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Reducing the Risk of Post-ERCP Pancreatitis

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Abstract:

Pancreatitis is the most common and potentially devastating complication of endoscopic retrograde cholangiopancreatography (ERCP), resulting in significant morbidity, occasional mortality, and increased healthcare expenditures. Accordingly, the prevention of post-ERCP pancreatitis (PEP) remains a major clinical and research priority. Strategies to reduce the incidence of PEP include thoughtful patient selection, appropriate risk-stratification, sound procedural technique, prophylactic pancreatic stent placement, and pharmacoprevention. Despite advances in all these areas, however, the incidence of PEP remains as high as 15% in high-risk cases. Thus, additional research

towards the goal of eliminating PEP is necessary. Herein is an evidence-based review of strategies to prevent pancreatitis after ERCP, focusing on recent important developments in the field.

Overview

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), occurring in 3-15% of cases, and resulting in substantial morbidity, occasional mortality, and healthcare expenditures in excess of $200 million annually in the United States.[1-3] About 5% of post-ERCP pancreatitis (PEP) will follow a severe course, requiring prolonged hospitalization and/or additional interventions to address anatomical complications.[1] Additionally, PEP is a significant source of endoscopist stress[4] and is believed to be the most common reason for malpractice lawsuits related to ERCP.[5] Accordingly, reducing the risk of PEP remains a major priority. Prevention strategies can be broadly divided into 5 areas: (1) appropriate patient selection, (2) risk stratification of patients undergoing ERCP and meaningful use of this information in clinical decision-making, (3) atraumatic and efficient procedural technique, (4) prophylactic pancreatic stent placement, and (5) pharmacoprevention.

Definition

PEP is most frequently diagnosed according to consensus criteria originally established in 1991: 1) new or increased abdominal pain that is clinically consistent with acute pancreatitis; *and* 2) associated pancreatic enzyme elevation at least three times the upper limit of normal twenty-four hours after the procedure; *and* 3) resultant

hospitalization (or prolongation of existing hospitalization) of at least two nights. This definition is straightforward and widely accepted, but is limited by its subjective nature. Specifically, the interpretation of post-ERCP pain and the decision to hospitalize a patient after the procedure are nonobjective and variable across practice styles and institutional policies. Thus, between-study and between-center comparisons of PEP rates are often invalid and must be interpreted with caution, and blinding to treatment allocation is particularly important in PEP prevention trials.

A proposed alternative to the consensus definition is the standard Atlanta Classification for the diagnosis of acute pancreatitis, which mandates presence of 2 of the 3 following features: 1) abdominal pain typical of acute pancreatitis; 2) at least a 3-fold elevation in serum amylase or lipase levels; and 3) evidence of pancreatitic inflammation on abdominal imaging.[6] A prospective comparative study demonstrated the Atlanta definition to be more sensitive,[7] however the clinical impact of this more sensitive diagnostic approach – which may only capture additional mild (self-limited) cases – is unclear. Furthermore, the radiation exposure and costs of systematic CT scanning in all patients with post-ERCP pain are not justified.

Patient selection

Judicious patient selection for ERCP remains the most important strategy for reducing the incidence of PEP. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) allow highly accurate pancreaticobiliary imaging while avoiding the significant risks of ERCP, especially in the confirmation or exclusion

of choledocholithiasis.[8-10] Additionally, these tests and other non-invasive modalities (such as radionucleotide-labeled scan and percutaneous drain fluid analysis) are very accurate in diagnosing a multitude of other pancreaticobiliary processes (eg; chronic pancreatitis, malignancy, and leaks), often obviating the need for diagnostic ERCP. The EPISOD study – a randomized trial of ERCP, manometry, and sphincterotomy for patients with unexplained pancreaticobiliary pain (formerly Type 3 sphincter of Oddi dysfunction) – has largely eliminated the role of ERCP in the evaluation of this challenging and complication-prone patient population.[11] Thus, the utilization of ERCP as a diagnostic test has steadily declined in favor of less invasive but equally accurate alternative tests, and ERCP has appropriately become a near-exclusively therapeutic procedure – strictly reserved for patients with a high pre-test probability of intervention.

Risk stratification:

Risk-stratification of patients based on established clinical and endosocopic characteristics can inform the decision-making process that surrounds: 1) proceeding with ERCP, 2) referral to a tertiary center for the procedure, 3) prophylactic stent placement, 4) pharmacoprevention (including the aggressiveness of fluid resuscitation), and 5) post-procedural hospital observation.

Risk factors for PEP can be divided into patient-related and procedure-related characteristics. The definite and probable patient-related factors that predispose to PEP are: a clinical suspicion of sphincter of Oddi dysfunction (SOD), a history of prior PEP, a history of recurrent pancreatitis, normal bilirubin, younger age, and female sex. The

definite and probable procedure-related risk factors for PEP are: difficult cannulation, pancreatic duct wire passages (see below), pancreatic sphincterotomy, ampullectomy, repeated or aggressive pancreatography, and short-duration balloon dilation of an intact biliary sphincter. Two recent systematic reviews have affirmed the association of most of these factors with PEP.[12, 13] Additional risk factors that have been implicated, but are not definitively accepted as independent predictors of PEP are precut (access) sphincterotomy, pancreatic acinarization, long-duration balloon dilation of an intact papilla, biliary sphincterotomy, self-expanding metal stent placement, non-dilated bile duct, intraductal papillary mucinous neoplasm, intraductal ultrasound, and Billroth 2 anatomy.

It is important to consider that predictors of PEP appear to be multiplicative in nature.[14, 15] For example, a widely referenced multi-center study by Freeman *et al.*, predating non-steroidal anti-inflammatory (NSAIDs) use and prophylactic pancreatic stent placement, showed that a young woman with a clinical suspicion of SOD, normal bilirubin, and a difficult cannulation has a risk of PEP in excess of 40%.[14] A more recent RCT confirmed this non-linear relationship, even with the use of NSAIDs and stents.[16] In addition, patients with a clinical suspicion of SOD, particularly women, are not only at increased risk for PEP in general, but are also more likely to develop severe pancreatitis and death.[14, 17] When considering the risk-benefit ratio of ERCP in this patient population, not only should the patient's overall risk of PEP be assessed, but their probability of experiencing a more catastrophic clinical course should also be considered and discussed.

Several clinical characteristics are thought to reduce the risk of PEP. First, biliary interventions in patients with a pre-existing biliary sphincterotomy probably confer a very low risk of PEP. Prior sphincterotomy will have generally separated the biliary and pancreatic orifices, allowing avoidance of the pancreas, and rendering pancreatic sphincter or duct trauma unlikely. Further, patients with significant chronic pancreatitis, in particular those with calcifications, are at lower risk for PEP because of gland atrophy, fibrosis, and consequent decrease in exocrine enzymatic activity.[14] Similarly, the progressive decline in pancreatic exocrine function associated with aging may protect older patients from pancreatic injury.[18] Lastly, perhaps due to post-obstructive parenchymal atrophy, patients with pancreatic head malignancy appear to be relatively protected as well.[19]

Endoscopist procedure volume is suggested to be a risk factor for PEP, although multi-center studies have not consistently confirmed this relationship, presumably because low-volume endoscopists tend to perform lower-risk cases. Nevertheless, potentially dangerous cases (based on either patient-related factors or anticipated high-risk interventions) are best referred to expert medical centers where a high-volume endoscopist with expertise in prophylactic pancreatic stent placement can perform the case, and where more experience with rescue from serious complications may improve clinical outcomes.[20] Similarly, trainee involvement in ERCP is a possible independent risk factor for PEP, although results of existing multivariable analyses are conflicting.[14, 21] Additional research focused on improving the process of ERCP training is necessary to minimize the potential contribution of trainee involvement to the induction of PEP.

Procedure technique:

Difficult cannulation and pancreatic duct injection are both independent predictors of PEP, thus interventions that improve the efficiency of cannulation and limit injection of contrast into the pancreas are likely to decrease risk. Guidewire-assisted cannulation accomplishes both by employing a small-caliber wire with a hydrophilic tip to negotiate the papilla, subsequently guiding passage of the catheter into the intended duct. Since the wire is thinner, softer, and more maneuverable than the cannula, it is easier to advance across a potentially narrow and off-angle orifice. Moreover, this process limits the likelihood of an inadvertent pancreatic or intramural papillary injection. Indeed, a meta-analysis of randomized controlled trials (RCTs) enrolling 3450 subjects demonstrates that guidewire-assisted cannulation reduces the risk of PEP by approximately 50% (RR 0.51, 95% CI 0.32 to 0.82).[22] Two subsequent RCTs that were underpowered to detect medium or small differences in PEP have not confirmed the protective benefit of wire-guided cannulation, but one of these studies did show benefit in terms of efficiency of cannulation.[23, 24] At this juncture, the literature in aggregate does suggest that wire-guided cannulation is the preferred approach, although gentle injection of contrast to better define anatomy is often employed when the wire does not advance seamlessly into either duct.

The most significant risk of wire-guided cannulation is pancreatic duct perforation, which may occur during intended biliary cannulation if the wire is actually in the pancreatic duct, where forceful advancement may result in sidebranch penetration. Similarly, excess force during intended pancreatic cannulation may result in perforation due to

variations in pancreatic ductal anatomy. Thus cautious wire advancement is critical and gentle injection of contrast is advisable if the wire does not travel seamlessly in its intended direction. A recent randomized trial demonstrated that control of the guidewire by the endoscopist – using the so-called short-wire technique – results in fewer complications (including PEP) than assistant control. This finding is mechanistically plausible because the controlling endoscopist is best suited to sense and quickly adjust to tactile feedback from the wire, reducing the likelihood of pancreatic injury. Even though I am personally an advocate for this technique, it is important to consider that the results of this study may have been influenced by its unblinded nature – given the aforementioned subjectivity in the definition of PEP, unmasking of clinicians caring for study subjects and those adjudicating the outcomes could have biased in favor of the endoscopist-control group. Additional data are needed before ERCP teams are expected to change their approach on this fundamental issue.

When initial cannulation attempts are unsuccessful, several alternative techniques are available to facilitate biliary access. The double-wire technique is a common second-line approach when initial cannulation attempts result in unintentional passage of the wire into the pancreas. The wire is left in the pancreatic duct, thereby straightening the common channel, partially occluding the pancreatic orifice, and providing a fluoroscopic reference vector, allowing subsequent biliary access alongside the existing pancreatic wire. This technique appears particularly helpful when cannulation is impeded by difficult anatomy, such as when there is a malignant biliary stricture or the ampulla is intradiverticular.[25] While those who use this technique frequently (author included)

espouse its benefits, a recent Cochrane Collaboration review suggests that the double-wire technique does not improve cannulation success but increases the risk of PEP compared to other techniques like pre-cut sphincterotomy and cannulation alongside a pancreatic stent.[26] However, all component studies in this meta-analysis were unblinded, the experience and comfort level of participating endoscopists with the double-wire technique in these studies is unclear, and most included patients did not receive rectal NSAIDs or a prophylactic stent. Thus, as we await additional data, double-wire cannulation remains a viable option for endoscopists experienced in this technique.

If employing the double-wire cannulation technique, it is important to consider that there is mounting evidence that pancreatic wire passage increases the risk of pancreatitis.[27-29] Along these lines, an RCT of difficult cannulation cases requiring this technique demonstrated that prophylactic pancreatic stent placement reduced the incidence of PEP in this patient population.[30] On this basis, some experts believe that a prophylactic pancreatic stent should be placed in all patients requiring double-wire cannulation. Others, however, believe that passage of a wire in the pancreas does not always predispose to PEP, and that pancreatitis in this context may be related to the preceding difficult cannulation. Thus if the double wire technique is employed early (within 2-3 cannulation attempts) in a low-risk patient, and the wire advances seamlessly in a typical pancreatic trajectory, stent placement may not be necessary if rectal indomethacin is given.

Additional alternative cannulation techniques include wire cannulation alongside a pancreatic stent, needle knife pre-cut sphincterotomy, transpancreatic septotomy, and fistulotomy. Although RCTs have attempted to determine the optimal rescue technique, it is likely that each of these methods is most appropriate in certain circumstances, depending on anatomic factors and operator experience. Based on existing evidence, the specific cannulation technique appears to be less important than implementing these techniques early in a challenging case. This principle is best demonstrated by a meta-analysis of six randomized trials which showed that early precut sphincterotomy significantly reduced the risk of PEP when compared to repeated standard cannulation attempts (2.5% vs. 5.3%, OR 0.47).[31] Additional observational and randomized data have also suggested that precut sphincterotomy, especially if successful, is not an independent risk factor for PEP as previously considered,[32-34] however the technique should be performed by endoscopists with adequate expertise to limit serious complications.[17] One recent study has reported that early pre-cut sphincterotomy without a prophylactic pancreatic stent is equivalent to, but more cost-effective than ongoing cannulation attempts alongside a prophylactic stent (with late pre-cut if necessary).[35] While these findings support the concept that early implementation of alternative techniques is advantageous, this study was profoundly underpowered (N=100; 4 outcome events) to detect a difference in PEP. Based on existing evidence, withholding a prophylactic stent after a difficult cannulation that is followed by pre-cut sphincterotomy should be strongly discouraged (see below).

Other technical strategies that reduce the risk of PEP include minimizing the frequency and vigor of pancreatic duct injection and avoiding balloon dilation of an intact sphincter. In coagulopathic patients with choledocholithiasis and native papillae, balloon dilation can be avoided by providing real-time decompression with a bile duct stent and repeating the ERCP with sphincterotomy and stone extraction when coagulation parameters have been restored. If this is not possible, and balloon dilation is mandatory, longer duration dilation (2–5 minutes) appears to result in lower rates of pancreatitis compared with 1-minute dilation.[36] Of note is that balloon dilation *after* biliary sphincterotomy to facilitate large stone extraction does not appear to increase the risk of PEP.[37]

Prophylactic pancreatic stent placement:

Pancreatic stent placement (PSP) is believed to reduce the risk of PEP by relieving pancreatic ductal hypertension that develops as a result of transient procedure-induced stenosis of the pancreatic orifice. Fourteen published RCTs and as at least as many non-randomized studies have consistently demonstrated that PSP reduces the risk of PEP by approximately 60%.[38, 39] Importantly, prophylactic pancreatic stents appear to profoundly reduce the likelihood of severe and necrotizing pancreatitis.[38, 39]

The demonstrated benefits of PSP must be weighed against several potential disadvantages. First, attempting to place a pancreatic duct (PD) stent with subsequent failure actually increases the risk of PEP above baseline by inducing injury to the pancreatic orifice, but providing no subsequent ductal decompression.[40] Second,

significant non-pancreatitis complications of PSP, such as stent migration and duct perforation, occur in up to 5% of cases.[41] Further, prolonged stent retention may induce ductal changes which resemble chronic pancreatitis.[42] PSP is associated with some patient inconvenience and increased costs by mandating follow-up abdominal radiography to ensure spontaneous passage of the stent and additional upper endoscopy to retrieve retained stents in approximately 10% of cases. Nevertheless, PSP is widely regarded as an effective means of preventing PEP, is commonly used in academic medical centers in the United States,[43] and is recommended by society guidelines.[44, 45] In light of the aforementioned concerns and the associated costs, however, PSP should be reserved for high-risk cases.[44, 46] Based on the known independent patient and procedure-related risk factors for PEP, experts have suggested that the following cases are appropriate for prophylactic stent placement: 1) clinical suspicion of SOD (whether or not manometry or therapeutic intervention performed), 2) Prior PEP, 3) difficult cannulation, 4) precut (access) sphincterotomy, 5) pancreatic sphincterotomy (major or minor papilla), 6) endoscopic ampullectomy, 7) aggressive instrumentation or injection of the pancreatic duct, and 8) balloon dilation of an intact biliary sphincter.[43, 47]

There is limited consensus regarding the optimal stent length and caliber.[43] Although an early study suggested improved outcomes with 3 or 4-French stents,[48] a subsequent RCT showed no difference in PEP rates but a higher insertion success rate with the 5-Fr stents.[49] However, a recent network meta-analysis comprising the broader prophylaxis literature suggests that 5-Fr stent are most effective.[50] Similarly, there is

little consensus regarding optimal stent length. Most experts agree that the intra-pancreatic tip of the stent should not rest at the pancreatic genu or in a side-branch,[47] however whether short stents (ending in the pancreatic head) or longer stents (ending in the body or tail) are preferable is unknown, and comparative effectiveness studies in this area are needed.

Pharmacoprevention:

The pharmacological prevention of PEP has been reinvigorated recently by unprecedented progress in this area, especially pertaining to the administration of rectal NSAIDs and aggressive hydration with lactated ringer's solution (LR). Other mechanistically intriguing agents undergoing further investigator include sublingual nitroglycerin, nafamostat, magnesium, calcineurin inhibitors, and hemin.[51] Although a discussion of these agents is outside the scope of this review, combination therapy including one or more of these medications in addition to rectal NSAIDs and LR is likely to represent the future of pharmacoprevention.

Rectal non-steroidal anti-inflammatory drugs

Although their exact mechanisms of action remain unclear, rectal indomethacin and diclofenac are believed to protect against PEP because they are potent inhibitors of phospholipase A2, which appears particularly important in initiating the inflammatory cascade that leads to pancreatitis.[52] At least 15 RCTs evaluating the efficacy of rectal NSAIDs have been published; recent meta-analyses of have consistently demonstrated an associated reduction in PEP in the range of 40-60%.[53-57] Two recent observational

studies comparing clinical practice eras before and after the routine administration of rectal NSAIDs have confirmed this benefit, providing some evidence of real-world clinical effectiveness.[58, 59]

Since the most high profile of the published RCTs supporting the use of rectal NSAIDs was conducted in high-risk subjects,[16] controversy has remained regarding the role of NSAIDs in average-risk cases. This controversy was further fueled by a recent single-center RCT enrolling consecutive (mostly average and low-risk) patients, which showed no benefit associated with rectal indomethacin.[60] However, subsequent meta-analyses restricted to studies enrolling average-risk cases highlight that this study is truly an outlier relative to the existing literature, and despite its inclusion, rectal NSAIDs appear effective in the average-risk patient population.[55, 57, 61] Most recently, the largest published RCT in PEP pharmacoprevention showed a 54% relative risk reduction associated with administration of rectal indomethacin compared to no intervention among 2014 average-risk subjects.[62] Although this study was not exclusively designed to assess the impact of rectal NSAIDs in average-risk cases and subjects were not blinded to study group assignment, the findings do support the universal use of indomethacin. In light of these data, the very low cost of NSAIDs, and their highly favorable safety profile, it is reasonable to administer these medications in all patients undergoing ERCP, as recommended by European Society of Gastrointestinal Endoscopy.[44]

Data on the timing of rectal NSAIDs administration are also evolving. Most RCTs administered the drug before ERCP whereas at least 4 administered it following the procedure. Existing meta-analyses suggest that the timing of administration does not impact efficacy.[53, 54, 57, 63] However, the aforementioned large-scale RCT evaluating the effect of indomethacin in >2000 average risk patients also compared pre-administration (30 minutes prior to ERCP) vs. post-administration (immediately after ERCP) among 586 high-risk subjects. In this subgroup, administration before ERCP reduced the risk of PEP by greater than 50%.[62] To reconcile the findings of this study with those of other trials in which NSAIDs were given after ERCP, our approach is to administer the medication at the beginning of cannulation, ensuring that it is not delivered too late in the event of a very long case (if delivered after ERCP) or too early (when delivered before ERCP) in the event cannulation is delayed (eg, case delay or difficulty advancing scope to papilla). This approach seems to integrate well into real-world clinical practice wherein accurately predicting 30 minutes before the next ERCP is challenging.

All but two published RCTs have evaluated a 100 mg dose of indomethacin or diclofenac; one study employed a 50 mg dose of diclofenac and another recent study employed a 100 mg dose of naproxen.[64] Thus, a 100 mg dose of indomethacin or diclofenac is most evidence-based. Since rectal NSAIDs are generally safe, there is ongoing interest in the utility of higher doses. Indeed, an observational study from Denmark suggests that the standard dose of rectal NSAIDs may not be as effective in patients with increased body weight.[65] An ongoing RCT comparing indomethacin at standard vs. high dose (150 mg immediately after ERCP followed by a 50 mg dose 4

hours later) will help answer this question. RCTs evaluating NSAIDs administered via non-rectal routes have demonstrated lack of efficacy in preventing PEP, and thus non-rectal delivery is not recommended.

Available data indicate that rectal NSAIDs are effective *in addition* to PSP in high-risk cases, but to date, there are no clinical trial data examining whether indomethacin is effective when administered *instead* of PSP. Since PSP is technically challenging, potentially dangerous, time consuming, and costly [66-69], major clinical and cost benefits in ERCP practice could be realized if rectal NSAIDs were to obviate the need for pancreatic stent placement. Two hypothesis-generating analyses suggest that the combination of NSAIDs and PSP is not superior to rectal NSAIDs alone.[70 71] An ongoing multi-center randomized non-inferiority trial comparing rectal indomethacin alone vs. the combination of indomethacin and prophylactic stent placement will hopefully provide concrete guidance for this critical management issue.[72] Until the results of this trial are available, however, the combination of rectal indomethacin and prophylactic stent placement should remain the standard approach to preventing PEP in high-risk patients.

Aggressive Lactated Ringer's solution

Aggressive intravenous fluid hydration with LR (which attenuates the acidosis that appears to promote zymogen activation and pancreatic inflammation) may be an effective intervention for PEP by favorably affecting physiologic (pH) and micro-anatomic (pancreatic parenchymal perfusion) parameters. Elegant preclinical models indicate that lactate reduces pancreatic injury though immunomodulatory mechanisms[73]

and a small RCT in non-ERCP pancreatitis observed less systemic inflammation in subjects who received LR compared to those who received saline.[74] Thus far, 4 RCTs[75-78] have shown lower PEP rates associated with LR administration. Three of these studies administered a prolonged infusion whereas the fourth evaluated the effect of a 1-liter bolus in conjunction with rectal indomethacin.[78] Additional large-scale studies are necessary to define the optimal infusion regimen, which would ideally be a bolus that can be delivered over a reasonable timeframe in the peri-procedural setting. Awaiting such data, our partly-evidence based approach is to infuse ~3 liters of LR in the peri-procedural setting to younger healthy patients. If they are admitted to the hospital with pain, LR is continued at a rate of 250-350 cc per hour overnight with close volume status assessment.

Summary:

a. *Pancreatitis is an important and potentially preventable complication of ERCP.*
b. *Thoughtful patient selection is critical in reducing PEP; in this era of highly accurate diagnostic alternatives, ERCP should be a near-exclusively therapeutic procedure.*
c. *Patients can be risk-stratified for PEP according to patient and procedure-related characteristics, guiding prophylactic interventions and facilitating early detection of the complication.*
d. *Contrast-facilitated cannulation, aggressive/repeated pancreatic injection, and dilation of an intact biliary sphincter should generally be avoided.*

e. *In the case of difficult cannulation, alternate techniques, such as pre-cut sphincterotomy or the double-wire technique, should be implemented early.*

f. *Prophylactic pancreatic stents should be placed in all high-risk cases.*

g. *Rectal NSAIDs should be administered in all high-risk cases and based on mounting evidence and a highly favorable risk-benefit ratio, should be considered in all patients undergoing ERCP.*

h. *Aggressive LR solution should be considered in the peri-procedural setting.*

i. *Ongoing research will further improve our ability to efficiently and effectively prevent PEP.*

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Table 1: Overview of PEP prevention strategies

1. Patient Selection

- ERCP should be a near-exclusively therapeutic procedure
- Use MRCP and EUS to select patients for ERCP who have a high likelihood of therapeutic intervention, in whom of the risk-benefit ratio is most favorable

2. Risk Stratification

- Stratify risk on the basis of validated patient and procedure-related predictors
- Risk stratification should inform whether to:

  1) Proceed with ERCP

  2) Refer to a tertiary center

  3) Place a prophylactiic pancreatic stent

  4) Administer rectal NSAIDs

5) Administer aggressive IVF

6) Observe in the hospital after ERCP

3. Procedural Technique

- Employ wire-guided cannulation technique
- Implement alternate cannulation techniques early in the case of challenging biliary access
- Avoid aggressive/repeated pancreatic injection and short-duration dilation of an intact biliary sphincter.

4. Prophylactic Pancreatic Stenting

- Ensure appropriate training and expertise in stent placement
- Place 3, 4, or 5-french temporary stents in high-risk cases
- Ensure that internal tip is not placed at the pancreatic duct genu or in a side branch

5. Pharmacoprevention

- Administer 100mg rectal indomethacin or diclofenac before, during, or after ERCP in high-risk cases
- Strongly consider rectal NSAIDs in average-risk cases
- Administer NSAIDs *in addition* to prophylactic stent placement in high-risk cases
- Consider aggressive IV Lactated Ringer's solution to prevent PEP and mitigate severity

Table 2: Definite and probable predictors of post-ERCP pancreatitis

Patient-related factors	Procedure-related factors
Suspected sphincter of Oddi dysfunction (SOD)	Difficult cannulation
Prior post-ERCP pancreatitis	Ampullectomy
History of recurrent pancreatitis	Pancreatic sphincterotomy
Younger age	Pancreatic wire passages
Female sex	Repeated or aggressive pancreatography
Normal bilirubin	Short-duration balloon dilation of an intact biliary sphincter