ERCP pancreatitis and hyperamylasemia were evaluated 24 hours following the procedure on the basis of clinical signs and laboratory parameters, and computed tomography/magnetic resonance imaging findings, if available. They concluded that there was no significant difference between the indomethacin and placebo groups in the incidence of either post-ERCP pancreatitis (5.8% vs. 6.9%) or hyperamylasemia (23.3% vs. 24.8%).[38]

Another randomized, open-label, two-arm, prospective clinical trial was conducted in which only patients at high risk of developing PEP were recruited. Patients were randomized to receive either 100 mg rectal diclofenac or no intervention immediately after ERCP. Among 144 recruited patients, 69 (47.9%) received diclofenac and 75 (52.1%) had no intervention. The differences in pancreatitis incidence and severity between both groups were not statistically significant. Overall, eleven patients (7.6%) developed PEP, in which seven were from the diclofenac group and four were in the control group.[39] Despite these findings, there has been a paradigm shift in recent years in terms of advanced endoscopists' practice patterns. In 2020, an online 16-item survey was e-mailed to 233 advanced endoscopists to capture current practice in the prevention of PEP among endoscopists in the United States. Most respondents reported using rectal NSAIDs for high-risk patients only (34; 59.7%) compared with respondents (23; 40.1%) who reported using rectal NSAIDs for prevention of PEP in average-risk patients undergoing ERCP.[40]

The Dutch Pancreatitis Study Group conducted two anonymous surveys among Dutch gastroenterologists in 2013 (n = 408) and 2020 (n = 575) for longitudinal views and attitudes pertaining to post-ERCP pancreatitis prophylaxis and recognition of post-ERCP pancreatitis risk factors reported that rectal NSAIDs remain the most applied PEP prophylaxis therapy in the Netherlands, followed by pancreatic duct stents and intensive intravenous hydration.[41]

The same authors recently conducted an analysis of prospectively collected data from a randomized clinical trial. They included patients with a moderate to high risk of developing post-ERCP pancreatitis, all of whom received rectal diclofenac monotherapy 100 mg prophylaxis. Administration was within 30 minutes before or after the ERCP at the discretion of the endoscopist. A total of 346 patients received rectal NSAIDs before ERCP and 63 patients received it afterwards. The incidence of PEP was lower in the group that received pre-procedure rectal NSAIDs (8%), compared to post-procedure (18%) [RR: 2.32; (1.21-4.46), P=0.02].[42] To summarize all published literature to date, a recent network meta-analysis was conducted which included 55 RCTs evaluating a total of 20 different interventions in over 17,000 patients. Findings conclusively showed that both rectal diclofenac and indomethacin were more efficacious than placebo for preventing PEP. Furthermore, rectal diclofenac was more efficacious than rectal indomethacin.[29]

Overall, the preponderance of the evidence regarding rectal NSAIDS is that their use is safe and likely effective in reducing the risk and/or severity of PEP.

B. Protease Inhibitors

Protease inhibitors, specifically gabexate mesilate, nafamostat, and ulinastatin, have been investigated both for treatment of acute pancreatitis and for preventing PEP. The pathogenesis of acute pancreatitis includes activation of proteases, which leads to the cascade of autodigestion in the pancreas and the release of inflammatory cytokines.[13] Use of protease inhibitors can halt the intra-acinar trypsinogen activation to trypsin, thereby preventing the inflammatory cascade that

may follow. While individual small studies have shown benefit of these pharmacological agents, their widespread use remains limited due to overall paucity of supportive data.

I. Gabexate Mesilate

The use of gabexate mesilate for prevent PEP dates back to the 1970s, when two Japanese studies showed that its use was safe and effective in PEP prophylaxis.[43,44] In 1996, gabexate mesilate was shown to be effective in preventing PEP in a prospective, multicenter, controlled trial involving 276 patients. The authors conducted a double-blind comparison of gabexate (1g given by intravenous (IV) infusion starting 30 to 90 minutes before endoscopy and continuing for 12 hours afterward) with placebo (mannitol and sodium chloride, administered in the same fashion). Although no significant difference was seen in the incidence of hyperenzynemia between the 2 groups, rate of PEP was significantly lower in the gabexate group than in the placebo group (5/208, 2.4% vs. 16/210, 7.6%; P=0.03).The authors concluded that prophylactic treatment with gabexate reduced pancreatic damage related to ERCP, as reflected by reductions in the extent but not the frequency of elevated enzyme levels and in the frequency of pancreatic pain and acute pancreatitis.[45] While the results of aforementioned trials were encouraging, the main drawback of the drug was the need for a continuous 12-hour infusion regimen, which was inconvenient and required an overnight hospital stay after ERCP. This overnight stay significantly added to the overall cost and inconvenience to the patient.

To offset these issues, Masci et al. conducted a comparative trial comparing a 6.5-hour infusion of 0.5 g gabexate to a 13-hour infusion of 1 g gabexate and found that the frequency of PEP was similar between the 2 groups.[46] A meta-analysis by Andriulli et al. evaluating six clinical trials published between 1978 and 1996 also showed that gabexate mesilate was effective in preventing PEP.[47] However, in a follow up multi-center placebo controlled trial published in 2002, the same authors did not find any beneficial effect of the drug administered in high-risk patients over a two-hour period, starting 30 min before the procedure.[48] In 2007, the same authors suggested that gabexate produced no significant benefit when compared to controls. In control and intervention groups, pancreatitis developed in 5.7% vs. 4.8%, hyperamylasemia in 40.6% vs. 36.9%, and pain in 1.7% vs. 8.9% patients respectively. Additionally, there was no significant benefit of both short-term (<6 hours) or long-term (>12 hours) gabexate administration.[49] Similar results have been reported by other high quality RCTs[50-52] and a meta-analysis of 8 cohort studies.[53] A more updated meta-analysis from 2021, which included 13 RCTs with 3,718 patients, concluded the use of gabexate mesilate led to lower PEP [OR: 0.66; (0.49-0.89)], especially in the subgroup of infusion starting more than 30 min prior to ERCP [RR: 0.45; (0.29-0.72)]. Importantly, the authors could neither report on the severity of PEP, nor on the optimal effective dose of gabexate mesilate. Additionally, similar trends were not seen with respect to post procedure abdominal pain and hyperamylasemia.[54]

In conclusion, despite conflicting evidence of efficacy, at the current time, neither the ASGE nor ESGE make any recommendations regarding the use of gabexate for PEP. Gabexate is not typically used on the context of ERCP in the United States.

II. Nafamostat Mesylate

Nafamostat mesylate (FUT-175; 6-amidino-2-naphthyl p-guanidino-benzoate di-methane-sulfonate) is a low molecular weight serine protease inhibitor which has a longer half-life than gabexate and is believed to be more potent.[55] Choi et al. conducted single-center, randomized, double-blinded, controlled trial in which patients were randomized to receive continuous infusion of 500 mL of 5% dextrose solution with or without 20 mg of nafamostat mesylate. Serum amylase and lipase levels were checked before ERCP, 4 and 24 hours after ERCP, and when clinically indicated. The authors reported a significant difference in the incidence of PEP between the nafamostat mesylate and control groups (3.3% vs. 7.4%, respectively; P = .018).[56] Similar favorable results have been reported by several additional RCTs in the past decade.[57,58] While the standard dosing (20 mg) was used in these trials, Park et al. conducted their trial to evaluate the use of high dose nafamostat mesilate (50 mg) for prevention

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of PEP in high-risk patients. Patients were divided into 3 groups: controls (group A), infusion with 20 mg of nafamostat mesilate (group B), or infusion with 50 mg of nafamostat mesilate (group C). The authors concluded that while 20 mg or 50 mg dosing was effective in preventing PEP, the preventive effect of high dose was not necessarily significant in high-risk patients.[59]

Despite supportive evidence, nafamostat has not been widely used because it is quite expensive and needs to be administered through the intravenous route. Its clinical utility has also been put into question by a recent multicenter randomized controlled trial that assessed the efficacy of nafamostat as well as incidence of PEP stratified by timing of drug administration i.e., pre- and post-ERCP. The authors found no evidence for the prophylactic effect of nafamostat against PEP, regardless of the timing of administration.[60]

III. Ulinastatin

Ulinastatin, another potent protease inhibitor extracted and purified from human urine, has been used in Japan for the treatment of acute pancreatitis.[61,62] Several randomized controlled trials have studied the beneficial effects of ulinastatin for PEP prophylaxis. Fujishiro conducted a multicenter randomized controlled trial in which patients were randomly divide into three groups based on the agent and dose given during and following the ERCP procedure: gabexate mesilate (900 mg), high-dose ulinastatin (450,000 units) and low-dose ulinastatin (150,000 units). The authors concluded that administration of low and high dose ulinastatin had similar effects to high-dose gabexate in the prevention of PEP.[63] In another multicenter, randomized, double-blind, placebo-controlled trial, patients were randomized to receive ulinastatin (150,000 U) or placebo by intravenous infusion for 10 minutes starting immediately before ERCP. Overall, six patients in the ulinastatin group and 15 patients in the placebo group developed pancreatitis (2.9% vs. 7.4%, P = .041). There were no cases of severe pancreatitis in either group and the authors concluded that prophylactic short-term administration of ulinastatin does indeed decrease the incidence of pancreatitis and hyperenzymemia after ERCP.[64]

In 2017, Zhu et al. conducted a systematic review and meta-analysis of 13 studies and concluded that prophylactic ulinastatin administration significantly reduced the PEP risk [RR 0.49; (0.33– 0.74), P=0.0006]; however, significant risk reduction occurred only in patients with low or average risk for PEP, with use of high-dosage ulinastatin (150,000 or 200,000 U), and when drug administration began prior to or during ERCP.[65] Despite some favorable data, other high quality studies have shown inconclusive results[66] and as a result, at present, gastrointestinal societies such as ESGE do not recommend the use of protease inhibitors for PEP prophylaxis.[25]

C. Other Pharmacological Agents

Octreotide, somatostatin, and sublingual nitrates are additional pharmacological agents that have been trialed for PEP prophylaxis, but their clinical significance remains uncertain, mostly owing to conflicting data. Given that somatostatin is a potent inhibitor of pancreatic secretion, several randomized controlled trials have been conducted to evaluate its efficacy. Poon et al. conducted a prospective double-blind controlled trial including 109 patients randomized to receive somatostatin infusion and 111 patients randomized to receive normal saline infusion (placebo). Both agents were started 30 minutes before ERCP and continued for 12 hours. The frequency of clinical pancreatitis was significantly lower in patients given somatostatin (3%) than in those given placebo (10%) (p = 0.03).[67] Similar findings were reported by another RCT in which the intervention group was administered a single bolus injection of natural somatostatin just before cannulation of the papilla.[68] In 2003, Poon et al. also conducted a follow up RCT to evaluate whether intravenous bolus somatostatin given after diagnostic ERCP could reduce the incidence of pancreatitis in a group of patients undergoing therapeutic interventions. The authors noted that frequencies of clinical pancreatitis (4.4% vs. 13.3%; p=0.010) and hyperamylasemia (26.0% vs. 38.5%; p=0.036) were both significantly lower in the somatostatin group compared with the placebo group.[69] Multiple systematic reviews and meta-analysis conducted in the past decade have shown an overall reduction in incidence of PEP with somatostatin administration. While short

term infusion (administered as a 4-hour continuous infusion) has not been shown to be beneficial,[70] both long term infusion of high dose (3 mg over 12 hours) or a single dose of 250 micrograms have been shown to efficacious in preventing PEP.[71-73]

Similarly, octreotide, a somatostatin analogue with longer half-life, has also yielded conflicting results in preventing PEP. While individual trials have shown contradictory results,[74,75] a large meta-analysis including 18 RCTs with 3,983 patients, concluded that the incidence of PEP was significantly lower for octreotide doses of at least 5 mg vs. control. There was a statistically significant difference in the incidence of post-ERCP hyperamylasemia in favor of octreotide for doses of 0.5 mg or more, but not for doses of less than 0.5 mg octreotide. Finally, there were no significant differences between octreotide and control for the incidence of severe post-ERCP pancreatitis and abdominal pain.[76] As a result of lack of supportive data, the ASGE makes no formal recommendations regarding the use of octreotide or somatostatin infusion for PEP prophylaxis. The ESGE offers "no recommendation" and the Japanese Gastroenterological Endoscopy Society recommends the use of somatostatin only in research settings.[77]

Sublingual nitroglycerin reduces basal pressure of the sphincter of Oddi and has been reported to reduce the risk of PEP. To assess the efficacy of prophylactic long-acting glyceryl trinitrate (GTN), Sudhindran conducted a large randomized, double-blind, placebo-controlled trial. While 24 patients (13 percent) developed pancreatitis, the incidence was significantly lower in the GTN group (8 percent vs. 18 percent; $P < 0.05$). Additionally, the only significant adverse effects attributable to GTN were hypotension and headache.[78] A meta-analysis of 11 RCTs compared GTN with placebo for PEP prevention. The study concluded that the overall incidence of PEP was significantly reduced by GTN treatment [RR 0.67; (0.52-0.87)], however it did not decrease the incidence of moderate to severe PEP [RR 0.70; (0.42- 1.15)]. Subgroup analyses further revealed that GTN administered by sublingual route was more effective than transdermal and topical routes in reducing the incidence of PEP.[79] Another recent randomized controlled trial, in which patients were randomly assigned to groups given diclofenac suppositories (50 mg) within 15 minutes after the endoscopic procedure alone (diclofenac-alone group, n = 442) or in combination with sublingual isosorbide dinitrate (5 mg) 5 minutes before the endoscopic procedure (combination group, n = 444), found that prophylaxis with a combination of rectal diclofenac and sublingual nitrate significantly reduced the overall incidence of PEP compared with diclofenac suppository alone.[80] At the present time, backed by moderate quality of evidence, the ESGE recommends administration of 5 mg sublingual GTN before ERCP in only those patients with a contraindication to NSAIDs or aggressive hydration.

2. NON-PHARMACOLOGICAL STRATEGIES

Aggressive intravenous fluid hydration, certain cannulation techniques and pancreatic duct stenting are among some the non-pharmacological strategies that have been employed to prevent post ERCP pancreatitis.

A. Fluid Therapy

The concept of aggressive hydration therapy for PEP emerged from animal models correlating diminished perfusion with pancreatic necrosis and observational human cohorts, suggesting that early aggressive fluid resuscitation improves clinical outcomes for acute pancreatitis.[81,82] The role of fluids in PEP was first evaluated by Cote et el. in a retrospective study that showed a decreased length of hospital stay in patients who received increased volumes of fluid in the first 24 hours after undergoing ERCP.[83] Several agents including normal saline (NS), lactated ringers (LR) and N-acetylcysteine (NAC) have been studied for PEP prevention, which act by either maintaining sufficient perfusion to the pancreas, thereby suppressing the inflammatory cascade within the pancreas or as strong antioxidants which inhibit the oxygen-derived free radicals that are thought to play a decisive role in the pathophysiology of acute pancreatitis. In 2005, Katsinelos et al. carried out a prospective, double-blind, placebo-controlled trial in which patients were randomized to receive intravenous NAC at a loading dose of 70 mg/kg 2 hours before and 35 mg/kg at 4-hour intervals for a total of 24 hours after the procedure, or to receive

normal saline solution as placebo. The overall incidence of PEP was 10.8%, with 12.1% in the NAC group and 9.6% in the placebo group. There were no statistical differences in the incidence or severity grades between the groups. This landmark trial did not show any beneficial effect of NAC on the incidence and the severity of ERCP-induced pancreatitis when compared to fluid alone.[84]

Similar findings were reported by another randomized controlled trial in which 55 patients were given NAC (two 600 mg doses orally 24 and 12 h before ERCP and 600 mg IV given, twice a day for two days after the ERCP) and 51 patients in the control group, who were given IV isotonic saline twice a day for two days after the ERCP. There were no significant differences in the rate of post-ERCP pancreatitis between two groups (10 patients overall, 4 in the NAC group and 6 in the control group). There were also no significant differences in baseline and post-ERCP serum and urine amylase activity between the two groups.[85] Despite these unfavorable results, a few additional studies have shown benefits of oral NAC. Nejad et al. conducted a prospective double blind RCT in which 100 patients were divided randomly into two groups; the NAC group where patients received 1200 mg NAC with 150 cc water orally 2 h before ERCP and the placebo group, where 150 cc water was prescribed as a placebo. A significantly lesser number of patients in the NAC group developed PEP (RR: 2.8; P=0.02).[86] Another large multi-center RCT in which patients across 7 referral centers of 4 countries were randomly assigned to four groups, received either 1200 mg oral NAC (group A), 100 mg rectal indomethacin (group B), NAC plus indomethacin (group C) or water as placebo (group D) one hour before procedure has shown similar results. The rates of PEP in groups A, B, C, D were 10.7%, 17.4%, 7.8%, 20% respectively suggesting that oral NAC plays a more significant role than rectal indomethacin and the combination of both showed the best result that suggests a synergistic effect in preventing PEP.[87]

Aggressive intravenous hydration (IVH) has been a mainstay of treatment for acute pancreatitis. It has been theorized that acidosis seen in patients with pancreatitis can perpetuate systemic inflammation and the pH-neutral LR solution would be a more appropriate resuscitation fluid than NS, which can cause a hyperchloremic metabolic acidosis.[88,89] Furthermore, it is known that hemoconcentration and decreased systemic perfusion are associated with an increased risk of pancreas necrosis and unfavorable outcomes.[90] So, the purpose of IVH is to perfuse the pancreatic microcirculation adequately, such that pancreatitis and its subsequent complications can be minimized or even prevented. A pilot study by Buxbaum et al. was conducted in 2013, in which patients undergoing first-time ERCP were randomly assigned to receive either aggressive hydration with LR (3 mL/kg/h during the procedure, a 20-mL/kg bolus after the procedure, and 3 mL/kg/h for 8 hours after the procedure, n = 39) or standard hydration with the same solution (1.5 mL/kg/h during and for 8 hours after procedure, n = 23). None of the patients who received aggressive IVH developed PEP, compared with 17% of patients who received standard hydration (P = .016).[91] Another large multicenter RCT of over 500 patients was conducted in Korea, showed similar results in that patient receiving vigorous periprocedural IVH with LR (initial bolus of 10 mL/kg before the procedure, 3 mL/kg/h during the procedure, for 8 hours after the procedure, and a post-procedure bolus of 10 mL/kg) had reduced incidence and severity of PEP compared to standard IVH (1.5 mL/kg/h during and for 8 hours after the procedure).[92]

Several additional studies, including systematic reviews and meta-analysis of RCTs, have shown benefit of aggressive hydration with LR for preventing PEP. The regimen proven to be most effective is 10–20 mL/kg bolus during or immediately after the procedure followed by 3 mL/kg/h for 8 h.[93-96] It is important to note that continuous aggressive hydration over a prolonged period of time is not beneficial, as proven by a recent randomized, double-blinded, controlled trial in which the "high-volume group" of patients received 3600 mL of intravenous LR at a rate of 150 mL/h starting 2 h before the ERCP and continued during and after the procedure to complete 24 h, while the control group received standard daily maintenance fluid volume. Patients in the high-volume group received significantly more fluid than the control group (3600 vs. 2413 ml, P < 0.001). However, PEP incidence was not different between the two groups, 14% vs. 15% [RR 0.93; (0.48–1.83), P = 0.84].[97]

A few studies have also compared outcomes of aggressive hydration with NS and LR for PEP prophylaxis. In an RCT, Alcivar-Leon et al. investigated the preventive efficacy of aggressive hydration with LR compared to normal volume NS and showed a statistically significant and clinically favorable effect of the former in PEP prevention (3.4% and 87%, respectively, RR 0.41; 95% CI 0.20–0.86; p = 0.016).[98] Another prospective multicenter RCT also showed significant differences in PEP incidence while comparing aggressive hydration with LR to aggressive hydration with NS and normal volume LR (3.0%, 95% CI 0.1–5.9 vs. 6.7%, 95% CI 2.5–10.9 vs. 11.6%, 95% CI 6.1–17.2, p = 0.03). Furthermore, aggressive hydration with NS treatments was not superior to normal volume LR [RR 0.57; (0.26–1.27), P=0.17].[94] The evidence in favor of aggressive hydration with LS has been furthered by a recent meta-analysis of 10 RCTs with over 2,000 patients, showing its superiority to standard hydration.[99]

At the current time, ASGE supports the use of LR solution for preventing PEP, but as this recommendation is backed by very low quality of evidence, additional investigations are warranted.[10] The ESGE recommends aggressive hydration with LR (3 mL/kg/hour during ERCP, 20 mL/kg bolus after ERCP, 3 mL/kg/hour for 8 hours after ERCP) in patients with contraindication to NSAIDs, provided they are not at risk of fluid overload and that a prophylactic pancreatic duct stent is not placed.[25]

B. Prophylactic Pancreatic Duct Stenting (PPDS)

The incidence of PEP increases when cannulation is difficult or prolonged, or if biliary or pancreatic sphincterotomy is performed.[3,100] It is believed that pancreatitis is precipitated due to impaired drainage of the pancreatic duct (PD), secondary to trauma and/or cautery induced papillary edema and/or spasm of the sphincter of Oddi, leading to acinar injury.[101,102] Prophylactic pancreatic duct stenting (PPDS) has been extensively studied as a measure to prevent the incidence of PEP. (Figure 2) Smithline et al. conducted a small RCT of 98 patients in which 48 patients were randomized to receive either a main pancreatic duct stent and 50 patients received no stent after biliary sphincterotomy. The study found no statistical difference in the incidence of PEP (18% of patients in the no-stent group vs. 14% of patients in the stent group). It is important to note that only high risk patients, i.e. those with sphincter of Oddi dysfunction, small common bile duct (CBD) diameter (< 10 mm), or those requiring pre-cut sphincterotomy, were included in the trial.[103] Despite these findings, multiple additional studies have shown beneficial effects

Figure 2a. A 5-Fr x 5 cm pancreatic duct stent with two internal flaps, two external flaps, and side holes. This is a common stent size used for prophylaxis during ERCP.

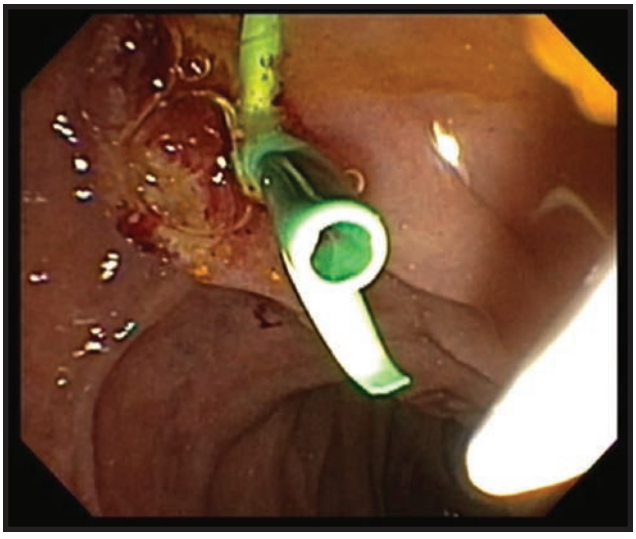

Figure 2b. A prophylactic pancreatic duct stent placed during ERCP for stone extraction.

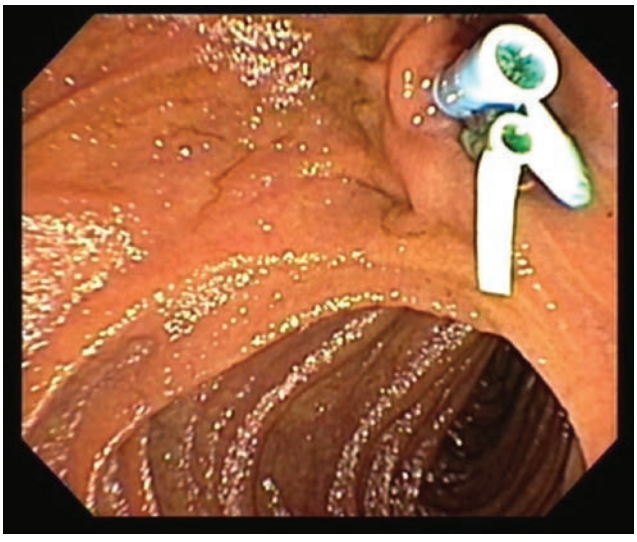

Figure 2c. A prophylactic pancreatic duct stent placed next to a plastic biliary stent.

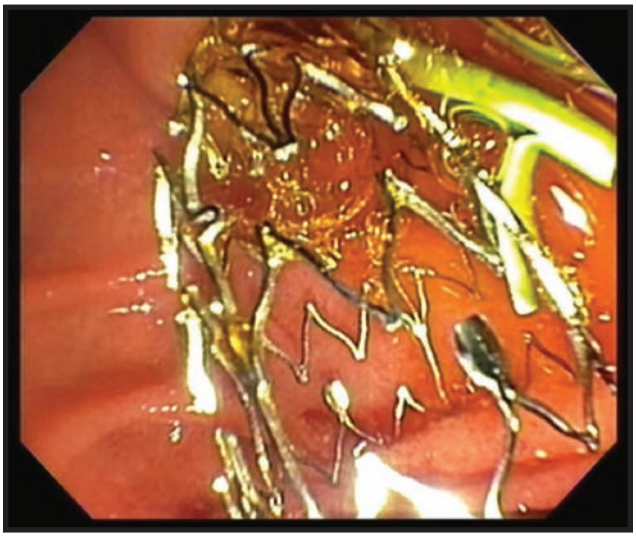

Figure 2d. A prophylactic pancreatic duct stent placed next to an uncovered metal biliary stent.

of PPDS, especially after biliary sphincterotomy in patients with pancreatic sphincter hypertension[104] and in patients requiring needle-knife and/or precut endoscopic sphincterotomy.[105]

Several meta-analyses in the past decade have reported results separately according to the patients' risk stratification for PEP. PPDS was beneficial in unselected [RR 0.23; (0.08 – 0.66)] as well as average-risk (OR 0.21-0.25)[85,149,152] and high-risk patients (OR 0.27-0.41).[106-108] A recent network meta-analysis comparing PPDS to rectal NSAIDs in average- and high-risk patients showed that compared to placebo, only PPDS reduced the risk of moderate and severe PEP in both patient groups [average-risk: RR 0.07; (0.002–0.58), high-risk: RR 0.20; (0.051–0.56)], significantly. Rectal NSAIDs also reduced the risk, but this effect was not significant [average-risk: RR 0.58; (0.22–1.3), high-risk: RR 0.58; (0.18–2.3)]. Furthermore, based on a cumulative ranking curve, PPDS was ranked as the best preventive method for PEP prophylaxis.[109] The clinical benefit of PPDS has been shown even in an unselected patient population by a multicenter RCT in which 167 patients undergoing first-time ERCP were enrolled. PPDS significantly reduced the rate of PEP [OR 0.43; (0.19 – 0.98); P = 0.04]. The number needed to treat to prevent one case of PEP by prophylactic stent insertion after inadvertent cannulation of the pancreatic duct, was 8.1 for the intention-to-treat population.[110] It should be noted that limiting the use of PPDS to high-risk patients has been shown to be the most cost-effective strategy.[111]

The ASGE recommends the use of PPDS for PEP prevention in high risk patients.[10] The ESGE recommends PPDS with a short 5-Fr pancreatic stent (with no internal flange, but with a flange or a pigtail on the duodenal side). Additionally, passage of the stent from the pancreatic duct should be evaluated within 5 to 10 days of placement.[25]

C. Cannulation Techniques

Cannulation technique is believed to be pivotal in the genesis of PEP and is important for successful cannulation. While cannulation with a sphincterotome appears to be the most efficient technique for biliary access, several studies have evaluated alternative techniques to lower the risk of PEP. Historically, a cannulation catheter a.k.a. a straight biliary catheter was the first choice for cannulation given its high flexibility and tip shape compared with the sphincterotome. Several studies have previously shown that use of sphincterotome has higher success rate to that of a standard catheter for the initial attempt at cannulation of the CBD, 84–97% vs. 62–75%[112,113] As a result, in recent times, most endoscopists use a sphincterotome because of its ability to bow the catheter tip by applying or releasing tension to the cutting wire,

facilitating alignment with the biliary duct, as well as the ability to perform sphincterotomy. (Figure 3) After initial engagement of the orifice of the major papilla, the sphincterotome is advanced into the biliary duct with the assistance of either contrast or guidewire.

In a reported case series, use of a hydrophilic guidewire with a sphincterotome was successful in achieving deep biliary cannulation in 174 of 183 patients (95%); 7.5% had elevations in amylase and lipase to 4 times normal, and clinical pancreatitis was seen in 2.3%.[114] However a prospective randomized study by Lella et al. found that while success at biliary cannulation was achieved with similar frequency with guidewire through a papillotome (98.5%) compared with a papillotome alone (97.5%), the rate of pancreatitis was significantly lower in the guidewire group (0% vs. 4%, $p < 0.05$).[115] In 2008, Bailey et al. conducted a single center RCT, in which over 400 patients were randomized to either primary contrast or guide-wire-assisted cannulation during ERCP. The authors found that PEP occurred in 29/413 (7.0%): 16 in the guide-wire arm, 13 in the contrast arm ($P = 0.48$). Cannulation was successful without crossover in 323/413 patients (78.2%): 167/202 (81.4%) in the guide-wire arm and 156/211 (73.9%) in the contrast arm ($P = 0.03$).[116] However follow up data, including two systematic reviews and meta-analysis, first by Cheung et al. comprising of 7 RCTs[117] and the other by Tse et al. comprising of 12 RCTs,[118] concluded that compared with the contrast-assisted cannulation technique, the guidewire-assisted cannulation technique increases the primary cannulation rate and reduces the risk of PEP.

Furthermore, several recent studies have shown that use of thinner guidewire (0.025-inch vs. 0.035-inch),[119] highly flexible-tip guidewire,[120] rotatable vs. conventional sphincterotome[121] and touch vs. no-touch technique,[122] does not influence the rates of ERCP related adverse events, particularly PEP.

Selective biliary cannulation fails in a small percent of cases, even in the hands of experienced endoscopists.[123] Prior studies have defined difficult cannulation based on the number of cannulation attempts (typically between 5 and 15) and/or the time spent on standard cannulation (typically greater than 5–30 min).[124] ESGE has defined

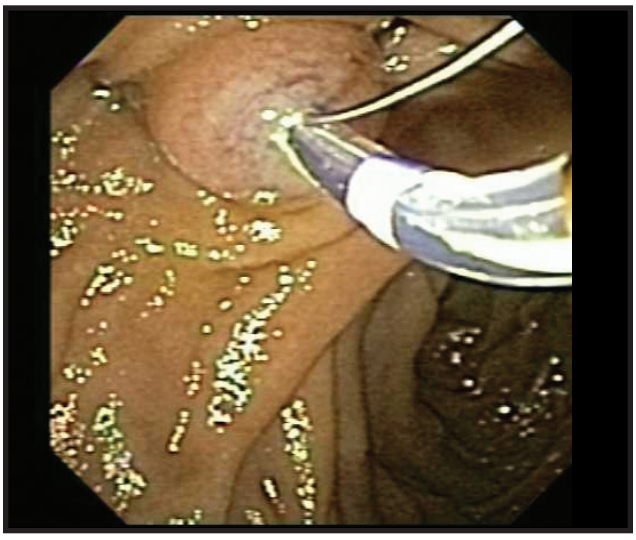

Figure 3. Biliary cannulation with a standard sphincterotome.

"difficult cannulation" as (i) > 5 contacts with the papilla or > 5 minutes of cannulation attempts, or (ii) > 1 unintended pancreatic duct cannulation/opacification.[125,126] Several studies have already shown that difficult biliary cannulation is one of the main risk factors for post-ERCP pancreatitis.[6,127-129] In an effort to reduce the risk of PEP and increasing the rate of successful cannulation in patients with difficult biliary cannulation, several alternative endoscopic techniques have been studied. The commonly deployed techniques include the double guidewire technique, transpancreatic biliary sphincterotomy and early pre-cut needle knife sphincterotomy.

I. Double Guidewire Technique

First described by Dumonceau et al. in 1998, the double-guidewire technique (DGT) consists of a combined maneuver: first, a guidewire is inserted and left in the pancreatic duct; second, a cannulation device is passed through the working channel alongside the guidewire. The tip of the device is positioned in the papilla, bending over the pancreatic wire, to attempt cannulation of the bile duct.[130] (Figure 4) Maeda et al. conducted the first pilot RCT evaluating DGT in comparison to standard methods in difficult CBD cannulation scenarios. The trial showed higher cannulation success rate with DGT, with no apparent added

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risk of PEP.[131] The superior rate of bile duct cannulation when using DGT has been attributed to the capability of the pancreatic guidewire to straighten both the PD and CBD while at the same time occupying the PD, thus facilitating CBD cannulation and reducing the risk of repeated PD cannulation.[132,133] PD cannulation is not prevented so much by the presence of the PD wire (one can simply place two wires into the PD during double-guidewire cannulation), but by the fact that the wire clearly shows the endoscopic and fluoroscopic position of the PD, thus allowing it to be avoided.

However, following these initial reports, in 2009 a large multicenter RCT showed that DGT was not superior to standard cannulation techniques in achieving CBD cannulation and it might be associated with a higher risk of PEP.[134] A recent systematic review and meta-analysis of 7 RCTs (577

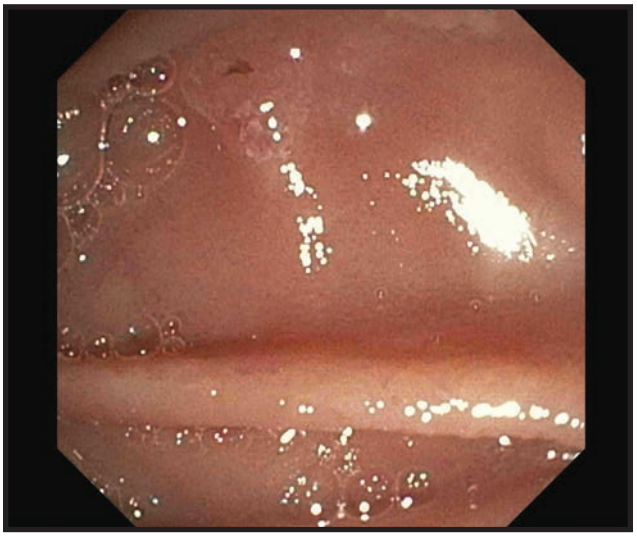

Figure 4a. Diminutive papilla seen at ERCP.

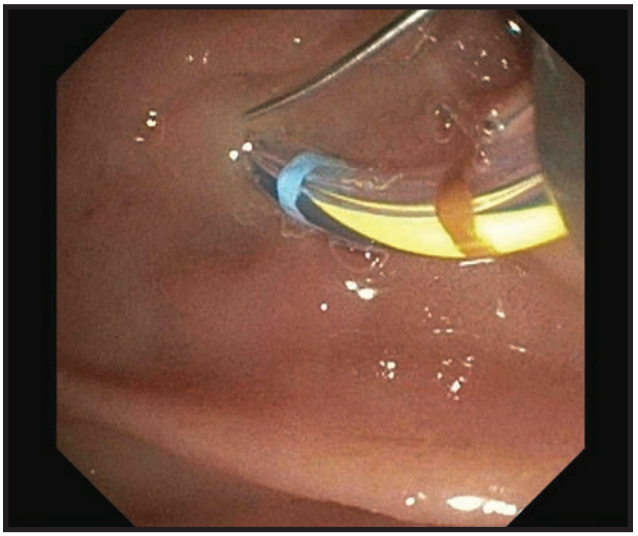

Figure 4b. Initial cannulation attempt only yields pancreatic duct access.

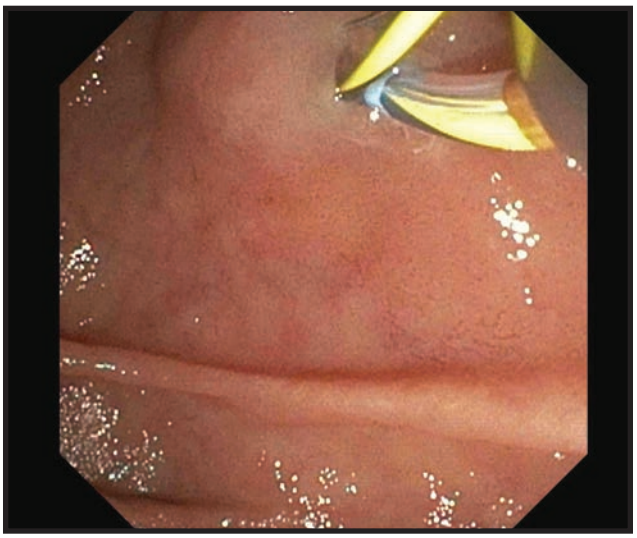

Figure 4c. The sphincterotome, now removed from the pancreatic wire and loaded with a 2nd wire, is used to obtain biliary access.

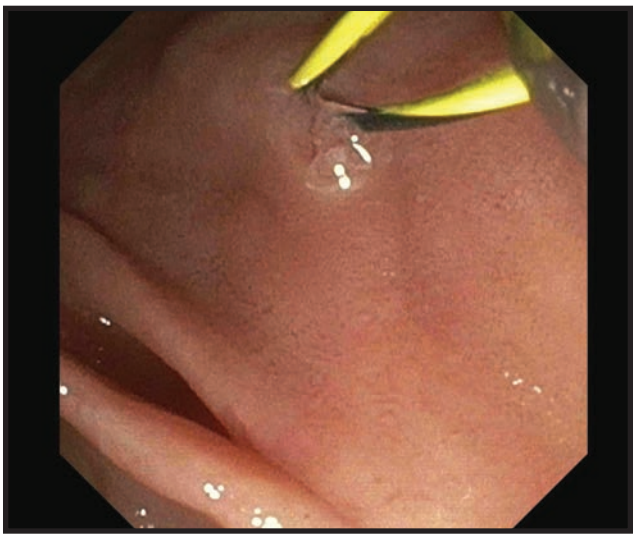

Figure 4d. After biliary access is obtained, both wires are left in place allowing any further maneuvers needed in either the bile duct or the pancreatic duct.

patients) showed that the use of DGT significantly increased PEP compared to other endoscopic techniques, RR 1.98; (1.14 – 3.42) and there was no significant difference in overall cannulation success, RR 1.04; (0.91 – 1.18) between DGT and other techniques.[135] Still, the DGT is frequently successful and is widely employed clinically.

II. Transpancreatic Biliary Sphincterotomy

Transpancreatic precut sphincterotomy (TPS) was first described by Goff in 1995 and it is performed by a standard traction sphincterotome wedged into the pancreatic orifice, with a cutting wire aimed in the biliary direction.[136] This technique takes advantage of the fact that the pancreatic duct is cannulated unintentionally, and the procedure is performed with a standard traction sphincterotome. Thus, the use of a free-hand needle knife is not required, and the depth of incision is potentially easier to control compared with needle-knife sphincterotomy. In 1999, a retrospective study showed that overall complication rates for standard sphincterotomy and transpancreatic sphincterotomy were comparable (2.1% vs. 1.96%). Additionally, there were no cases of PEP after transpancreatic duct pre-cut sphincterotomy.[137] While successful cannulation rates and mean cannulation times with this technique have been reported to be comparable to DGT (91.2% vs. 91.9% and 14.1 ± 13.2 min vs. 15.4 ± 17.9 min, P = 0.732, respectively), the overall incidence of PEP was significantly lower (38.2% vs. 10.8%, P < 0.011).[138] Similar results have been reported by several case series,[139] comparative studies,[140,141] a recent systematic review and meta-analysis of 4 RCTs.[142]

While the safety and efficacy of TPS has been extensively reported, there remain concerns about the long-term effects of this technique, with the possibility of pancreatic stenosis, as seen in the cases of therapeutic pancreatic sphincterotomies.[143,144] For comparing outcomes with DGW technique, Pecsi et al. conducted a meta-analysis of 14 studies which showed that rates of PEP did not differ between the two techniques; however, when assessing data from comparative retrospective studies, the former proved to be worse than needle-knife fistulotomy OR 4.62; (1.36–15.72).[145] Similar findings have been reported by a recent prospective, multicenter, randomized controlled trial, in which if the ERCP

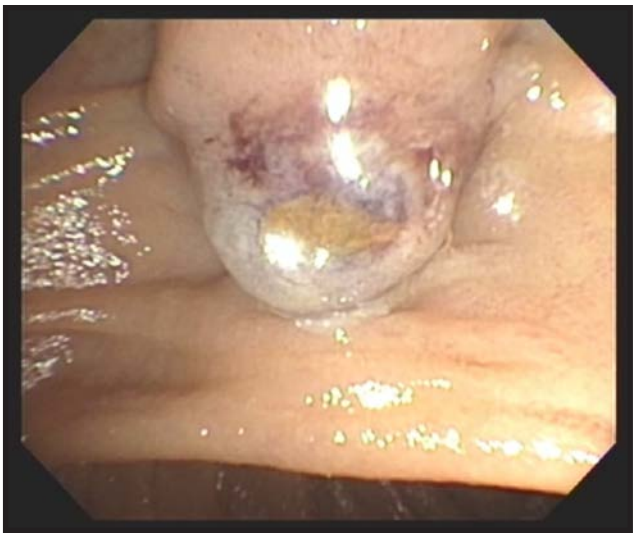

Figure 5a. Impacted stone at ampulla; a common finding that prompts needle knife papillotomy.

procedure fulfilled the definition of difficult cannulation and a guidewire entered the pancreatic duct, randomization to either TPS or to DGW was performed. 203 patients were randomized to either group, TPS (104 patients) and DGW (99 patients). PEP developed in 14/104 patients (13.5%) in the TPS group and 16/99 patients (16.2%) in the DGW group (P = 0.69). The rate of successful deep biliary cannulation was significantly higher with TPS (84.6% [88/104]) than with DGW (69.7% [69/99]; P = 0.01.[146] Based on the current body of evidence, the ESGE recommends using TPS but after failure of DGW technique in cases of difficult biliary cannulation.[25] In practice, the choice and order of techniques tried is left to the operator.

III. Needle-Knife Papillotomy (NKPP) and Needle-Knife Fistulotomy (NKF)

Both NKPP and NKP are considered as "precut" techniques when standard biliary cannulation fails. (Figures 5 and 6) Precutting is considered a second-line salvage technique because it has been repeatedly identified as an independent risk factor for PEP, and it carries an adverse event rate as high as 24.3%.[147] However, a growing collection of RCTs suggest an alternative explanation: that papillary trauma resulting from unsuccessful conventional cannulation is the actual reason for higher rates of PEP after precutting.[125]

NKPP technique was first described by

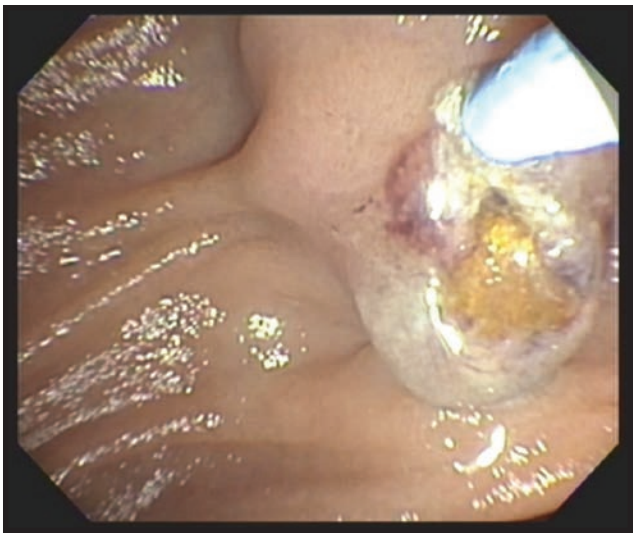

Figure 5b. Needle knife papillotomy on same patient as Figure 4a allows both biliary access and stone dislodgement.

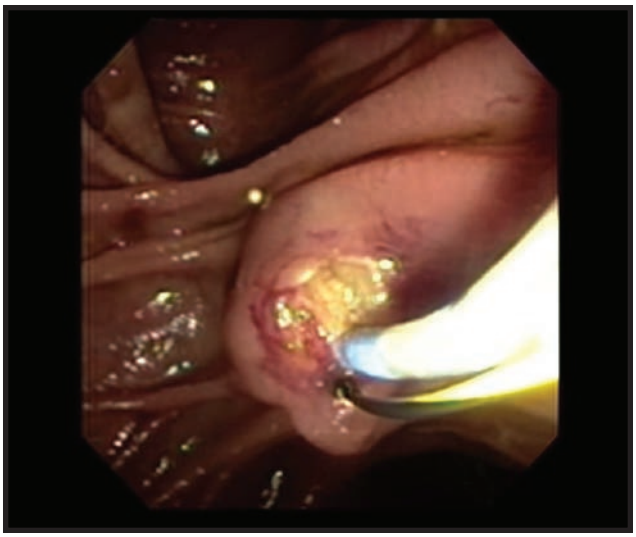

Figure 6. Needle knife fistulotomy. Note guidewire in pancreatic duct. Site of fistula is above the papillary orifice.

Huibregtse et al. in 1986 and involves performing an incision started at the papillary orifice, which is then extended upward between the 11 and 1 o'clock positions. Step by step the incision is extended until successful biliary cannulation is achieved.[148] While this technique has been in practice for several decades, there have been concerns about its safety profile, with high reported rates of PEP, perforation and bleeding, especially in inexperienced hands.[149,150] With the NKF procedure, a small incision is made on the bulging intraduodenal segment of the CBD, and the needle is moved in an upward direction starting 3 to 5 mm above the papillary orifice. If biliary cannulation through the opening is not possible, the incision is progressively extended in the same direction. It is important to remember that either of these techniques must be individualized based upon the anatomy (size, morphology, and orientation) of the major duodenal papillae.[151] It has been suggested that NKPP may be carried out more safely for patients with small and flat papillae, and NKF is more suitable for patients with bulging and impacted stone papillae, but in practice both can be employed in any patient the operator feels is suitable.[152,153]

It is crucial to note that studies in which early precut sphincterotomy (i.e., papillotomy and fistulotomy) was compared with persistent standard cannulation (with late precutting as needed), have found that while early precutting was associated with improved primary cannulation success RR 1.32; (1.04-1.68), the incidences of PEP and overall cannulation success did not significantly differ between groups. Additionally, subgroup analysis found a reduction in PEP risk in the early precut group after the exclusion of trainee participation RR 0.29; (0.10-0.86). So it is possible that precutting in expert hands may reduce the risk of PEP, possibly by increasing the technical success of primary cannulation.[154] A recent study showed that among patients who underwent NKF as an initial procedure for biliary access, those undergoing "early" NKF i.e., after 5 min, 5 attempts, or 2 pancreatic passages and "late" NKF i.e., after at least 10 min of unsuccessful standard biliary cannulation, late NFK was associated with a higher time to create a fistula and an increased risk of pancreatitis. PEP rates were 2.5%, 4% and 8.2%, respectively, among the three groups.[155]

Mavrogiannis et al. conducted a randomized controlled trial in which 153 patients with choledocholithiasis were randomized to undergo either NKF (n = 74) or NKPP (n = 79). PEP rates were significantly lower with NKF vs. NKPP, 0% and 7.59% ($p < 0.05$).[156] In another recent prospective controlled trial, patients were randomized accounting for variation in the types of major duodenal papillae. A total of 75 and 113 patients were allocated to the NKPP and NKF

groups, respectively. There was no difference in the rates of PEP between the two techniques, 6.6% in the NKPP group and 5.3% in the NKF group.[157] Facciorusso conducted a network meta-analysis of 17 RCTs with over 2,000 patients and concluded that early needle-knife techniques outperformed persistence with standard cannulation techniques in terms of decreasing PEP rate, RR 0.61; (0.37-1.00), whereas both early needle-knife techniques and transpancreatic sphincterotomy led to lower PEP rates as compared with pancreatic guidewire-assisted technique [RR 0.49 (0.23-0.99) and 0.53 (0.30-0.92)], respectively.[158]

3. COMBINATION THERAPEUTIC STRATEGIES

I. Rectal NSAIDs and Fluid Therapy

Several studies have also evaluated the efficacy of combining rectal NSAIDs with fluid therapy to lower the incidence of PEP. Mok et al. conducted a randomized, double-blinded, placebo-controlled trial in which patients were assigned to standard normal saline solution (NS) + placebo, NS + rectal indomethacin, LR + placebo, or LR + rectal indomethacin. PEP occurred in 3 patients (6%) in the LR + rectal indomethacin group vs. 10 (21%) in the NS + placebo group (P = .04).[159] However, the authors used a 1-L bolus of LR or NS before ERCP instead of aggressive hydration as suggested by earlier trials. Based on several network meta-analysis, the combination of rectal NSAIDs with aggressive hydration has also been shown to be the best intervention for preventing PEP.[160-162] But the utility of combination therapy has also been questioned by a recent open-label, multicenter RCT, in which patients were randomly assigned (1:1) to a combination of aggressive hydration and rectal NSAIDs (100 mg diclofenac or indomethacin; aggressive hydration group) or rectal NSAIDs (100 mg diclofenac or indomethacin) alone (control group). Aggressive hydration comprised 20 mL/kg intravenous Ringer's lactate solution within 60 min from the start of ERCP, followed by 3 mL/kg per h for 8 h. The study showed that aggressive periprocedural hydration did not reduce the incidence of PEP in patients with moderate to high risk of developing this complication who routinely received prophylactic rectal NSAIDs.[163] The ESGE also recommends against the routine combination of rectal NSAIDs with other measures to prevent PEP.

Taking the cumulative evidence into account, an updated network meta-analysis including studies evaluating 18 regimens among 16,241 patients, was conducted by Park et al. Based on integral analysis of predictive interval plots, and expected mean ranking and surface under the cumulative ranking curve values, combination prophylaxis with indomethacin + LR, followed by indomethacin + normal saline, was found to be the most efficacious modality of these for the overall prevention of PEP.[164]

II. Rectal NSAIDs and Pancreatic Duct Stenting

Elmunzer et al. conducted a multicenter, randomized, placebo-controlled, double-blind clinical trial, where patients at elevated risk for PEP received a single dose of rectal indomethacin or placebo immediately after ERCP. Among patients at high risk for post-ERCP pancreatitis, most of whom (>80%) had undergone pancreatic stent placement (PSP), rectal indomethacin significantly reduced the incidence of PEP.[19] A follow-up retrospective cost analysis showed that a prevention strategy employing rectal indomethacin alone could save approximately $150 million annually in the United States compared with a strategy of PSP alone, and $85 million compared with a strategy of indomethacin and PSP combination.[165] A retrospective analysis of over 700 patients showed that the incidence of PEP did not differ for rectal indomethacin vs. combination of rectal indomethacin and pancreatic stenting groups (5.1% vs. 6.1%).[166] Akbar et al. conducted a large network meta-analysis of 29 studies and showed that the combination of rectal NSAIDs and stents was not superior to either approach alone. Furthermore, pooled results showed that rectal NSAIDs alone were superior to PD stents alone in preventing post-ERCP pancreatitis [OR 0.48; (0.26-0.87)].[106] While data on combination therapy remains weak, it is important to note that studies have shown that negative effect of failed pancreatic stent placement, especially in patients with elevated risk for PEP, may be fully attenuated by use of rectal NSAID.[167] Additionally, data suggests that use of combination rectal NSAIDs and PSP maybe

Table 1. Interventions and estimated* risk of post ERCP pancreatitis (*includes low, moderate, and high-risk patients)

Intervention	Reported incidence of post ERCP pancreatitis
Rectal non-steroidal anti-inflammatory drugs (NSAIDS)	8%
1. Rectal indomethacin	3.2% to 9.2%
2. Rectal diclofenac	5.4% to 7.5%
Protease inhibitors	
1. Gabexate mesilate	3.4% to 5.8% (dosing dependent)
2. Nafamostat mesylate	2.1% to 9%
3. Ulinastatin	1.6% to 7.3%
Other pharmacological agents	
1. Octreotide	2.4% to 5.5%
2. Somatostatin	5.6% to 8.9%
3. Glyceryl trinitrate	8%; 5.1% (transdermal), 7.8% (sublingual)
Fluid therapy	3%-6.7%
Prophylactic pancreatic duct stenting	1%-20%
Cannulation Techniques	
1. Double guidewire technique	10%-17%
2. Transpancreatic biliary sphincterotomy (TPS)	3.2%-11.9%
3. Needle-knife papillotomy (NKPP)	1%-7.6%
4. Needle-knife fistulotomy (NKF)	3.9%-4.5%
Combination therapies	
1. Rectal NSAIDs and Fluid therapy	1%-6%
2. Rectal NSAIDs and Pancreatic Duct Stenting	1.1%-11.1%
3. Rectal NSAIDs and topical epinephrine	5.3% to 6.7%

beneficial in lowering the risk of PEP when DGT technique for cannulation is utilized.[168]

III. Rectal NSAIDs and Topical Epinephrine

A recent retrospective study by Torun et al. concluded that submucosal epinephrine injection in conjunction with rectal indomethacin significantly reduced the incidence of PEP,[169] however comparative effectiveness, multicenter, double-blinded, randomized trials have not shown any benefit compared to rectal indomethacin alone.[170,171] A large multicenter RCT in China, terminated at the interim analysis for safety concerns and futility, showed that combination of rectal indomethacin with papillary epinephrine spraying in fact increased the risk of PEP compared with indomethacin alone.[172]

CONCLUSION

PEP remains the most serious adverse event associated with ERCP. A variety of factors have been studied in an effort to reduce the frequency

and severity of PEP, but no single factor has been found to be universally successful. In practice, a combination of medications and techniques is often employed to lower the PEP rate as low as possible, recognizing that some patients will still develop pancreatitis. The interventions and estimated risk of PEP is summarized in Table 1. ■

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