Curr Treat Options Gastro (2022) 20:445–468
DOI 10.1007/s11938-022-00395-w

Pancreas(C Forsmark, Section Editor)

# Post-ERCP Pancreatitis — What Is the Best Approach for Prevention?

*David E. Jonason, MD*[1]
*Mohammad Bilal, MD*[2]
*Guru Trikudanathan, MD*[3,*]

**Address**
[1]Department of Medicine, University of Minnesota Medical Center, Minneapolis, MN, USA
[2]Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA
[*,3]Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota Medical Center, MMC 36, 420 Delaware Street SE, Minneapolis, MN 55455, USA
Email: triku001@umn.edu

Published online: 19 July 2022


This article is part of the Topical Collection on *Pancreas*.

**Keywords** Endoscopic retrograde cholangiopancreatography · Post-ERCP pancreatitis · Pancreatic duct stent · Rectal NSAIDs

## Abstract

*Purpose of Review* Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most common adverse event following ERCP. The purpose of this review is to highlight prevention strategies and recent developments in this area and summarize current recommendations to reduce PEP rates.

*Recent Findings* PEP prevention continues to rely heavily on use of peri-procedural rectal non-steroidal anti-inflammatory drugs (NSAIDs) and intravenous aggressive hydration (AH) while shying away from more invasive maneuvers such as pancreatic stents except in high-risk cases. Comparative studies of medical therapy, AH, and pancreatic stents are beginning to emerge.

*Summary* Acute pancreatitis remains the most common adverse event following ERCP. Prevention continues to evolve and requires a multi-disciplinary approach of careful risk assessment and procedural planning, peri-operative pharmacotherapy, selective AH, and pancreatic stenting for high-risk patients.

## Introduction

Post-ERCP pancreatitis (PEP) is the most frequent adverse event following ERCP with an incidence ranging from 5 to 10% [1, 2]. The course of PEP can range from mild with a brief hospital admission to a more severe fulminant course with multi-organ failure and rarely death. The estimated financial burden of PEP is $200 million per year [2]. In this article, we review risk factors associated with PEP and discuss strategies for prevention and management.

## Definitions

The consensus definition of PEP requires abdominal pain with an amylase level > 3 × normal for > 24 h post-ERCP [1, 3••]. Modifications include utilizing lipase and defining clinical pancreatitis as "new or worsened abdominal pain" [4••, 5]. The 2012 Atlanta classification does not differentiate PEP from acute pancreatitis characterized by abdominal pain, serum lipase, or amylase 3 × the upper limit of normal (ULN), and associated imaging findings. The European Society of Gastrointestinal Endoscopy (ESGE) utilizes the modified consensus criteria and requires new or prolonged hospital admission. Severity is determined by the revised Atlanta classification based on organ failure duration [6]. A serum amylase or lipase should be checked 2–6 h post-ERCP for patients with abdominal pain. Levels < 1.5 × and < 4 × the ULN, respectively, are low risk for PEP and acceptable for discharge [5, 7••].

## Mechanism of Injury

Mechanical injuries to the sphincter of Oddi, ampulla, and biliary or pancreatic ducts during instrumentation with guidewires and catheters can result in edema or perforation of the pancreatic duct, outflow obstruction, and leakage of pancreatic enzymes caustic to surrounding tissue. Hydrostatic, chemical, and allergic reactions can occur with contrast injection and thermal injuries with electrocautery. Superimposed infections may develop from bacterial introduction via contaminated instruments or intestinal flora [1]. These injuries stimulate an inflammatory, cytokine-driven cascade with the degree of injury depending on whether the inflammation is localized to the pancreatic parenchyma or initiates a systemic inflammatory response syndrome (SIRS).

# Risk Factors

PEP risk factors are categorized into three groups related to patient characteristics, provider characteristics, and procedural techniques. The first major multicenter study to describe independent risk factors for PEP prospectively followed 2347 patients for 30 days following endoscopic sphincterotomy (ES). Higher PEP rates were seen in cases with sphincter of Oddi dysfunction (SOD), difficulty with bile duct cannulation, use of precut

sphincterotomy, and when combined with percutaneous intervention [4••]. Multiple additional risk factors have since been described.

## Patient-Related Risk Factors

Independent patient-related risk factors include SOD, female gender, younger age, normal serum bilirubin, and history of previous pancreatitis or PEP [1, 3••, 4••, 5, 8, 9]. Other potential risk factors include primary sclerosing cholangitis (PSC), hilar tumors, nondilated extrahepatic bile ducts, pancreas divisum, and absence of chronic pancreatitis (Table 1) [1, 3••, 4••, 5, 8–11]. These factors when combined further increase PEP risk.

**Table 1 Independent risk factors for post-ERCP pancreatitis**

| Risk factor | PEP incidence (%) with vs. without risk factor |
|---|---|
| **Patient-related** | |
| Sphincter of oddi dysfunction (SOD) | 23–24 vs. 4–10 |
| Female | 10–17 vs. 3–12 |
| Previous PEP | 20–28 vs. 4–14 |
| Previous Pancreatitis | 13–21 vs. 3–14 |
| Age (<60 years) | 6–18 vs. 3–9 |
| Normal serum bilirubin | 4–10 vs. 1–4 |
| Pancreas divisum | 19–24 vs. 6–14 |
| Primary sclerosing cholangitis (PSC) | 8 vs. 3 |
| Nondilated extrahepatic bile duct | 4–16 vs. 2–14 |
| Absence of chronic pancreatitis | 4–15 vs. 3–16 |
| **Procedure-related** | |
| Prolonged Cannulation attempts (attempts>10 min or 5 attempts) | 11–26 vs. 3–14 |
| Pancreatic guidewire passage>1 | 11 vs. 3 |
| Inadvertent pancreatic duct cannulation or contrast injection | 9–17 vs. 2–13 |
| Precut sphincterotomy | 10–18 vs. 3–15 |
| Pancreatic sphincterotomy | 24–30 vs. 5–13 |
| Sphincteroplasty | 9–16 vs. 3–7 |
| Intraductal ultrasound (IDUS) | 8 vs. 3 |
| Non-prophylactic pancreatic stent placement | 19–23 vs. 5–13 |
| Sphincter of oddi manometry | 24–28 vs. 5–10 |
| Metallic biliary stent placement | 8 vs. 5 |

PEP- post-ERCP pancreatitis

### Provider and Facility-Related Risk Factors

Endoscopist experience and procedural volume do not significantly impact PEP rates though improve successful bile duct cannulation [4••, 8]. Multicenter international studies show similar PEP rates among expert and non-expert endoscopists and low and high–volume centers [9, 12, 13]. However, higher-risk populations are more frequently treated at high-volume centers and may confound reports.

### Procedure-Related Risk Factors

Guidewire passage into the pancreatic duct (PD) > 1 × and deep PD cannulation are predominant risk factors followed by PD contrast injection and prolonged biliary cannulation (> 10 min or 5 attempts) [14••, 15, 16]. Others include precut ES, pancreatic sphincterotomy, ampullectomy, minor papillectomy, failure to clear bile duct stones, and intraductal ultrasound (IDUS) (Table 1) [1, 3••, 4••, 5, 8–10, 14••, 15, 17]. Fully covered and uncovered self-expanding metal stents (SEMS) increase PEP risk compared to polyethylene stents placed for biliary obstruction [16, 18, 19, 20•].

## Management

The principles of PEP management are similar as for other causes of acute pancreatitis with aggressive and judicious intravenous fluid resuscitation with Ringer's lactate (LR) at 5–10 ml/kg/h in the initial 24 h, bowel rest and pain management [21]. A single-center retrospective study evaluated the role of repeat ERCP for salvage pancreatic stent (PS) placement to attenuate PEP progression. All 14 of 64 patients with severe PEP who underwent salvage ERCP (5 without and 9 with prior PS) within 10 h had a significant improvement in pain, amylase/lipase level, and SIRS resolution by 24 h post treatment ($P = 0.003$). No delayed adverse events occurred [22]. Larger prospective studies are needed before salvage ERCP can be incorporated into clinical practice.

## Prevention

It is important for endoscopists to know factors proven to reduce PEP and appropriate instances when these can be applied. Methods of cannulation, papillary balloon dilation, type of electrocautery used, prophylactic

pancreatic stenting, rectal NSAIDs, and aggressive hydration (AH) have all been examined in this regard and are further discussed below.

## Cannulation Techniques

Selective biliary cannulation failure rates are as high as 18% in some reports [23•]. Wire-guided cannulation (WGC) has gained traction over traditional contrast-assisted due to improved cannulation success rates, reduced papillary trauma, avoidance of PD contrast injection, decreased need for precut ES, and overall reduced risk for PEP [24–26]. However, even experts endure complications with WGC such as creation of a false tract, intramural dissection, perforation, and PD injury, predisposing to PEP. PEP rates have been reported as high as 9% with WGC. The risk is greater after inadvertent PD guidewire insertion versus PD opacification (*OR* 2.64 vs 1.89) [15, 27, 28]. More centers are adopting the short-wire system with the endoscopist controlling the wire during cannulation as it was shown to decrease PEP due to reduced trauma related to tactile feedback. A recent trial randomized 216 patients with native papilla cannulation for standard biliary indications to endoscopist versus assistant-controlled attempt. This study was halted at interim analysis due to overwhelming risk of PEP in the assistant-controlled arm (*OR* 2.8 vs 9.3; $P = 0.049$) [29]. In cases of difficult selective biliary cannulation (i.e., > 5 contacts with the papilla, > 5 min of attempts, or > 1 unintended PD cannulation), early utilization of advanced techniques may help to improve access and reduce risk of PEP. Advanced techniques include double-guidewire technique (DGWT), wire-guided cannulation over a pancreatic stent (WGC-PS), and early precut ES.

### *Double Guidewire Technique*

The DGWT utilizes a guidewire inserted into the PD to straighten the common channel and facilitate deep biliary access using a second wire. It initially showed success in cases of a tortuous major papilla, or one located in a duodenal diverticulum [30, 31]. Later studies found no improvement in successful cannulation and increased PEP rates compared to other methods [24, 32–35]. Notably, pancreatic stenting was not performed in most of these studies. A recent RCT randomized 100 patients with intact papilla and inadvertent pancreatic wire placement during ERCP for biliary therapy to DGWT or WGC-PS. The primary outcome assessed was successful selective biliary cannulation within 5 min without need for needle knife precut (NK-precut) ES. All participants had a prophylactic PS placed and no rectal NSAIDs were used. DGWT showed superior initial selective biliary cannulation compared to WGC-PS (90% vs 54%; $P < 0.01$) and decreased need for NK-precut (10% vs 46%; $P < 0.01$). After inclusion of NK-precut, the overall successful cannulation rate between both intention-to-treat groups was remarkably high at 98%. Also noteworthy, the overall PEP rate (2%) was low in this otherwise high-risk cohort [23•].

Discordances in reported selective biliary cannulation success rates with DGWT may be explained by differences in study inclusion criteria (i.e., if only patients with difficult biliary cannulation are included or in combination with cases of inadvertent PD wire passage). Similarly, differences in reported PEP rates can be attributed to whether or not a PS is placed [36]. Regardless, the above results are encouraging and support early DGWT as a useful strategy to gain deep biliary access particularly in cases of inadvertent pancreatic wire placement. When employed, simultaneous placement of a prophylactic PS is needed which has shown to significantly reduce PEP rates with minimal added risk [7••, 23•, 36, 37•].

### *Wire-Guided Cannulation over a Pancreatic Stent*

WGC-PS uses a PS in place of a wire to straighten the common channel and guide wire cannulation of the bile duct. It has proven to be an effective technique in facilitating difficult biliary cannulation and decreasing the need for precut ES [38]. Additionally, it offers protective measures in cases where repeated inadvertent pancreatic cannulation occurs. Initial studies showed similar rates of successful biliary cannulation and PEP compared to DGWT [38, 39]. In the most recent comparative trial, it was inferior to the DGWT for initial selective biliary cannulation; however overall successful cannulation rates were the same after NK-precut was included [23•]. A multicenter retrospective study found that patients with native papilla requiring ERCP for biliary intervention who underwent WGC-PS immediately after incidental pancreatic guidewire insertion versus repeated WGC had a decreased PEP (8.7% vs 19%; *OR*: 0.31; $P = 0.001$) and PEP severity (moderate and severe PEP; 2.2% vs 6.4%; $P = 0.04$) although rates of difficult cannulation and overall successful biliary cannulation were not changed (66% vs 70%; $P = 0.39$ and 98% vs 96%; $P = 0.21$) [40]. Overall, WGC-PS may be less effective than DGWT for initial biliary cannulation. However, after including NK-precut, overall cannulation success rates are similar and both techniques significantly reduce the risk for PEP provided a PS is placed. While the ESGE recommends the use of DGWT in cases of difficult selective biliary cannulation where inadvertent pancreatic wire insertion occurs, WGC-PS may be considered an alternative based on endoscopist preference, particularly in cases where multiple PD cannulations are made.

### *Precut Sphincterotomy*

Precut ES is considered to be a second-line salvage for selective biliary access. It previously was identified to be a significant independent risk factor for PEP. However, PEP rates related to precut technique do not differ from those of standard sphincterotomy suggesting the risk may be operator-dependent [5, 10, 12, 41, 42]. Alternatively, papillary trauma from preceding unsuccessful conventional cannulation may be responsible for PEP. A single-center RCT randomized 333 patients to very early precut (after two failed attempts of WGC) or primary precut ($n = 151$) to identify the true incidence of PEP.

Cannulation success rates were the same (92.7%) for both groups but the rates of PEP were significantly lower with primary precut (0.67% vs 5.2%; $P = 0.04$) [43•]. While this suggests that precut ES may be less of an independent risk factor for PEP than once thought, these results should not be extrapolated to support the use of primary precut as a first-line technique for deep biliary access. This study primarily included patients with a dilated common bile duct (CBD) from obstructive biliary disease (ideal for precut), with ERCPs performed by an expert endoscopist, excluded cases of papillary distortion, and did not include rectal indomethacin administration which may have negated the difference observed [44]. Also, biliary cannulation success rates by primary precut were lower than those reported in prior studies using DGWT or WGC-PS and salvage NK-precut [23•]. Nonetheless, studies continue to show that early precut results in improved primary cannulation success and reduced PEP rates compared to persistent standard cannulation [45–47]. The ESGE recommends using early NK-precut ES in cases of difficult biliary cannulation [7••]. This technique should be reserved for expert endoscopists, and indications should be evaluated on a case-by-case basis. Transpancreatic biliary sphincterotomy is preferable over NK when dealing with small, flat, or intradiverticular papilla, or when anatomy is highly distorted as in malignancy. The efficacy of NK papillotomy tends to diminish as the CBD diameter decreases, particularly under 4 mm [48–50].

### *Papillary Balloon Dilation*

Endoscopic papillary balloon dilation (EPBD) as an adjunct to biliary ES for large biliary stone extraction is standard of care. Both the American Society for Gastrointestinal Endoscopy (ASGE) and ESGE recommend ES with sequential EPBD over ES alone for the removal of large CBD stones due to multiple studies showing improved complete clearance, decreased need for mechanical lithotripsy (ML), and an improved safety profile including reduced risk for PEP [5, 51•, 52–54]. EPBD alone without ES has the advantages of anatomic and functional preservation of the sphincter of Oddi (ideal for younger patients), reduced bleeding risk (useful in patients on anticoagulants or low platelets), and fewer late stone recurrences. Prior RCTs found a higher incidence of PEP with EPBD alone compared to biliary ES and increased need for ML [55, 56]. However, the recent MARVELOUS trial (RCT including 19 Japanese institutions involving 171 patients with large CBD stones) showed that EPBD alone compared to ES resulted in significantly higher single-session stone extraction rates (90.7% vs 78.8%; $P = 0.04$) and decreased the need for ML (30.2% vs 48.2%; $P = 0.02$) with comparable overall rates of early adverse events including PEP (4.7% vs 5.9%) [57•]. More RCTs comparing these techniques are needed in the western population. While PEP incidence with EPBD is thought to be impacted by the duration of inflation, a new meta-analysis showed no difference between short (15–20 s) and long (1–5 min) dilation groups in the complete stone removal, the need for ML, and rates of PEP, bleeding, biliary infection, or perforation [58, 59].

In cases of very large (> 10 mm) and difficult CBD stones, the use of a limited ES followed by endoscopic papillary large-balloon dilation (EPLBD) with a balloon diameter of 12–20 mm remains first-line treatment [54]. A large systematic review showed overall adverse events (PEP, bleeding, and perforation) to be lower with ES and EPLBD compared to ES monotherapy (8.3% vs 12.7%, *OR* 1.60; $P < 0.001$) [60]. Large ES cuts independently increase the risk for bleeding as opposed to limited ES and do not improve therapeutic effect [61]. Balloon dilation diameter should not exceed that of the distal CBD to avoid increased risk for perforation [62]. Studies are now showing that EPLBD alone is comparable to EPLBD following ES regarding the initial stone extraction, the need for ML, the risk of PEP, and the total procedure time [63, 64]. Additional comparison studies are needed before this becomes common practice.

### *Electrocautery*

The type of electrocautery current used during ES influences the degree of thermal tissue injuries and by extension risk for PEP. Pure cutting improves cutting ability and produces less edema while low voltage coagulating current is better for hemostasis. A mixed current combines both types either simultaneously in a blended cut or in a pulsed alternating fashion (i.e., endocut or pulsecut mode). A meta-analysis of four RCTs showed increased bleeding with pure cut compared to mixed current with similar rates of pancreatitis [65]. Compared to blended current, endocut and pulsecut mode produces fewer uncontrolled cuts and bleeding though rates of perforation and PEP do not differ [66–69].

## Pancreatic Stents

Pancreatic stents have long been studied for PEP prevention. They maintain anterograde flow of enzymes and reduce intraductal pressure following pancreatic duct trauma. They reduce the incidence of PEP and nearly eliminate the development of severe PEP (*OR* 0.22–0.26) [70–75]. Yet, only 4% of average to high-risk ERCPs includes a prophylactic PS [76]. Practitioner reluctance is attributed to inexperience and concern for induced PEP [77, 78]. Failed placement (~5–10%), stent migration, and ductal perforation are other concerns [79]. Most published success rates are from high-volume tertiary centers with expert endoscopists.

Which patients are likely to benefit from prophylactic pancreatic stents is of ongoing discussion. Their efficacy has been thoroughly demonstrated in high-risk cases (i.e., inadvertent PD cannulation/wire insertion or precut ES). The data is less clear for low- to average-risk individuals [72, 75, 80]. Most of the meta-analyses published over the last decade highlighting their effectiveness excluded non-high-risk patients [70–75]. However, three such studies did show benefit in average-risk individuals (*OR* 0.21 and 0.25) [70, 71, 73]. One also demonstrated a significant risk reduction in unselected mixed-risk groups (*RR*: 0.23; 95% *CI*: 0.08–0.66) [73]. A more recent RCT involving

4 European tertiary referral centers and 167 unselected patients who had inadvertent pancreatic cannulation during first-time ERCP also found that those randomized to pancreatic stenting had significantly reduced PEP rates compared to those observed (*OR*: 0.43; 95% *CI*: 0.19–0.98; *P* = 0.04; NNT: 8.1) [81•]. The ESGE recommends prophylactic PS placement in selected patients at high risk for PEP (inadvertent guide-wire insertion of the PD and with DGWT) [7••].

A 5-French (Fr) PS appears more efficacious than a 3-Fr (96.9% vs 3.1%) [82]. This is attributed to easier placement, better decompression, lower rates of early dislodgement, and decreased need for endoscopic retrieval [83, 84]. Stents with a duodenal flange or pigtail that are also devoid of an internal flange should be used to reduce intraductal migration and facilitate spontaneous passage, respectively [7••, 85]. Stent length has less of a clear impact [86, 87]. Stents should be left for a minimum of 12–24 h though most are kept for 5–10 days before re-evaluation for spontaneous passage. Earlier removal negates their protective effects [88, 89]. While pancreatic stents are effective in high-risk cases, certain questions still remain. Ideal stent characteristics, the risk of attempting to stent a difficult PD, and the consequences of failed placement should be weighed carefully.

## Rectal NSAIDs

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) have become a first-line modality for PEP prevention after a landmark trial in 2012 demonstrated lower PEP rates and decreased severity of pancreatitis in high-risk patients who received post-procedural indomethacin compared to placebo. While a majority of these patients simultaneously received a PS, post-hoc analysis suggested NSAIDs to be beneficial regardless of concurrent PS placement [90••]. Numerous meta-analyses have since evaluated their efficacy with an overwhelming majority showing reduction in PEP incidence (*OR* 0.24 to 0.63) [91–96]. This effect has been demonstrated with both average-risk and high-risk procedures as well as unselected patients. Their use primarily reduces the incidence of mild PEP (NNT 8 to 21) and to a lesser extent moderate-to-severe PEP (NNT 33–39) [91–96]. Diclofenac and indomethacin are both effective. The most frequently studied dose is 100 mg [91]. Rectal administration is superior to alternative routes [96–102]. In a recent prospective analysis of a RCT, 409 moderate-to-high risk patients undergoing ERCP were randomized to 100 mg of rectal diclofenac monotherapy 30 min before (*n* = 346) or after (*n* = 63) based on endoscopist preference. Those who received pre-procedural treatment had lower PEP rates (8% vs 18%; *RR*: 2.32; 95% *CI*: 1.21–4.46; *P* = 0.02) shortened hospital stays (1 day; interquartile range [IQR] 1–2 days vs 1 day; IQR 1–4 days; *P* = 0.02) and were less likely to be admitted to the ICU (0.3% [1 patient] vs 6% [4 patients]; *P* = 0.002) [103•]. Overall, the efficacy of rectal NSAIDs along with their excellent safety profile has made them an attractive prophylactic measure for most field experts. ESGE guidelines recommend routine use of 100 mg pre-procedural rectal indomethacin or diclofenac in all patients unless a contraindication exists. The ASGE also recommends

their use in all high-risk patients and consideration in average-risk patients [7••, 104].

## PS vs. Rectal NSAIDS

The emergence of rectal NSAIDs has led to question the ongoing need for pancreatic stents. Comparison trials are now emerging (Table 2). In a recent abstract, 321 patients with naïve papilla were randomized to receive a prophylactic PS, 50 mg of rectal diclofenac, or both. Five patients (PS 2/101, NSAID 1/106, and combination 2/102) developed mild PEP with an overall occurrence of 1.6% and no significant difference among groups [105]. NSAIDs were concluded to be noninferior though more information is needed regarding study inclusion/exclusion criteria, biliary access technique, and frequency of PD cannulation. Conclusions based on naïve papilla alone cannot be extrapolated to patients of moderate or high risk. A noninferiority RCT compared pancreatic stenting plus pharmacological prophylaxis against pharmacological monotherapy for PEP prevention in high-risk individuals ($n = 414$). PEP incidence was similar (12.6% vs 15.9%) and NSAID monotherapy again deemed noninferior [106•]. However, the difference in PEP rates was 3.3% with an upper boundary 95% *CI* of 10.2% which is greater than the prespecified noninferiority margin of 5%. Thus, the study actually failed to show noninferiority of pharmacological monotherapy prophylaxis. In contrast, a large network meta-analysis of 29 trials ($n = 7862$) comparing four preventative strategies against PEP in high-risk patients found that pancreatic stenting had the highest SUCRA probability (0.81; 95% *CI*: 0.80–0.83) of being ranked the best prophylactic treatment [107•]. A second meta-analysis showed that only pancreatic stents reduced the risk of moderate and severe PEP in both average and high-risk patients compared to NSAIDs and placebo [108•]. In one of the largest exploratory meta-analyses to date involving 55 RCTs ($n = 7062$), 20 PEP interventions including combination therapies were analyzed and efficaciously graded for PEP prophylaxis. Pancreatic stents, rectal NSAIDs, and rectal NSAIDs plus standard hydration were all associated with reduced odds for PEP compared to placebo. The GRADE confidence rating was low to moderate for 98.3% of the pairwise comparisons [109•].

Over the last decade, the use of rectal NSAIDs in the USA has steadily increased (though remained < 50% as of 2018) with a simultaneous abrupt decline in the use of pancreatic stents from 40.7% in 2013 to a nadir of 3% in 2017 [110•]. With this, PEP rates have increased from 4.3% in 2011 to 5.2% in 2017 (*OR*: 1.23; 95% *CI*: 1.04–0.46; $P = 0.016$). Mortality rates from PEP have nearly doubled from 2.8 to 4.4% (*OR*: 1.62; 95% *CI*: 1.10–2.38; $P = 0.014$) [111•]. Whether this is related to inadequate use of rectal NSAIDs, a decline in use of pancreatic stents or both is not entirely clear. The SVI (stent vs indomethacin) trial is an ongoing multicenter (nine academic medical centers in the USA), double-blinded, non-inferiority study analyzing PEP prevention rates in 1430 high-risk patients receiving indomethacin and PD stenting versus indomethacin monotherapy. These results are eagerly expected to reach a verdict on this quintessential debate [112••].

**Table 2 Comparison trials of pharmacotherapy, fluids, and pancreatic stents for PEP prevention**

| Study | Year | *N* | Population characteristics | Method | PEP prophylaxis methods analyzed | PEP incidence/ impact |
|---|---|---|---|---|---|---|
| Dubravcsik et al | 2021 | NSAID (4296) PDS (1239) | Average and high risk | Network Meta-analysis of RCTs | PS vs rectal NSAIDs vs placebo | PS: (avg-risk: *RR* = 0.07, 95% *CI* [0.002–0.58], high-risk: *RR* = 0.20, 95% *CI* [0.051–0.56]) Rectal NSAID: (avg-risk: *RR* = 0.58, 95% *CI* [0.22–1.3], high-risk: *RR* = 0.58, 95% *CI* [0.18–2.3]) |
| Koshitani et al | 2021 | 321 | Naïve papillae | RCT (abstract) | PS vs rectal NSAIDs vs PS + rectal NSAIDs | PS: 2%, rectal NSAIDS: 0.94% PS + rectal NSAIDs: 2% *P* > 0.05 |
| Akshintala et al | 2021 | 17,062 | Low, moderate and high risk | Network meta-analysis | Fluids vs HV fluids vs fluids + rectal NSAIDs vs HV fluids + rectal NSAIDs vs IM NSAIDs vs rectal NSAIDs vs PS vs PS + fluids vs placebo | NS + rectal NSAID (*OR* 0.02, 95% *CI* 0.00–0.40), IM NSAID (0.24, 0.09–0.69), HVLR + rectal NSAID (0.30, 0.16–0.55), HVLR (0.31, 0.12–0.78), 5–7 Fr PS (0.35, 0.26–0.48), rectal diclofenac (0.36, 0.25–0.52), 3 Fr PS (0.47, 0.26–0.87), rectal indomethacin (0.60, 0.50–0.73) |
| Njei et al | 2020 | 7862 | High risk | Network meta-analysis | PS vs rectal NSAIDs vs HV fluids vs rectal NSAIDs + HV fluids vs placebo | NSAIDs (B = −0.69, 95% *CI* [−1.18; −0.21]), PS (B = −1.25, 95% *CI* [−1.81 to −0.69]), LR (B = −0.67, 95% *CI* [−1.20 to −0.13]), LR + NSAIDs (B = −1.58; 95% *CI* [−3.0 to −0.17]) |

**Table 2** (continued)

| Study | Year | *N* | Population characteristics | Method | PEP prophylaxis methods analyzed | PEP incidence/ impact |
|---|---|---|---|---|---|---|
| Sotoudehmanesh et al | 2019 | 414 | High risk | RCT | Rectal NSAIDs + sublingual isosorbide dinitrate + HV fluids + PS vs rectal NSAIDs + sublingual isosorbide dinitrate + HV fluids | PS + pharmacotherapy 12.6% pharmacotherapy (15.9%) $P = 0.59$ |

*RCT*, randomized control trial
*PEP*, post-ERCP pancreatitis
*NSAID*, non-steroidal anti-inflammatory drugs
*PS*, pancreatic stent
*HV*fluids, high volume fluids
*IM*, intramuscular
*Avg risk*, average risk
*NS*, normal saline
*HVLR*, high volume lactate ringers

## Intravenous Aggressive Hydration

Intravenous (IV) aggressive hydration (AH) improves the hemodynamics and microcirculation of the pancreas and is increasingly gaining traction for PEP prevention. A pilot study demonstrated that in patients undergoing first time ERCP, AH with LR at 3 ml/kg/h intraoperatively followed by a post-operative 20 ml/kg bolus and fixed infusion at 3 ml/kg/h for 8 h versus standard hydration (SH) resulted in significantly lower PEP rates (0% vs 17%; $P = 0.016$) [113•]. Several meta-analyses have since confirmed AH to be a protective factor in PEP reduction compared to SH [114–116]. It has also been associated with reduced PEP severity and length of hospital stay [117, 118]. However, there appears to be no added benefit in patients already receiving rectal NSAIDs. A large multicenter RCT involving 22 Dutch hospitals randomly assigned moderate-to-high risk patients ($n = 826$) to a combination of AH and rectal NSAIDs (100 mg diclofenac or indomethacin) or rectal NSAID and SH. The incidence of PEP was similar (8% vs 9%, respectively; *RR*: 0.84; $P = 0.53$) and there was no difference in serious adverse events, number of ICU admissions, or 30-day mortality [119•]. Of note, AH varied slightly from what was originally defined and SH included normal saline (NS) rather than LR. The major limitation to AH is that it is too time- and resource-intensive to be adopted in the outpatient setting. Additionally, fluid overload has been a reported side effect even after excluding patients at risk for this complication [120].

## Alternative Therapies

Alternative pharmacotherapies for PEP prevention have been evaluated as well (Table 3).

### *Nitrates*

Multiple meta-analyses have supported the use of sublingual nitrate to prevent PEP [121–123]. Efficacy appears limited to high-incidence groups and does not reduce PEP severity.

### *Somatostatin*

A recent meta-analysis showed that a long-term somatostatin infusion of 10–24 h reduced PEP rates in high-risk individuals. No benefit was observed in low-risk patients or with short infusions or bolus dosing [124].

### *Protease Inhibitors*

While initial studies showed promising use of Nafamostat, a recent multicenter RCT showed no statistically significant change in PEP frequency in Nafamostat groups compared to placebo [125–127].

**Table 3 Alternative medical therapies for PEP prevention**

| Pharmacotherapy | Proposed mechanism of action | Demerits/side effects |
|---|---|---|
| Nitrates (i.e., isosorbide dinitrate) | Sphincter of Oddi smooth muscle relaxation, increased pancreatic blood flow | Risk for hypotension, headaches, dizziness, lightheadedness, nausea, flushin |
| Somatostatin analogs (i.e., Octreotide) | Reduce sphincter of Oddi pressure, pancreatic enzyme secretion and cytokine upregulation | Expensive and long infusions reduce practicality. Steatorrhea, diarrhea, malabsorption, GI cramping, nausea |
| Protease Inhibitors (i.e., gabexate and nafamostat mesylate, etc.) | Inhibition of trypsinogen and other proteases important for cytokine production, inflammation and clotting | Insulin resistance, nausea, diarrhea, cholelithiasis/nephrolithiasis, LFT elevation, rash, hypercholesterolemia, insomnia, agranulocytosis, hypertensive crisis |
| Tacrolimus | Prevention of $Ca^{2+}$ signaling and activation of NF-kB via Calcineurin inhibition | Immunosuppression, opportunistic infection, insulin resistance, headache, hyperkalemia, renal toxicity, tremor |
| Epinephrine | Arterial vasoconstriction resulting in reduced papillary edema and PD hypertension | Anxiety, restlessness, agitation, headache, tremor, dizziness. lightheadedness, insomnia, weakness, parkinsonian tremor |

### *Tacrolimus*

The use of tacrolimus for PEP prevention is a new concept. In a study of 337 liver transplant patients who had undergone 937 ERCPs for biliary complications related to liver transplantation, a tacrolimus trough level > 2.5 ng/mL was associated with up to 79% reduced rates of PEP (*OR* 0.21; 95% *CI* 0.06–0.72; $P = 0.01$) [128].

### *Epinephrine*

Although prior RCTs suggested that the use of topical epinephrine may be preventative for PEP, the results of the three recent RCTs have shown topical epinephrine to have no protective benefit and in fact may even increase PEP risk when combined with rectal NSAIDs [129–131].

### *Other Pharmacological Agents*

Corticosteroids, calcium-channel blockers, antibiotics, heparin, and allopurinol among other drugs have proven ineffective for PEP prevention in prospective clinical trials and meta-analyses [132–139].

## How We Approach Prevention of PEP?

As research continues to progress so do the techniques and strategies for PEP prevention. In our high-volume tertiary care referral center for pancreaticobiliary diseases, we perform over 1500 ERCPs a year. For diagnostic studies, we prioritize the use of advanced imaging techniques including MRCP, endoscopic ultrasound, CT imaging, and abdominal ultrasound whenever possible. Prior to any ERCP, we perform a thorough assessment to determine all possible risk factors (patient and procedural) for PEP. Rectal indomethacin is administered pre-ERCP for patients of all risk levels unless a clear contraindication exists. Patients with contraindications receive AH with LR (at 3 ml/kg/h intraoperatively followed by a post-operative 20 ml/kg bolus and infusion at 3 ml/kg/h for 8 h). In cases of inadvertent PD cannulation, we use a combination of DGWT and WGC-PS depending on a case-by-case basis. We place a PS for PEP prophylaxis whenever inadvertent pancreatic duct cannulation takes place. We recommend the use of 5-Fr polyethylene stents to be kept in place for 1–2 weeks prior to assessment of spontaneous passage. In patients who are undergoing ERCP for primary biliary indications, pancreatic duct injection is minimized.

## Conclusions

Though our knowledge behind the risk factors and mechanisms of PEP continues to expand, its incidence remains high, and it is still considered the most common adverse event of ERCP. A multifactorial preventative approach is essential to minimizing this risk. This includes careful patient selection, comprehensive assessment of PEP risk factors, tailored procedural techniques, and evidence-based prophylactic measures. Preventative procedural techniques include WGC, minimized cannulation attempts and contrast injections, and placement of a temporary PS in high-risk patients. Proven effective medical measures include the routine use of pre-procedural rectal NSAIDs and AH with LR when possible. Numerous other pharmacological measures are of ongoing research and discovery. Large-scale prospective RCTs are still needed to further evaluate additional treatment modalities.

## Declarations

**Conflict of Interest**
David Jonason declares that he has no conflict of interest.

Mohammad Bilal declares that he has no conflict of interest.

Guru Trikudanathan is a consultant for Boston Scientific Corporation.

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc. 2004;59(7):845–64. https://doi.org/10.1016/s0016-5107(04)00353-0.
2. Kochar B, Akshintala VS, Afghani E, Elmunzer BJ, Kim KJ, Lennon AM, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc. 2015;81(1):143-9.e9. https://doi.org/10.1016/j.gie.2014.06.045.
3.•• Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37(3):383–93. https://doi.org/10.1016/s0016-5107(91)70740-2.
Described complications of biliary sphincterotomy including the development of PEP, from which the consensus definition was born.

4.•• Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335(13):909–18. https://doi.org/10.1056/nejm199609263351301.

One of the first studies to describe independent risk factors for PEP following sphincterotomy.

5. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy. 2014;46(9):799–815. https://doi.org/10.1055/s-0034-1377875.

6. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11. https://doi.org/10.1136/gutjnl-2012-302779.

7.•• Dumonceau JM, Kapral C, Aabakken L, Papanikolaou IS, Tringali A, Vanbiervliet G, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2020;52(2):127–49. https://doi.org/10.1055/a-1075-4080.

The most recent ESGE guidelines for PEP prevention.

8. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc. 2001;54(4):425–34. https://doi.org/10.1067/mge.2001.117550.

9. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy. 2007;39(9):793–801. https://doi.org/10.1055/s-2007-966723.

10. Masci E, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. Endoscopy. 2003;35(10):830–4. https://doi.org/10.1055/s-2003-42614.

11. von Seth E, Arnelo U, Enochsson L, Bergquist A. Primary sclerosing cholangitis increases the risk for pancreatitis after endoscopic retrograde cholangiopancreatography. Liver Int. 2015;35(1):254–62. https://doi.org/10.1111/liv.12640.

12. Testoni PA, Mariani A, Giussani A, Vailati C, Masci E, Macarri G, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. Am J Gastroenterol. 2010;105(8):1753–61. https://doi.org/10.1038/ajg.2010.136.

13. Swahn F, Nilsson M, Arnelo U, Löhr M, Persson G, Enochsson L. Rendezvous cannulation technique reduces post-ERCP pancreatitis: a prospective nationwide study of 12,718 ERCP procedures. Am J Gastroenterol. 2013;108(4):552–9. https://doi.org/10.1038/ajg.2012.470.

14.•• Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, et al. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol. 2009;104(1):31–40. https://doi.org/10.1038/ajg.2008.5.

A comprehensive multicenter prospective study that identified numerous high-risk patient and procedure-related risk factors for PEP.

15. Nakai Y, Isayama H, Sasahira N, Kogure H, Sasaki T, Yamamoto N, et al. Risk factors for post-ERCP pancreatitis in wire-guided cannulation for therapeutic biliary ERCP. Gastrointest Endosc. 2015;81(1):119–26. https://doi.org/10.1016/j.gie.2014.06.005.

16. Shin SH, So H, Cho S, Kim N, Baik GH, Lee SK, et al. The number of wire placement in the pancreatic duct and metal biliary stent as risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 2020;35(7):1201–7. https://doi.org/10.1111/jgh.14957.

17. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc. 2005;62(3):367–70. https://doi.org/10.1016/j.gie.2005.04.020.

18. Xia MX, Zhou YF, Zhang M, Wang W, Wu J, Wang TT, et al. Influence of fully covered metal stenting on the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis: A large multicenter study. J Gastroenterol Hepatol. 2020;35(12):2256–63. https://doi.org/10.1111/jgh.15122.

19 Martinez NS, Inamdar S, Firoozan SN, Izard S, Lee C, Benias PC, et al. Evaluation of post-ERCP pancreatitis after biliary stenting with self-expandable metal stents vs. plastic stents in benign and malignant obstructions. Endosc Int Open. 2021;9(6):E888-e94. https://doi.org/10.1055/a-1388-6964.

20.• Coté GA, Kumar N, Ansstas M, Edmundowicz SA, Jonnalagadda S, Mullady DK, et al. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. Gastrointest Endosc. 2010;72(4):748–54. https://doi.org/10.1016/j.gie.2010.05.023.

A well-done study that identified an increased risk for PEP with SEMS compared to polyethylene stents placed for malignant biliary obstruction.

21. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13(4 Suppl 2):e1–15. https://doi.org/10.1016/j.pan.2013.07.063.

22. Kerdsirichairat T, Attam R, Arain M, Bakman Y, Radosevich D, Freeman M. Urgent ERCP with pancreatic stent placement or replacement for salvage of post-ERCP pancreatitis. Endoscopy. 2014;46(12):1085–94. https://doi.org/10.1055/s-0034-1377750.

23.• Eminler AT, Parlak E, Koksal AS, Toka B, Uslan MI. Wire-guided cannulation over a pancreatic stent

method increases the need for needle-knife precutting in patients with difficult biliary cannulations. Gastrointest Endosc. 2019;89(2):301–8. https://doi.org/10.1016/j.gie.2018.08.034.

A RCT showing improved primary biliary cannulation with DGWT compared to WGC-PS though equally high success rates after including NK-precut, and very low PEP rates with use of a PS.

24. Tse F, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database Syst Rev. 2012;12(12):Cd009662. https://doi.org/10.1002/14651858.CD009662.pub2.
25. Adler DG. Guidewire cannulation in ERCP: from zero to hero! Gastrointest Endosc. 2018;87(1):202–4. https://doi.org/10.1016/j.gie.2017.06.003.
26. Tse F, Yuan Y, Moayyedi P, Leontiadis GI. Guide wire-assisted cannulation for the prevention of post-ERCP pancreatitis: a systematic review and meta-analysis. Endoscopy. 2013;45(8):605–18. https://doi.org/10.1055/s-0032-1326640.
27 Bassan MS, Sundaralingam P, Fanning SB, Lau J, Menon J, Ong E, et al. The impact of wire caliber on ERCP outcomes: a multicenter randomized controlled trial of 0.025-inch and 0.035-inch guidewires. Gastrointest Endosc. 2018;87(6):1454–60. https://doi.org/10.1016/j.gie.2017.11.037.
28. Lee TH, Park DH, Park JY, Kim EO, Lee YS, Park JH, et al. Can wire-guided cannulation prevent post-ERCP pancreatitis? A prospective randomized trial. Gastrointest Endosc. 2009;69(3 Pt 1):444–9. https://doi.org/10.1016/j.gie.2008.04.064.
29 Buxbaum J, Leonor P, Tung J, Lane C, Sahakian A, Laine L. Randomized trial of Endoscopist-controlled vs. assistant-controlled wire-guided cannulation of the bile duct. Am J Gastroenterol. 2016;111(12):1841–7. https://doi.org/10.1038/ajg.2016.268.
30. Dumonceau JM, Devière J, Cremer M. A new method of achieving deep cannulation of the common bile duct during endoscopic retrograde cholangiopancreatography. Endoscopy. 1998;30(7):S80. https://doi.org/10.1055/s-2007-1001379.
31. Gotoh Y, Tamada K, Tomiyama T, Wada S, Ohashi A, Satoh Y, et al. A new method for deep cannulation of the bile duct by straightening the pancreatic duct. Gastrointest Endosc. 2001;53(7):820–2. https://doi.org/10.1067/mge.2001.113387.
32. Tse F, Yuan Y, Bukhari M, Leontiadis GI, Moayyedi P, Barkun A. Pancreatic duct guidewire placement for biliary cannulation for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database Syst Rev. 2016;5:Cd010571. https://doi.org/10.1002/14651858.CD010571.pub2.
33. Sasahira N, Kawakami H, Isayama H, Uchino R, Nakai Y, Ito Y, et al. Early use of double-guidewire technique to facilitate selective bile duct cannulation: the multicenter randomized controlled EDUCATION trial. Endoscopy. 2015;47(5):421–9. https://doi.org/10.1055/s-0034-1391228.
34. Krill JT, DaVee T, Edwards JS, Slaughter JC, Yachimski PS. Risk of post-endoscopic retrograde cholangiopancreatography pancreatitis after double-guidewire biliary cannulation in an average-risk population. Pancreas. 2018;47(6):748–52. https://doi.org/10.1097/mpa.0000000000001070.
35. Tse F, Yuan Y, Moayyedi P, Leontiadis GI, Barkun AN. Double-guidewire technique in difficult biliary cannulation for the prevention of post-ERCP pancreatitis: a systematic review and meta-analysis. Endoscopy. 2017;49(1):15–26. https://doi.org/10.1055/s-0042-119035.
36. Haseeb A, Freeman ML. Guidewire in the pancreatic duct: key to risk and rescue for post-ERCP pancreatitis. Gastrointest Endosc. 2019;89(2):309–10. https://doi.org/10.1016/j.gie.2018.10.013.
37.• Ito K, Fujita N, Noda Y, Kobayashi G, Obana T, Horaguchi J, et al. Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial. J Gastroenterol. 2010;45(11):1183–91. https://doi.org/10.1007/s00535-010-0268-7.

This RCT found a significantly reduced PEP incidence in patients with pancreatic guidewire insertion who had a PS placed versus no stent.

38. Coté GA, Mullady DK, Jonnalagadda SS, Keswani RN, Wani SB, Hovis CE, et al. Use of a pancreatic duct stent or guidewire facilitates bile duct access with low rates of precut sphincterotomy: a randomized clinical trial. Dig Dis Sci. 2012;57(12):3271–8. https://doi.org/10.1007/s10620-012-2269-2.
39. Yang MJ, Hwang JC, Yoo BM, Kim JH, Ryu HK, Kim SS, et al. Wire-guided cannulation over a pancreatic stent versus double guidewire technique in patients with difficult biliary cannulation. BMC Gastroenterol. 2015;15:150. https://doi.org/10.1186/s12876-015-0381-4.
40. Hakuta R, Hamada T, Nakai Y, Isayama H, Kogure H, Takahara N, et al. Early pancreatic stent placement in wire-guided biliary cannulation: a multicenter retrospective study. J Gastroenterol Hepatol. 2019;34(6):1116–22. https://doi.org/10.1111/jgh.14453.
41. Cennamo V, Fuccio L, Zagari RM, Eusebi LH, Ceroni L, Laterza L, et al. Can early precut implementation reduce endoscopic retrograde cholangiopancreatography-related complication risk? Meta-analysis of randomized controlled trials. Endoscopy. 2010;42(5):381–8. https://doi.org/10.1055/s-0029-1243992.
42. Gong B, Hao L, Bie L, Sun B, Wang M. Does precut technique improve selective bile duct cannulation or

increase post-ERCP pancreatitis rate? A meta-analysis of randomized controlled trials. Surg Endosc. 2010;24(11):2670–80. https://doi.org/10.1007/s00464-010-1033-y.

43.• Maharshi S, Sharma SS. Early precut versus primary precut sphincterotomy to reduce post-ERCP pancreatitis: randomized controlled trial (with videos). Gastrointest Endosc. 2021;93(3):586–93. https://doi.org/10.1016/j.gie.2020.06.064.

This RCT showed reduced risk for PEP in primary precut technique versus early precut.

44. Krafft MR, Freeman ML. Precut biliary sphincterotomy in ERCP: Don't reach for the needle-knife quite so fast! Gastrointest Endosc. 2021;93(3):594–6. https://doi.org/10.1016/j.gie.2020.08.005.

45. Chen J, Wan JH, Wu DY, Shu WQ, Xia L, Lu NH. Assessing quality of precut sphincterotomy in patients with difficult biliary access: an updated meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2018;52(7):573–8. https://doi.org/10.1097/mcg.0000000000001077.

46. Tang Z, Yang Y, Yang Z, Meng W, Li X. Early precut sphincterotomy does not increase the risk of adverse events for patients with difficult biliary access: a systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. Medicine (Baltimore). 2018;97(36): e12213. https://doi.org/10.1097/md.0000000000012213.

47. Sundaralingam P, Masson P, Bourke MJ. Early precut sphincterotomy does not increase risk during endoscopic retrograde cholangiopancreatography in patients with difficult biliary access: a meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol. 2015;13(10):1722-9.e2. https://doi.org/10.1016/j.cgh.2015.06.035.

48. Lopes L, Dinis-Ribeiro M, Rolanda C. Safety and efficacy of precut needle-knife fistulotomy. Scand J Gastroenterol. 2014;49(6):759–65. https://doi.org/10.3109/00365521.2014.898085.

49. Katsinelos P, Gkagkalis S, Chatzimavroudis G, Beltsis A, Terzoudis S, Zavos C, et al. Comparison of three types of precut technique to achieve common bile duct cannulation: a retrospective analysis of 274 cases. Dig Dis Sci. 2012;57(12):3286–92. https://doi.org/10.1007/s10620-012-2271-8.

50. Testoni PA, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48(7):657–83. https://doi.org/10.1055/s-0042-108641.

51.• Buxbaum JL, Abbas Fehmi SM, Sultan S, Fishman DS, Qumseya BJ, Cortessis VK, et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. Gastrointest Endosc. 2019;89(6):1075–105.e15. https://doi.org/10.1016/j.gie.2018.10.001.

Recent ASGE guidelines regarding use of ES followed by EPBD for large biliary stone extraction over ES alone.

52. Liu Y, Su P, Lin Y, Lin S, Xiao K, Chen P, et al. Endoscopic sphincterotomy plus balloon dilation versus endoscopic sphincterotomy for choledocholithiasis: a meta-analysis. J Gastroenterol Hepatol. 2013;28(6):937–45. https://doi.org/10.1111/jgh.12192.

53. Madhoun MF, Wani S, Hong S, Tierney WM, Maple JT. Endoscopic papillary large balloon dilation reduces the need for mechanical lithotripsy in patients with large bile duct stones: a systematic review and meta-analysis. Diagn Ther Endosc. 2014;2014: 309618. https://doi.org/10.1155/2014/309618.

54. Manes G, Paspatis G, Aabakken L, Anderloni A, Arvanitakis M, Ah-Soune P, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2019;51(5):472–91. https://doi.org/10.1055/a-0862-0346.

55. Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. Am J Gastroenterol. 2004;99(8):1455–60. https://doi.org/10.1111/j.1572-0241.2004.30151.x.

56. Weinberg BM, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Database Syst Rev. 2006;4:Cd004890. https://doi.org/10.1002/14651858.CD004890.pub2.

57.• Kogure H, Kawahata S, Mukai T, Doi S, Iwashita T, Ban T, et al. Multicenter randomized trial of endoscopic papillary large balloon dilation without sphincterotomy versus endoscopic sphincterotomy for removal of bile duct stones: MARVELOUS trial. Endoscopy. 2020;52(9):736–44. https://doi.org/10.1055/a-1145-3377.

Recent RCT comparing EPLBD + ES versus EPLBD monotherapy for large bile duct stone removal.

58. Wang Q, Fu L, Wu T, Ding X. The ballooning time in endoscopic papillary balloon dilation for removal of bile duct stones: a systematic review and meta-analysis. Medicine (Baltimore). 2021;100(11): e24735. https://doi.org/10.1097/md.0000000000024735.

59. Liao WC, Tu YK, Wu MS, Wang HP, Lin JT, Leung JW, et al. Balloon dilation with adequate duration is safer than sphincterotomy for extracting bile duct stones: a systematic review and meta-analyses. Clin Gastroenterol Hepatol. 2012;10(10):1101–9. https://doi.org/10.1016/j.cgh.2012.05.017.

60. Kim JH, Yang MJ, Hwang JC, Yoo BM. Endoscopic papillary large balloon dilation for the removal of bile duct stones. World J Gastroenterol. 2013;19(46):8580–94. https://doi.org/10.3748/wjg.v19.i46.8580.

61. Park SJ, Kim JH, Hwang JC, Kim HG, Lee DH, Jeong S, et al. Factors predictive of adverse events following endoscopic papillary large balloon

dilation: results from a multicenter series. Dig Dis Sci. 2013;58(4):1100–9. https://doi.org/10.1007/s10620-012-2494-8.
62. Kim TH, Kim JH, Seo DW, Lee DK, Reddy ND, Rerknimitr R, et al. International consensus guidelines for endoscopic papillary large-balloon dilation. Gastrointest Endosc. 2016;83(1):37–47. https://doi.org/10.1016/j.gie.2015.06.016.
63. Liu P, Lin H, Chen Y, Wu YS, Tang M, Lai L. Comparison of endoscopic papillary large balloon dilation with and without a prior endoscopic sphincterotomy for the treatment of patients with large and/or multiple common bile duct stones: a systematic review and meta-analysis. Ther Clin Risk Manag. 2019;15:91–101. https://doi.org/10.2147/tcrm.S182615.
64. Park JS, Jeong S, Lee DK, Jang SI, Lee TH, Park SH, et al. Comparison of endoscopic papillary large balloon dilation with or without endoscopic sphincterotomy for the treatment of large bile duct stones. Endoscopy. 2019;51(2):125–32. https://doi.org/10.1055/a-0639-5147.
65. Verma D, Kapadia A, Adler DG. Pure versus mixed electrosurgical current for endoscopic biliary sphincterotomy: a meta-analysis of adverse outcomes. Gastrointest Endosc. 2007;66(2):283–90. https://doi.org/10.1016/j.gie.2007.01.018.
66. Akiho H, Sumida Y, Akahoshi K, Murata A, Ouchi J, Motomura Y, et al. Safety advantage of endocut mode over endoscopic sphincterotomy for choledocholithiasis. World J Gastroenterol. 2006;12(13):2086–8. https://doi.org/10.3748/wjg.v12.i13.2086.
67. Tanaka Y, Sato K, Tsuchida H, Mizuide M, Yasuoka H, Ishida K, et al. A prospective randomized controlled study of endoscopic sphincterotomy with the Endocut mode or conventional blended cut mode. J Clin Gastroenterol. 2015;49(2):127–31. https://doi.org/10.1097/mcg.0000000000000096.
68. Parlak E, Köksal A, Öztaş E, Dişibeyaz S, Ödemiş B, Yüksel M, et al. Is there a safer electrosurgical current for endoscopic sphincterotomy in patients with liver cirrhosis? Wien Klin Wochenschr. 2016;128(15–16):573–8. https://doi.org/10.1007/s00508-014-0677-3.
69. Li DF, Yang MF, Chang X, Wang NN, Tan FF, Xie HN, et al. Endocut versus conventional blended electrosurgical current for endoscopic biliary sphincterotomy: a meta-analysis of complications. Dig Dis Sci. 2019;64(8):2088–94. https://doi.org/10.1007/s10620-019-05513-w.
70. Akbar A, Abu Dayyeh BK, Baron TH, Wang Z, Altayar O, Murad MH. Rectal nonsteroidal anti-inflammatory drugs are superior to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a network meta-analysis. Clin Gastroenterol Hepatol. 2013;11(7):778–83. https://doi.org/10.1016/j.cgh.2012.12.043.
71 Vadalà di Prampero SF, Faleschini G, Panic N, Bulajic M. Endoscopic and pharmacological treatment for prophylaxis against postendoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis and systematic review. Eur J Gastroenterol Hepatol. 2016;28(12):1415–24. https://doi.org/10.1097/meg.0000000000000734.
72. Fan JH, Qian JB, Wang YM, Shi RH, Zhao CJ. Updated meta-analysis of pancreatic stent placement in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. World J Gastroenterol. 2015;21(24):7577–83. https://doi.org/10.3748/wjg.v21.i24.7577.
73. Mazaki T, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol. 2014;49(2):343–55. https://doi.org/10.1007/s00535-013-0806-1.
74. Shi QQ, Ning XY, Zhan LL, Tang GD, Lv XP. Placement of prophylactic pancreatic stents to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a meta-analysis. World J Gastroenterol. 2014;20(22):7040–8. https://doi.org/10.3748/wjg.v20.i22.7040.
75. Choudhary A, Bechtold ML, Arif M, Szary NM, Puli SR, Othman MO, et al. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. Gastrointest Endosc. 2011;73(2):275–82. https://doi.org/10.1016/j.gie.2010.10.039.
76. Issak A, Elangovan A, Ferguson RD, Waghray N, Sandhu DS. Underutilization of prophylactic rectal indomethacin and pancreatic duct stent for prevention of post-ERCP Pancreatitis. Endosc Int Open. 2021;9(7):E979–85. https://doi.org/10.1055/a-1460-7776.
77. Coté GA, Keswani RN, Jackson T, Fogel E, Lehman GA, McHenry L, et al. Individual and practice differences among physicians who perform ERCP at varying frequency: a national survey. Gastrointest Endosc. 2011;74(1):65-73.e12. https://doi.org/10.1016/j.gie.2011.01.072.
78. Hanna MS, Portal AJ, Dhanda AD, Przemioslo R. UK wide survey on the prevention of post-ERCP pancreatitis. Frontline Gastroenterol. 2014;5(2):103–10. https://doi.org/10.1136/flgastro-2013-100323.
79. Freeman ML, Overby C, Qi D. Pancreatic stent insertion: consequences of failure and results of a modified technique to maximize success. Gastrointest Endosc. 2004;59(1):8–14. https://doi.org/10.1016/s0016-5107(03)02530-6.
80. Freeman ML. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Clin Gastroenterol Hepatol. 2007;5(11):1354–65. https://doi.org/10.1016/j.cgh.2007.09.007.
81.• Phillip V, Pukitis A, Epstein A, Hapfelmeier A, Haf D, Schwab M, et al. Pancreatic stenting to prevent post-ERCP pancreatitis: a randomized multicenter trial.

Endosc Int Open. 2019;7(7):E860–e8. https://doi.org/10.1055/a-0886-6384.
Describes the benefit of a prophylactic PS for PEP reduction in an unselected population undergoing ERCP with inadvertent PD wire insertion.
82. Afghani E, Akshintala VS, Khashab MA, Law JK, Hutfless SM, Kim KJ, et al. 5-Fr vs. 3-Fr pancreatic stents for the prevention of post-ERCP pancreatitis in high-risk patients: a systematic review and network meta-analysis. Endoscopy. 2014;46(7):573–80. https://doi.org/10.1055/s-0034-1365701.
83. Chahal P, Tarnasky PR, Petersen BT, Topazian MD, Levy MJ, Gostout CJ, et al. Short 5Fr vs long 3Fr pancreatic stents in patients at risk for post-endoscopic retrograde cholangiopancreatography pancreatitis. Clin Gastroenterol Hepatol. 2009;7(8):834–9. https://doi.org/10.1016/j.cgh.2009.05.002.
84. Zolotarevsky E, Fehmi SM, Anderson MA, Schoenfeld PS, Elmunzer BJ, Kwon RS, et al. Prophylactic 5-Fr pancreatic duct stents are superior to 3-Fr stents: a randomized controlled trial. Endoscopy. 2011;43(4):325–30. https://doi.org/10.1055/s-0030-1256305.
85. He Q, Wang L, Peng C, Zou X, Zhan Q, Xu Y, et al. Modified prophylactic 5-fr pancreatic duct stent enhances the rate of spontaneous dislodgement: a multicenter randomized controlled trial. United Eur Gastroenterol J. 2018;6(10):1519–26. https://doi.org/10.1177/2050640618804729.
86. Fujisawa T, Kagawa K, Ochiai K, Hisatomi K, Kubota K, Sato H, et al. Prophylactic efficacy of 3- or 5-cm pancreatic stents for preventing post-ERCP pancreatitis: a prospective, randomized trial. J Clin Gastroenterol. 2016;50(3):e30–4. https://doi.org/10.1097/mcg.0000000000000397.
87. Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, et al. Pancreatic stents for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis should be inserted up to the pancreatic body or tail. World J Gastroenterol. 2018;24(22):2392–9. https://doi.org/10.3748/wjg.v24.i22.2392.
88. Moffatt DC, Pradermchai K, Avula H, Sherman S, Fogel EL, Lehman GA. Moderate and severe postendoscopic retrograde cholangiopancreatography pancreatitis despite prophylactic pancreatic stent placement: the effect of early prophylactic pancreatic stent dislodgement. Can J Gastroenterol. 2011;25(4):215–9. https://doi.org/10.1155/2011/678540.
89. Cha SW, Leung WD, Lehman GA, Watkins JL, McHenry L, Fogel EL, et al. Does leaving a main pancreatic duct stent in place reduce the incidence of precut biliary sphincterotomy-associated pancreatitis? A randomized, prospective study. Gastrointest Endosc. 2013;77(2):209–16. https://doi.org/10.1016/j.gie.2012.08.022.
90.•• Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15):1414–22. https://doi.org/10.1056/NEJMoa1111103.
A landmark trial showing the benefits of rectal NSAIDs in reducing PEP rates in high-risk patients.
91. Serrano JPR, de Moura DTH, Bernardo WM, Ribeiro IB, Franzini TP, de Moura ETH, et al. Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Endosc Int Open. 2019;7(4):E477–86. https://doi.org/10.1055/a-0862-0215.
92. Yaghoobi M, Alzahrani MA, McNabb-Baltar J, Martel M, Barkun AN. Rectal indomethacin prevents moderate to severe post-ERCP pancreatitis and death and should be used before the procedure: a meta-analysis of aggregate subgroup data. J Can Assoc Gastroenterol. 2018;1(2):67–75. https://doi.org/10.1093/jcag/gwy006.
93. Lyu Y, Cheng Y, Wang B, Xu Y, Du W. What is impact of nonsteroidal anti-inflammatory drugs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2018;18(1):106. https://doi.org/10.1186/s12876-018-0837-4.
94. He X, Zheng W, Ding Y, Tang X, Si J, Sun LM. Rectal indomethacin is protective against pancreatitis after endoscopic retrograde cholangiopancreatography: systematic review and meta-analysis. Gastroenterol Res Pract. 2018;2018:9784841. https://doi.org/10.1155/2018/9784841.
95. Yu LM, Zhao KJ, Lu B. Use of NSAIDs via the rectal route for the prevention of pancreatitis after ERCP in all-risk patients: an updated meta-analysis. Gastroenterol Res Pract. 2018;2018:1027530. https://doi.org/10.1155/2018/1027530.
96. Liu L, Li C, Huang Y, Jin H. Nonsteroidal anti-inflammatory drugs for endoscopic retrograde cholangiopancreatography postoperative pancreatitis prevention: a systematic review and meta-analysis. J Gastrointest Surg. 2019;23(10):1991–2001. https://doi.org/10.1007/s11605-018-3967-7.
97. Puig I, Calvet X, Baylina M, Isava Á, Sort P, Llaó J, et al. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. PLoS ONE. 2014;9(3):e92922. https://doi.org/10.1371/journal.pone.0092922.
98. Sethi S, Sethi N, Wadhwa V, Garud S, Brown A. A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas. 2014;43(2):190–7. https://doi.org/10.1097/mpa.0000000000000090.
99. Ding X, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis.

Gastrointest Endosc. 2012;76(6):1152–9. https://doi.org/10.1016/j.gie.2012.08.021.
100. Yaghoobi M, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, et al. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013;38(9):995–1001. https://doi.org/10.1111/apt.12488.
101. Sun HL, Han B, Zhai HP, Cheng XH, Ma K. Rectal NSAIDs for the prevention of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. Surgeon. 2014;12(3):141–7. https://doi.org/10.1016/j.surge.2013.10.010.
102. Yuhara H, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T, Mine T. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: protease inhibitors and NSAIDs in a meta-analysis. J Gastroenterol. 2014;49(3):388–99. https://doi.org/10.1007/s00535-013-0834-x.
103.• Sperna Weiland CJ, Smeets X, Verdonk RC, Poen AC, Bhalla A, Venneman NG, et al. Optimal timing of rectal diclofenac in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. Endosc Int Open. 2022;10(3):E246–e53. https://doi.org/10.1055/a-1675-2108.
Demonstrated a reduced incidence of PEP in patients receiving pre-procedural rectal NSAIDS versus post-procedure.
104. Chandrasekhara V, Khashab MA, Muthusamy VR, Acosta RD, Agrawal D, Bruining DH, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017;85(1):32–47. https://doi.org/10.1016/j.gie.2016.06.051.
105. Koshitani T, Konaka Y, Mita M, Nakagawa S. Prophylaxis of post-ERCP pancreatitis using temporary pancreatic stents vs rectal nonsteroidal anti-inflammatory drugs: a randomized controlled trial. Pancreas. 2021;50(7):1072–3. https://doi.org/10.1097/MPA.0000000000001904.
106.• Sotoudehmanesh R, Ali-Asgari A, Khatibian M, Mohamadnejad M, Merat S, Sadeghi A, et al. Pharmacological prophylaxis versus pancreatic duct stenting plus pharmacological prophylaxis for prevention of post-ERCP pancreatitis in high risk patients: a randomized trial. Endoscopy. 2019;51(10):915–21. https://doi.org/10.1055/a-0977-3119.
One of the first direct comparison trials to evaluate pharmacotherapy + PS versus pharmacotherapy in PEP prevention of high-risk patients.
107.• Njei B, McCarty TR, Muniraj T, Sharma P, Jamidar PA, Aslanian HR, et al. Comparative effectiveness of pharmacologic and endoscopic interventions for prevention of post-ERCP pancreatitis: a network meta-analysis. Endosc Int Open. 2020;8(1):E29–e40. https://doi.org/10.1055/a-1005-6366.
A network meta-analysis comparing PS to pharmacotherapy and hydration therapy for PEP prevention.
108.• Dubravcsik Z, Hritz I, Keczer B, Novák P, Lovász BD, Madácsy L. Network meta-analysis of prophylactic pancreatic stents and non-steroidal anti-inflammatory drugs in the prevention of moderate-to-severe post-ERCP pancreatitis. Pancreatology. 2021;21(4):704–13. https://doi.org/10.1016/j.pan.2021.04.006.
A network meta-analysis comparing PS to rectal NSAIDs in reduction of moderate-severe PEP in average and high-risk patients.
109.• Akshintala VS, Sperna Weiland CJ, Bhullar FA, Kamal A, Kanthasamy K, Kuo A, et al. Non-steroidal anti-inflammatory drugs, intravenous fluids, pancreatic stents, or their combinations for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(9):733–42. https://doi.org/10.1016/s2468-1253(21)00170-9.
The largest exploratory meta-analysis to date comparing PS, pharmacotherapy, hydration therapy, and combination therapy for PEP prevention.
110.• Smith ZL, Elmunzer BJ, Cooper GS, Chak A. Real-world practice patterns in the era of rectal indomethacin for prophylaxis against post-ERCP pancreatitis in a high-risk cohort. Am J Gastroenterol. 2020;115(6):934–40. https://doi.org/10.14309/ajg.0000000000000623.
Describes current practice trends in the USA with reduced use of prophylactic pancreatic stents and suboptimal use of rectal NSAIDs during ERCP.
111.• Mutneja HR, Vohra I, Go A, Bhurwal A, Katiyar V, Palomera Tejeda E, et al. Temporal trends and mortality of post-ERCP pancreatitis in the United States: a nationwide analysis. Endoscopy. 2021;53(4):357–66. https://doi.org/10.1055/a-1220-2242.
Shows an increased PEP rate and mortality in the USA over the last decade corresponding to a decline in use of pancreatic stents and suboptimal use of rectal NSAIDs.
112.•• Elmunzer BJ, Serrano J, Chak A, Edmundowicz SA, Papachristou GI, Scheiman JM, et al. Rectal indomethacin alone versus indomethacin and prophylactic pancreatic stent placement for preventing pancreatitis after ERCP: study protocol for a randomized controlled trial. Trials. 2016;17(1):120. https://doi.org/10.1186/s13063-016-1251-2.
An ongoing multicenter, double-blinded, non-inferiority study comparing PEP prevention rates in high-risk patients receiving indomethacin and PD stenting versus indomethacin monotherapy.
113.• Buxbaum J, Yan A, Yeh K, Lane C, Nguyen N, Laine L. Aggressive hydration with lactated Ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol. 2014;12(2):303–7.e1. https://doi.org/10.1016/j.cgh.2013.07.026.
One of the first studies demonstrating efficacy in aggressive hydration for PEP prevention.
114. Wang RC, Jiang ZK, Xie YK, Chen JS. Aggressive hydration compared to standard hydration with lactated ringer's solution for prevention of post

endoscopic retrograde cholangiopancreatography pancreatitis. Surg Endosc. 2021;35(3):1126–37. https://doi.org/10.1007/s00464-020-07477-9.

115. Wu M, Jiang S, Lu X, Zhong Y, Song Y, Fan Z, et al. Aggressive hydration with lactated ringer solution in prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Medicine (Baltimore). 2021;100(16): e25598. https://doi.org/10.1097/md.0000000000025598.
116. Radadiya D, Devani K, Arora S, Charilaou P, Brahmbhatt B, Young M, et al. Peri-procedural aggressive hydration for post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis prophylaxsis: meta-analysis of randomized controlled trials. Pancreatology. 2019;19(6):819–27. https://doi.org/10.1016/j.pan.2019.07.046.
117. Sagi SV, Schmidt S, Fogel E, Lehman GA, McHenry L, Sherman S, et al. Association of greater intravenous volume infusion with shorter hospitalization for patients with post-ERCP pancreatitis. J Gastroenterol Hepatol. 2014;29(6):1316–20. https://doi.org/10.1111/jgh.12511.
118. DiMagno MJ, Wamsteker EJ, Maratt J, Rivera MA, Spaete JP, Ballard DD, et al. Do larger periprocedural fluid volumes reduce the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis? Pancreas. 2014;43(4):642–7. https://doi.org/10.1097/mpa.0000000000000101.
119.• Sperna Weiland CJ, Smeets X, Kievit W, Verdonk RC, Poen AC, Bhalla A, et al. Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT): a multicentre, open-label, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2021;6(5):350–8. https://doi.org/10.1016/s2468-1253(21)00057-1.

A multicenter, RCT directly comparing rectal NSAIDs + AH versus rectal NSAIDs alone and showing no change in PEP incidence.

120. Park CH, Paik WH, Park ET, Shim CS, Lee TY, Kang C, et al. Aggressive intravenous hydration with lactated Ringer's solution for prevention of post-ERCP pancreatitis: a prospective randomized multicenter clinical trial. Endoscopy. 2018;50(4):378–85. https://doi.org/10.1055/s-0043-122386.
121. Lyu Y, Wang B, Cheng Y, Xu Y, Du W. Comparative efficacy of 9 major drugs for postendoscopic retrograde cholangiopancreatography pancreatitis: a network meta-analysis. Surg Laparosc Endosc Percutan Tech. 2019;29(6):426–32. https://doi.org/10.1097/sle.0000000000000707.
122. Ding J, Jin X, Pan Y, Liu S, Li Y. Glyceryl trinitrate for prevention of post-ERCP pancreatitis and improve the rate of cannulation: a meta-analysis of prospective, randomized, controlled trials. PLoS ONE. 2013;8(10): e75645. https://doi.org/10.1371/journal.pone.0075645.
123. Tomoda T, Kato H, Ueki T, Akimoto Y, Hata H, Fujii M, et al. Combination of diclofenac and sublingual nitrates is superior to diclofenac alone in preventing pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology. 2019;156(6):1753-60.e1. https://doi.org/10.1053/j.gastro.2019.01.267.
124. Wang G, Xiao G, Xu L, Qiu P, Li T, Wang X, et al. Effect of somatostatin on prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis and hyperamylasemia: a systematic review and meta-analysis. Pancreatology. 2018;18(4):370–8. https://doi.org/10.1016/j.pan.2018.03.002.
125. Matsumoto T, Okuwaki K, Imaizumi H, Kida M, Iwai T, Yamauchi H, et al. Nafamostat mesylate is not effective in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. Dig Dis Sci. 2021;66(12):4475–84. https://doi.org/10.1007/s10620-020-06782-6.
126. Yu G, Li S, Wan R, Wang X, Hu G. Nafamostat mesilate for prevention of post-ERCP pancreatitis: a meta-analysis of prospective, randomized, controlled trials. Pancreas. 2015;44(4):561–9. https://doi.org/10.1097/mpa.0000000000000310.
127. Ohuchida J, Chijiiwa K, Imamura N, Nagano M, Hiyoshi M. Randomized controlled trial for efficacy of nafamostat mesilate in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas. 2015;44(3):415–21. https://doi.org/10.1097/mpa.0000000000000278.
128. Thiruvengadam NR, Forde KA, Chandrasekhara V, Ahmad NA, Ginsberg GG, Khungar V, et al. Tacrolimus and indomethacin are safe and effective at reducing pancreatitis after endoscopic retrograde cholangiopancreatography in patients who have undergone liver transplantation. Clin Gastroenterol Hepatol. 2020;18(5):1224-32.e1. https://doi.org/10.1016/j.cgh.2019.10.014.
129. Luo H, Wang X, Zhang R, Liang S, Kang X, Zhang X, et al. Rectal indomethacin and spraying of duodenal papilla with epinephrine increases risk of pancreatitis following endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol. 2019;17(8):1597-606.e5. https://doi.org/10.1016/j.cgh.2018.10.043.
130. Kamal A, Akshintala VS, Talukdar R, Goenka MK, Kochhar R, Lakhtakia S, et al. A randomized trial of topical epinephrine and rectal indomethacin for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. Am J Gastroenterol. 2019;114(2):339–47. https://doi.org/10.14309/ajg.0000000000000049.
131. Dar HA, Shah A, Javid G, Khan MA, Singh B, Sheikh NA, et al. Randomized trial of high-dose rectal diclofenac suppository and epinephrine spray on duodenal papilla for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Indian J Gastroenterol. 2021;40(5):483–91. https://doi.org/10.1007/s12664-021-01161-z.

132. Zheng M, Bai J, Yuan B, Lin F, You J, Lu M, et al. Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis. BMC Gastroenterol. 2008;8:6. https://doi.org/10.1186/1471-230x-8-6.
133. Barkay O, Niv E, Santo E, Bruck R, Hallak A, Konikoff FM. Low-dose heparin for the prevention of post-ERCP pancreatitis: a randomized placebo-controlled trial. Surg Endosc. 2008;22(9):1971–6. https://doi.org/10.1007/s00464-007-9738-2.
134. Prat F, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, et al. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. Gastrointest Endosc. 2002;56(2):202–8. https://doi.org/10.1016/s0016-5107(02)70178-8.
135. Bai Y, Gao J, Zhang W, Zou D, Li Z. Meta-analysis: allopurinol in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis. Aliment Pharmacol Ther. 2008;28(5):557–64. https://doi.org/10.1111/j.1365-2036.2008.03756.x.
136. Li S, Cao G, Chen X, Wu T. Low-dose heparin in the prevention of post endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2012;24(5):477–81. https://doi.org/10.1097/MEG.0b013e328351097f.
137. Abbasinazari M, Mohammad Alizadeh AH, Moshiri K, Pourhoseingholi MA, Zali MR. Does allopurinol prevent post endoscopic retrograde cholangio- pancreatography pancreatitis? A randomized double blind trial. Acta Med Iran. 2011;49(9):579–83.
138. Räty S, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. J Gastrointest Surg. 2001;5(4):339–45; discussion 45. https://doi.org/10.1016/s1091-255x(01)80059-7.
139. Akshintala VS, Hutfless SM, Colantuoni E, Kim KJ, Khashab MA, Li T, et al. Systematic review with network meta-analysis: pharmacological prophylaxis against post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013;38(11–12):1325–37. https://doi.org/10.1111/apt.12534.

## Publisher's Note