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Prevention of ERCP-induced Pancreatitis

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Abstract:

Pancreatitis is a common, costly, and occasionally devastating complication of endoscopic retrograde cholangiopancreatography (ERCP). Since post-ERCP pancreatitis (PEP) is important and potentially preventable, a comprehensive approach to risk reduction should be employed by all who perform ERCP. Strategies to reduce the incidence of PEP, which should be considered in every case, include thoughtful patient selection, 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. To this end, there are several ongoing and upcoming initiatives that will help elucidate the pathophysiology of PEP and optimize prophylactic interventions. Herein is an evidence-based review of approaches to prevent pancreatitis after ERCP, as well as an overview of pressing research questions in this important area.

1. Overview

Despite important advances over the last several decades, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) remains the most frequent complication of ERCP, occurring in 2-15% of cases, and accounting for substantial morbidity, occasional mortality, and increased healthcare expenditures (58, 80). Approximately 10% of those who develop PEP will follow a severe clinical course that results in prolonged hospitalization and/or additional interventions, leading to significant patient suffering (58, 80). It's been estimated that >700,000 ERCPs are performed annually in the United States. Assuming a mid-range post-ERCP pancreatitis rate of 5%, more than 35,000 cases of PEP occur in the US each year; average Medicare reimbursement for PEP is approximately $6000, resulting in an estimated annual cost burden in excess of $200 million (1). Furthermore, PEP is a source of significant endoscopist stress (78) and has been the most common reason for malpractice lawsuits relating to ERCP (33). Given the magnitude of this problem, prevention of PEP remains a major clinical and research priority.

2. 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 a syndrome of 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 (36, 58). This definition is straightforward and widely accepted, but is primarily limited by its subjective

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nature. Specifically, the interpretation of post-ERCP pain and the decision to hospitalize a patient after the procedure – both central to the consensus diagnosis of PEP – are nonobjective and variable across practice styles and institutional policies. Indeed, practitioners with a lower threshold to hospitalize patients after ERCP may observe a higher rate of PEP, and vice versa. Thus, between-study and between-center comparisons of PEP rates 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 clinical definition 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 cross-sectional imaging (14). A prospective comparative study demonstrated that the clinical definition is more sensitive than the consensus definition, (9) however the clinical impact of this more sensitive diagnostic approach – which may only capture additional mild (self-limited) cases – is unclear. Further, the radiation exposure and costs of systematic CT scanning in all patients with post-ERCP pain are not justified.

Given the limitations of both definitions, additional research aiming to elucidate a practical and accurate diagnostic tool for PEP is of substantial importance. Ideally, this tool would be objective, applicable early in the course of disease, and would reliably diagnose patients destined to develop a clinically important adverse course, in whom hospitalization (and other interventions) is likely to be beneficial.

3. Pathophysiology

Our understanding of the mechanisms underlying PEP has evolved slowly and remains limited. As the only true human model for the study of acute pancreatitis, fully elucidating the pathophysiology of PEP is of substantial importance, not only to guide the development of novel pharmacologic interventions, but also to expand our understanding of pancreatitis in general. It is hypothesized that PEP results from some combination of mechanical, thermal, chemical, allergic, or infectious injury, and/or increased pancreatic duct hydrostatic pressure. This initial injury leads to premature intra-pancreatic activation of trypsinogen (111), which – in patients with genetic or environmental predisposition – incites the inflammatory cascade. The relative contribution of each of the aforementioned injurious factors remains unclear and is probably variable, but no single factor appears dominant. Thus a multifactorial approach involving several complimentary pharmacologic and mechanical prophylactic measures addressing different mechanisms of injury may be the most effective approach to PEP prevention. Alternatively, interventions that impact downstream inflammatory targets (e.g. zymogen activation or the early inflammatory cascade) or patient predisposition (e.g. microbiome) may prove most effective. A principal objective of an upcoming large-scale comparative effectiveness trial of indomethacin and prophylactic stent placement is to develop a robust repository of biological specimens from study participants to drive translational research elucidating the pathophysiology of PEP and pancreatitis in general.

4. Framework for a Comprehensive Approach to PEP Prevention

Since PEP is potentially preventable, a comprehensive approach to risk reduction should be employed by all who perform ERCP (**Figure 1**). Preventive 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.

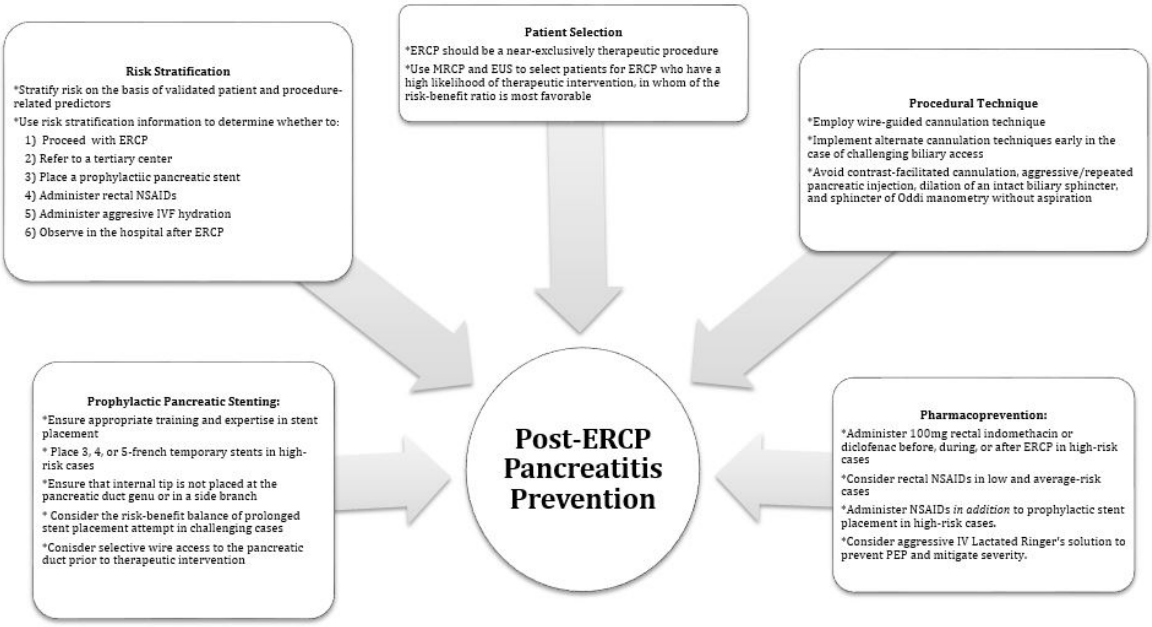

Figure 1: Framework for a comprehensive approach to post-ERCP pancreatitis prevention

All five strategy areas should be considered in every case, and the latter two implemented when appropriate.

5. Patient Selection

Thoughtful patient selection prior to ERCP remains the most important strategy in 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 (68, 108, 112). Two large meta-analyses have demonstrated that EUS is highly sensitive and specific in the detection of bile duct stones (sensitivity 89-94%; specificity 94-95%) (62, 133). Similarly, MRCP has a sensitivity of 85 to 92% and a specificity of 93 to 97% for the same indication, (112, 136) although MRI appears less sensitive than EUS for stones smaller than 6 mm (19, 143). Additionally, EUS, MRI, 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 (e.g. chronic pancreatitis, malignancy, and leaks), often obviating the need for ERCP (37, 61, 82).

Indeed, the utilization of ERCP as a diagnostic procedure has steadily declined in favor of less invasive but equally accurate alternative tests, and ERCP has appropriately become a near-exclusively therapeutic procedure reserved for patients with a high pre-test probability of intervention (93, 96). This trend is consistent with recent clinical practice guidelines on the role of endoscopy in the evaluation of choledocholithiasis and the National Institutes of Health consensus statement on ERCP for diagnosis and therapy, both favoring less invasive tests over ERCP in the *diagnosis* of biliary disease (2, 32).

An exception to the widespread practice of reserving ERCP for patients with a high likelihood of therapeutic intervention has been the evaluation of patients with suspected sphincter of oddi dysfunction (SOD), for which an accurate, less-invasive alternative to ERCP-guided sphincter of Oddi manometry (SOM) remains elusive (40, 113). Even when considering patients for SOM, however, thoughtful clinical judgment is necessary to select those who are most likely to benefit from the procedure. A recent multi-center randomized trial (the EPISOD study) has demonstrated that there appears to be no role for

ERCP in patients with suspected SOD but no laboratory or radiographic abnormalities (previously known as type 3 SOD) (34). Additional studies are necessary to determine whether diagnostic ERCP with SOM is truly beneficial in cases of suspected type 2 biliary or pancreatic SOD (recurrent unexplained pancreatitis). Pending such studies, many experts believe ERCP remains reasonable in such cases after careful assessment of the risk-benefit ratio and detailed informed consent. Another possible exception to the therapeutic ERCP trend may be the evaluation of biliary complications in liver transplant recipients, for whom a recent retrospective study suggested that *diagnostic* ERCP is a reasonable and efficient clinical approach in this patient population based on a high likelihood of therapeutic intervention and a very low rate of complications, in particular PEP (48).

6. Recognizing Patients at Increased Risk for PEP

A substantial amount of research over the last two decades has contributed to our understanding of the independent risk factors for post-ERCP pancreatitis. These risk factors can be divided into patient-related and procedure-related characteristics. The definite and probable patient-related risk factors that predispose to PEP are: a clinical suspicion of sphincter of SOD (regardless of whether or not sphincter of Oddi manometry is performed) (35, 53, 56, 58, 87, 89, 121), a history of prior PEP (27, 56, 59, 135), a history of recurrent pancreatitis (89), normal bilirubin (56, 94), younger age,(27, 85, 90, 140) and female gender (56, 89, 140). The definite and probable procedure-related risk factors for PEP are: difficult cannulation (56, 58, 135), pancreatic sphincterotomy (27, 56), ampullectomy (46, 107), repeated or aggressive pancreatography (56, 58, 85, 89), and short-duration balloon dilation of an intact biliary sphincter (20-22) (15, 44, 139). Two recent systematic reviews have affirmed that most of these factors are independently associated with PEP (26, 43). Additional risk factors that have been implicated, but are not concretely accepted as independent predictors of PEP are precut (access) sphincterotomy (see below) (58, 89, 135), pancreatic duct wire passage (see below), biliary sphincterotomy, self-expanding metal stent placement, non-dilated bile duct, intraductal papillary mucinous neoplasm, and Billroth 2 anatomy.

Operator (endoscopist)-dependent characteristics have also been implicated in the risk of PEP. Endoscopist procedure volume is suggested to be a risk factor for PEP, although multi-center studies have not confirmed this trend, presumably because low-volume endoscopists tend to perform lower-risk cases (56, 58, 85, 109). 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 (64, 65). Similarly, trainee involvement in ERCP is a possible independent risk factor for PEP, although results of existing multivariable analyses are conflicting (27, 56). It stands to reason that inexperienced trainees may augment procedure-related risk factors, such as prolonging a difficult cannulation or delivering excess electrosurgical current during an inefficient pancreatic sphicterotomy, etc. Therefore, an improved understanding of the process of ERCP training is necessary to minimize the contribution of trainee involvement to the development of PEP. Future research focused on defining ERCP training metrics and developing an evidence-based list of appropriate fellow cases based on stage of training and skill level is needed. Further, defining the optimal parameters that guide trainee-attending scope exchange during any particular case or intervention is necessary in order to maximize learning potential while minimizing patient risk.

Several additional points regarding clinical risk stratification are worth considering. First, predictors of PEP appear synergistic in nature (56). For example, a widely referenced multi-center study by Freeman *et al.*, predating 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% (56). Second, patients with a clinical suspicion of SOD, particularly women, are not only at increased risk for PEP in general, but appear more likely to develop severe pancreatitis and death (56, 58, 132). 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 dramatic clinical course should also be considered and discussed. Additionally, several clinical characteristics are thought to significantly 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 making pancreatic sphincter or duct trauma unlikely. Further, patients with chronic pancreatitis, in particular those with calcific pancreatitis, are at low risk for PEP because of gland atrophy, fibrosis, and consequent decrease in exocrine enzymatic activity (56). Similarly, the progressive decline in pancreatic exocrine function associated with aging may protect older patients from pancreatic injury (83). Lastly, perhaps due to post-obstructive parenchymal atrophy, patients with pancreatic head malignancy appear to be relatively protected as well (12).

While understanding these aforementioned risk factors and incorporating them into clinical decision-making are important aspects of preventing PEP, additional research focused on developing more robust risk-stratification tools based upon existing literature and future multi-center studies is important. Such risk stratification instruments are unlikely to be developed using conventional statistical models (ie; multivariable regression analysis), and may require the use of novel, more advanced prediction methods involving artificial intelligence, such as machine learning – a technique that has already been successfully utilized in both business and medicine (137). In addition, a more specific understanding of how these tools' output should concretely direct clinical management is necessary.

7. Meaningful Use of Risk-Stratification Information

Armed with risk assessment information, clinicians can better inform patients about adverse events and tailor costly and potentially dangerous risk-reducing strategies. For example, prophylactic pancreatic stent placement and consideration of post-procedure hospital observation are appropriate for a patient predicted to be at high risk for PEP, but are not justified in low-risk cases.

Patient-related characteristics are not modifiable, but can be used (at least in part) to predict the risk of PEP prior to ERCP, allowing appropriate case selection and a meaningful discussion with the patient regarding the risk-benefit ratio of the procedure. For example, a young woman with suspected biliary SOD but moderate symptoms that are partially responsive to pain modulating therapy may elect to forgo ERCP after understanding her elevated risk of severe PEP. Procedural risk factors may occasionally be modified during the case (see below), but in combination with patient-related factors, allow a global assessment of a patient's overall risk profile, guiding clinical management. Indeed, the ability to risk-stratify patients can concretely influence the decision-making process that surrounds 1) proceeding with ERCP, 2) referral to a tertiary center, 3) fluid resuscitation, 4) prophylactic stent placement, 5)

pharmacoprevention, and 6) post-procedural hospital observation.

8. Procedure Technique

Efficient and atraumatic technical practices during ERCP are central to minimizing the risk of pancreatitis. Many of the procedure-related risk factors listed above, while predisposing to PEP, are mandatory elements of a successful case. Even though these high-risk interventions are unavoidable for execution of the clinical objective, certain strategies can be utilized to minimize procedure-related risk.

As mentioned, difficult cannulation and pancreatic duct injection are both independent risk factors for PEP. As such, interventions that improve the efficiency of cannulation and limit injection of contrast into the pancreas are likely to decrease the risk of pancreatitis. Guidewire-assisted cannulation accomplishes both, representing a major paradigm shift in ERCP practice. In contrast to conventional contrast-assisted cannulation, which may lead to inadvertent injection of the pancreatic duct or contribute to papillary edema, guidewire-assisted cannulation employs a small-diameter wire with a hydrophilic tip that is initially advanced into the duct, subsequently guiding passage of the catheter. Since the wire is thinner 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. A recent Cochrane Collaboration meta-analysis, which included 12 randomized controlled trials involving 3450 subjects, indeed confirms that guidewire-assisted cannulation reduces the risk of PEP by approximately 50% (RR 0.51, 95% CI 0.32 to 0.82) (134). A more recent prospective cohort study and randomized control trial revealed no difference in PEP between the contrast and guidewire-assisted groups (76, 88). However the results of these studies have been questioned for a multitude of reasons, including small sample sizes and selection bias.

When initial cannulation attempts are unsuccessful, alternative techniques to facilitate biliary access include pre-cut sphincterotomy, needle-knife fistulotomy, transpancreatic septomotomy, double-wire cannulation, and wire cannulation alongside a pancreatic stent (20, 131). While these techniques can be immensely helpful in gaining biliary access during challenging cases, some have been implicated as procedure-related risk factors for PEP. In many cases, however, the risk of PEP is actually driven by the preceding prolonged cannulation time that leads to increasing papillary trauma/edema. Therefore, implementing alternate cannulation techniques early in the case and in rapid succession is an important aspect of reducing PEP. 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) (23). Additional observational and randomized data have also suggested that precut sphincterotomy, especially if successful, is not an independent risk factor for PEP (66, 101, 129). Further studies are needed to help define the exact point at which the risk-benefit ratio favors precut sphincterotomy over repeated cannulation attempts, although the natural tendency to continue standard cannulation attempts beyond 5-10 minutes should be controlled, and alternative strategies should be attempted early in a difficult case.

The double wire technique is a common second-line approach when initial cannulation attempts result in repeated unintentional passage of the wire into the pancreas. The wire can be left in the pancreatic duct (PD), thereby straightening the common channel and partially occluding the pancreatic orifice, allowing subsequent biliary cannulation alongside the existing pancreatic wire. The double wire technique has been shown

to improve cannulation success compared to standard methods, (72) although some data suggest a higher incidence of PEP when a wire is passed into the PD (70, 100, 138). Furthermore, a recent randomized controlled trials of difficult cannulation cases requiring double wire technique demonstrated that prophylactic pancreatic stent placement reduced the incidence of PEP in this patient population (73). On this basis, some experts believe that a prophylactic pancreatic stent should be placed in all patients requiring double wire cannulation, or when the wire inadvertently passes more than once into the pancreas. Others, including the author, however, believe that placement of a wire in the pancreas does not independently predispose to PEP, and that pancreatitis in this context is generally related to the preceding difficult cannulation. If the double wire technique is employed early in a low-risk patient (within 2-3 cannulation attempts), and the wire advances seamlessly into the PD in a typical pancreatic trajectory, pancreatic stent placement may not be necessary, particularly if rectal indomethacin is administered.

Other technical strategies that reduce the risk of PEP include limiting the frequency and vigor of pancreatic duct injection, performing SOM using the aspiration technique (120), and avoiding short-duration balloon dilation of an intact sphincter, especially without prophylactic pancreatic stent placement (84). In coagulopathic patients with choledocholithiasis and native papillae, balloon dilation can be avoided by providing real-time decompression with an endobiliary 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 (84). Of note, is that balloon dilation *after* biliary sphincterotomy to facilitate large stone extraction does not appear to increase the risk of PEP (69, 95).

9. Procedure Equipment

Recent advances in ERCP equipment have increased technical success rates, but have unfortunately not reduced the risk of post-ERCP pancreatitis (57). In particular, the use of a sphincterotome has been shown to improve cannulation success compared with a standard cannula, but does not result in lower PEP rates (116). Similarly, comparative effectiveness studies evaluating sphincterotomes of various diameters have shown no difference in the risk of PEP (3, 60). There are no comparative effectiveness data evaluating the effect of various guidewires on the risk of pancreatitis (123).

Along these same lines, the type of contrast medium used during pancreatography does not appear to affect the incidence of PEP (63), and it remains unclear (but unlikely) that the now commonly used microprocessor controlled electrosurgical generators offer any protection over the previously popular pure-cut current for thermal injury-induced pancreatitis (54).

Overall, it appears that equipment has little to no impact on post-ERCP pancreatitis. Therefore practitioners should use the devices with which they are most comfortable for any particular indication in order to maximize technical success and efficiency, the latter of which is likely inversely related to the risk of PEP.

10. Prophylactic Pancreatic Stent Placement

One of many proposed mechanisms of PEP implicates impaired pancreatic ductal drainage caused by trauma-induced edema of the papilla. Pancreatic stent placement (PSP) is therefore thought 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. Twelve published randomized controlled trials and as at least as many non-randomized trials have consistently

demonstrated that PSP reduces the risk of PEP by approximately 60% (31, 92). Equally importantly, prophylactic pancreatic stents appear to profoundly reduce the likelihood of severe and necrotizing pancreatitis (31, 92).

It is important to keep in mind that the demonstrated benefits of PSP must be weighed against several potential disadvantages. First, attempting to place a 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 (30). Second, significant non-pancreatitis complications induced by PSP, such as stent migration and duct perforation, occur in ~4% of cases (92). Further, prolonged stent retention may induce ductal changes which resemble chronic pancreatitis (11), although the long term clinical relevance of these changes remains unclear. Finally, 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 5-10% of cases (24, 144).

Despite these considerations, PSP is widely regarded as an effective means of preventing PEP, is commonly used in academic medical centers in the United States (21), and is recommended by the European Society of Gastrointestinal Endoscopy (46). In light of the aforementioned concerns and the associated costs, however, PSP should be reserved for high-risk cases (38, 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 PD 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 (21, 55). Furthermore, preliminary studies have suggested that “salvage” PSP may be beneficial early in the course of PEP for patients who did not originally receive a stent, or in the case of early stent dislodgement (77, 86). Additional studies that include a control group are necessary to fully evaluate PSP for this indication.

Several questions surrounding PSP remain. First, the true magnitude of benefit of PSP remains unclear as none of the randomized controlled trials evaluating this intervention were blinded in nature. Studies without treatment allocation blinding are often biased in favor of the intervention and exaggerate perceived effects. Second, there is limited consensus regarding the optimal stent length and caliber (21). An early study suggested improved outcomes with 3 or 4-French stents (110), a subsequent trial showed no difference in PEP rates but a higher insertion success rate with the 5-Fr stents (24), and a recent network meta-analysis comprising the broader prophylaxis literature suggests that 5-Fr stent are most effective (4). 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 (55), 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.

Finally, the acceptable amount of time that can be spent on the insertion process in cases of difficult pancreatic access is unknown. While the merits of PSP have been clearly presented above, if achieving pancreatic access proves difficult, there is presumably a point of diminishing returns when the risk of additional attempts outweighs the benefit of stent placement, especially if insertion eventually proves unsuccessful. Future clinical studies are unlikely to answer this question in a methodologically rigorous fashion, therefore endoscopists should be aware of this important

clinical balance, and use their best judgment regarding the acceptable duration of time for stent insertion. One potential approach to circumvent this problem in cases of anticipated stent placement (for example ampullectomy or SOD cases) is to place and maintain a guidewire in the pancreatic duct early in the case in order to guarantee pancreatic duct access later on, avoiding the occasional phenomenon of failing to identify the pancreatic orifice due to the anatomic distortion that develops as a consequence of trauma, edema, or bleeding. Another approach is to place the prophylactic pancreatic stent prior to therapeutic intervention.

11. Pharmacoprevention

Pharmacoprevention for PEP has been a major research priority in the last 3 decades. Since 1977, nearly 100 randomized controlled trials (RCT) have evaluated over 35 pharmacologic agents, with largely disappointing results. Unfortunately, clinical trials in this area have suffered from inadequate sample sizes, low methodological quality, and negative, conflicting, or inconclusive results. Moreover, the pessimism surrounding PEP pharmacoprevention had been amplified by prior positive meta-analyses of agents that were subsequently disproved by further clinical investigation (7, 8). Until recently, no medication for the prevention of PEP had been adopted into widespread clinical use.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In the last decade, research focusing on rectal NSAIDs has provided renewed hope for pharmacoprevention. Four studies evaluating the protective effects of single-dose rectal indomethacin (97, 125) or diclofenac (79, 99) were reported between 2003-2008, and demonstrated conflicting, but generally encouraging results (79, 97, 99, 125). A meta-analysis of these RCTs, involving 912 patients, demonstrated a robust 64% reduction in PEP associated with rectal NSAIDs (relative risk [RR] 0.36, 95% CI 0.22 to 0.60) and no increase in associated adverse events (51).

Despite this meta-analysis, however, NSAIDs were seldom used in clinical practice due to the absence of conclusive RCT evidence (47). Moreover, it remained unclear whether NSAIDs provide incremental benefit over temporary pancreatic stent placement in high-risk cases. Therefore a large-scale, multi-center, methodologically rigorous RCT was conducted to definitively evaluate the efficacy of prophylactic rectal indomethacin for preventing PEP in high-risk cases (50). In this study, rectal indomethacin was associated with a 7.7% absolute risk reduction (number needed to treat = 13) and a 46% relative risk reduction in PEP (p=0.005). Additional RCTs of low-dose rectal diclofenac (105), the combination of rectal diclofenac plus infusion somatostatin (75), and the combination of indomethacin plus sublingual nitroglycerin (124) also demonstrated benefit. To date, eight RCTs of rectal NSAIDs have been published and recent meta-analyses (118, 128) have refined our estimates of effectiveness. On the basis of these data, 100 mg of rectal indomethacin or diclofenac can be recommended immediately before or after ERCP in all high-risk cases.

Controversy, however, remains within the advanced endoscopy community regarding the role of NSAIDs in low-risk cases. The aforementioned large-scale RCT – which represents the most definitive study of rectal NSAIDs to date – only enrolled subjects at elevated risk for pancreatitis, leading to the perception that these medications may only be effective in high-risk cases. A *post hoc* analysis of this RCT, however, demonstrated that the benefit associated with indomethacin was consistent across the entire spectrum of enrolled subjects' risk for PEP. In other words, among study subjects, those at mildly elevated risk (e.g. difficult cannulation) derived similar benefit to those at more substantially elevated risk (e.g. suspicion of SOD and pancreatic sphincterotomy),

suggesting that the indomethacin's relative risk reduction may be equivalent in all risk groups, including average risk cases (unpublished data). This observation is corroborated by data from the other published RCTs, which have demonstrated that rectal NSAIDs are effective in both high and average-risk cases (118, 128). In light of the very low cost of a single dose of NSAIDs, its highly favorable safety profile, and the above-mentioned data supporting its efficacy in low-risk cases, it is reasonable to consider these medications in all patients undergoing ERCP. The European Society of Gastrointestinal Endoscopy recommends rectal indomethacin or diclofenac for *all* patients undergoing ERCP as a grade A recommendation (45).

RCTs evaluating NSAIDs administered via non-rectal routes have demonstrated lack of efficacy in preventing PEP. Specifically, single RCTs of intravascular valdecoxib (18), oral diclofenac (28), and intramuscular diclofenac (117) have all yielded negative results. Even though these studies were underpowered and prone to type II statistical error, there are no existing data to support administration of prophylactic NSAIDs via any non-rectal route. Practitioners may be tempted to administer intravenous NSAIDs because of their widespread availability on anesthesia carts, their relative ease of delivery compared to suppository insertion, and the perception that their efficacy is a class effect. Endoscopists, however, should resist this temptation because of the above-mentioned data suggesting that IV NSAIDs are not effective, as well as the absence of proof of a class effect. Indeed, indomethacin and diclofenac are postulated to be specifically effective because they are particularly potent inhibitors of phospholipase A2 compared to other NSAIDs.

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 (39, 52, 130, 144), major clinical and cost benefits in ERCP practice could be realized if rectal NSAIDs were to obviate the need for pancreatic stent placement. A *post hoc*, hypothesis-generating analysis of the aforementioned indomethacin RCT suggested that subjects who received indomethacin alone were less likely to develop PEP than those who received a pancreatic stent alone or the combination of indomethacin and stent, even after adjusting for imbalances in PEP risk between groups (49). Additionally, a recent network meta-analysis comparing the data supporting PSP with those supporting prophylactic NSAIDs suggested that the combination of NSAIDs and PSP is not superior to rectal NSAIDs alone (5). Confirmatory research focusing on whether PSP remains necessary in the era of indomethacin prophylaxis is critical. To this end, a multi-center randomized non-inferiority trial comparing rectal indomethacin alone vs. the combination of indomethacin and prophylactic stent placement is in its final planning phase, should begin enrolling subjects late 2015, and will hopefully provide concrete guidance for this critical management issue. 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.

Other Agents

A recent systematic review of PEP pharmacoprevention aiming to provide an evidence-based research roadmap in this area identified bolus-administration somatostatin, sublingual nitroglycerin, and nafamostat as promising agents for which there is a high priority of additional confirmatory research. Topical epinephrine, aggressive intravenous administration of lactated ringer's solution, gabexate, ulinastatin, secretin, and antibiotics were identified as warranting exploratory research to justify a confirmatory RCT (81).

Somatostatin

Somatostatin is a potent inhibitor of pancreatic exocrine function and may therefore prevent or mitigate the pathophysiologic processes that lead to pancreatic inflammation. Six of the 12 RCTs comparing somatostatin to placebo have yielded positive results. Benefit has been demonstrated more consistently with bolus administration (4 of 6 published studies positive) than with infusion (3 of 8 published studies positive). All four published meta-analyses have suggested benefit associated with somatostatin, especially when delivered as a bolus, with a number needed to treat of approximately 12 (6, 8, 104, 114). Additionally, an RCT of somatostatin in combination with diclofenac demonstrated benefit (75). Given these inconclusive but promising results, a high-quality confirmatory RCT of bolus somatostatin (the most practical and likely cost-effective approach) is necessary.

Nitroglycerin

Nitroglycerin is a smooth muscle relaxant that may lower sphincter of Oddi (SO) pressure and increase pancreatic parenchymal blood flow.(126) Seven placebo-controlled RCTs have examined the effect of nitroglycerin on PEP. Three of these studies demonstrated a significant reduction in PEP (67, 98, 127), while the remaining four showed no benefit (16, 17, 74, 102). The two RCTs that used sublingual administration yielded positive results (67, 127). However, these results have been questioned because neither study defined pancreatitis according to the consensus definition (36), which may have contributed to the higher than expected event rates (18% (127) and 25% (67)). Transdermal administration of nitroglycerin has yielded conflicting results, with three RCTs showing no benefit (17, 74, 102), and one achieving a positive outcome (98). One RCT evaluating the role of intravenous nitroglycerin in preventing PEP in moderate to high-risk cases was terminated prematurely because of an interim analysis suggesting futility and a concerning frequency of adverse hemodynamic events (16). Five meta-analyses have demonstrated an approximately 30-40% reduction in risk associated with the use of nitroglycerin in the prevention of PEP (10, 13, 25, 42, 119). Since nitroglycerin is postulated to work by reducing SO pressure, it is unclear whether it would provide incremental benefit over pancreatic stent placement. Nevertheless, sublingual nitroglycerin may have a role in lower-risk cases, in resource-limited environments, or in place of pancreatic stent insertion. A recent small comparative effectiveness RCT demonstrated that the combination of sublingual nitroglycerin plus rectal indomethacin was more effective than indomethacin alone in a study sample that largely did not receive a pancreatic stent (124). Another methodologically rigorous large-scale multicenter RCT is warranted to confirm the effectiveness of combined sublingual nitroglycerin and rectal indomethacin in the appropriate patient population (high-risk cases in environments where stenting is not widely available). In the interim, sublingual nitroglycerin may be reasonable to consider in patients with a NSAIDs allergy or as an adjunct to rectal NSAIDs in high-risk cases that do not receive a prophylactic pancreatic stent.

Nafamostat mesylate

Nafamostat mesylate is a low molecular weight protease inhibitor that inhibits trypsin, a proteolytic enzyme considered to play an initial role in the pathogenesis of pancreatitis. Nafamostat has a half-life 20-times longer and a potency 10 to 100-times greater than gabexate mesylate, another protease inhibitor that has been the focus of much prior research and has been utilized in clinical practice in parts of the world (45). Three RCTs have identified a significant reduction in PEP associated with nafamostat: Yoo *et al.* 2011, n = 266 (2.8% vs. 9.1% in the nafamostat group vs. control group, p = 0.03) (141), Choi *et al.* 2009, n = 704 (3.3% vs. 7.4% in the nafamostat vs. group control, p = .018),(29) and Park *et al.,* n = 608 (three arms: 13.0% in control group vs. 4.0% in 20 mg nafamostat group vs. 5.1% in 50 mg nafamostat group, p < 0.0001) (106). A recent meta-analysis demonstrated an approximately

60% benefit associated with nafamostat (RR = 0.41; 95%CI 0.28-0.59) (142). Major concerns related to the use of nafamostat are its high cost, need for a prolonged intravenous infusion (7-25 hours), and apparent absence of benefit in high-risk cases. In light of these potentially prohibitive disadvantages, statistical modeling analyses are necessary to determine whether a confirmatory RCT could show a magnitude of benefit large enough to justify use of nafamostat in clinical practice.

Epinephrine

Epinephrine sprayed directly upon the papilla at the time of ERCP has been postulated to prevent PEP through direct relaxation of the SO and reduction of papillary edema by decreasing capillary permeability (103). Two RCTs have been conducted to evaluate the effect of topical epinephrine application on the papilla. In the study by Matsushita *et al.*, patients were randomized to 10 ml of either 0.02% epinephrine or saline sprayed on the papilla after diagnostic ERCP (91). PEP occurred in 4 of the 185 subjects in the control group compared to none of the 185 subjects in the epinephrine group; however this difference did not meet statistical significance (p = 0.12). In a subsequent study by Hua *et al.*, a total of 941 subjects undergoing diagnostic ERCP were randomized to 20 mL of 0.02% epinephrine or saline sprayed upon the papilla after ERCP (71). The incidence of pancreatitis was higher in the control group (31/480, 6.45%) than in the epinephrine group (9/461, 1.95%) (p = 0.009). Limitations of this study include the exclusion of all 'therapeutic' ERCP and the atypical definition of PEP (elevated serum amylase levels associated with at least two clinical symptoms 6–24 hours after ERCP), reducing the external validity of the results in this era of high-quality diagnostic pancreaticobiliary imaging. Because it works primarily by SO relaxation, the impact of topical epinephrine in addition to pancreatic stent placement is unclear, but this agent may be effective as a 'surrogate' stent, or in situations that do not warrant prophylactic stent placement. Even though topical epinephrine was categorized in research class 3, given the potential benefit, safety, low cost, and widespread availability of this agent, a large-scale confirmatory RCT in the appropriate patient population (high-risk therapeutic ERCP, limited availability of pancreatic stents) may be warranted (122).

Aggressive intravenous fluid (IVF)

Mechanistically, aggressive intravenous fluid (IVF) hydration with lactated Ringer's solution (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. Recently, two observational studies (41, 115) and a pilot RCT (22) have suggested the potential benefit of IVF in reducing both the incidence and severity of PEP. This RCT had a very small sample size, defined PEP atypically (abdominal pain & pancreatic enzyme elevation 2 or 8 hours after ERCP; no hospitalization requirement), and administered IVF over 8-10 hours, a schedule that is likely unrealistic in the US.

Because IVF administration can be dangerous in older persons or in those with sodium retaining states and the volume of infusion at which the risk-benefit ratio of IVF is optimized remains unknown, additional research is necessary to establish an evidence-based approach. Since data supporting its use in non-ERCP pancreatitis are robust and many practitioners already administer IVF for PEP prevention, large-scale RCTs may be warranted despite the absence of robust preliminary PEP data.

12. Future Directions

Despite the approaches outlined above, up to 15% of high-risk patients will still develop PEP. Appropriate patient selection, sound procedural technique, NSAIDs, and pancreatic stents have been effective in *improving* the problem, however

additional research in multiple areas is necessary to achieve the goal of *eliminating* PEP. To this end there are at least 13 active registered pharmacoprevetion RCTs evaluating topical epinephrine, hemin, magnesium, antibiotics, NSAIDs, and aggressive IVF hydration, among others. In addition, there are ongoing comparative effectiveness trials assessing the optimal timing and dose of rectal NSAIDs. As mentioned, an RCT comparing rectal indomethacin alone vs. indomethacin + PSP is in it's final planning phase. These and future studies should aim to improve the quality of PEP prevention research, embracing adequate sample sizes, strict patient follow up, adherence to the intention-to-treat principle, blinding (especially in prophylactic stent trials), strict use of the consensus definition (until more accurate diagnostic criteria or tests are validated), and involvement of a data and safety monitoring board to ensure methodologic rigor and study data integrity.

13. References

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