

Review

An Insight on Pharmacological and Mechanical Preventive Measures of Post-ERCP PANCREATITIS (PEP)—A Review

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Abstract: Pancreatitis is the most common complication following endoscopic retrograde cholangio-pancreatography (ERCP). With the progress of research in many drugs and technologies, promising efficacy has been achieved in preventing post-ERCP pancreatitis (PEP). Recently, combined prevention has received more attention in order to further reduce the incidence of PEP. However, there is no review about the combined prevention of PEP. This review summarizes the medication and ERCP techniques that are used to prevent PEP and emphasizes that appropriate combination prevention approaches should be based on risk stratification.

Keywords: endoscopic retrograde cholangio-pancreatography (ERCP); post-ERCP pancreatitis; pharmacological prevention; mechanical prevention; combined prevention



Citation: Zhang, Y.; Liang, Y.; Feng, Y. An Insight on Pharmacological and Mechanical Preventive Measures of Post-ERCP PANCREATITIS (PEP)—A Review. *Gastroenterol. Insights* **2022**, *13*, 387–403. <https://doi.org/10.3390/gastroent13040038>

Academic Editors: Raymond Tang and Rashid N. Lui

Received: 5 November 2022

Accepted: 30 November 2022

Published: 2 December 2022

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1. Introduction

Endoscopic retrograde cholangio-pancreatography (ERCP) is an important procedure to diagnose and treat hepatobiliary and pancreatic diseases. Pancreatitis is one of the most common and severe complications after ERCP, with the reported incidence ranging from 3.47% to 9.70% in recent studies [1,2]. The generally accepted definition of post-ERCP pancreatitis (PEP) was advanced by Cotton et al. in 1991 [3], which included the new or exacerbating pancreatic-type abdominal pain, accompanied by serum amylase exceeding at least three times the upper limit of the normal value occurring within 24 h post-ERCP, as well as hospital admission duration for more than one day. The severity of PEP was also defined according to the consensus criteria, which is shown in Table 1. In addition, Banks et al. [4] proposed the classification of acute pancreatitis which was used in some studies. Although differences in the criteria for defining PEP and severity classification are likely to influence the reported rates, the majority of PEP is assumed to be mild. In contrast, severe pancreatitis has a lower incidence, but still is a major contributing factor in the death of patients.

The majority of relevant references in this review use the Cotton et al. consensus to define PEP. The mechanism of post-ERCP pancreatitis (PEP) is still unclear, which could be associated with mechanical injury, thermal injury, chemical or allergic injury, etc. These factors activate proteolytic enzymes within acinar cells, ultimately leading to cellular injury and autodigestion of the pancreas [5]. Recently, various research is being conducted to explain the mechanism and etiologies of PEP. This review mainly introduces the precautionary measures to prevent PEP.

Table 1. Severity grading of PEP.

Types	Severity Grading		
	Mild	Moderate	Severe
Cotton et al. [3]	<ul style="list-style-type: none"> • Clinical pancreatitis • Amylase at least three times more than normal at 24 h after the procedure • Requiring admission or prolongation of planned admission to 2–3 days 	<ul style="list-style-type: none"> • Requiring hospitalization of 4–10 days 	<ul style="list-style-type: none"> • Hospitalization for more than 10 days OR • Hemorrhagic pancreatitis, phlegmon pseudocyst, or intervention OR • Need for percutaneous drainage or surgery
Bank et al. [4]	<ul style="list-style-type: none"> • No organ failure • No local or systemic complications 	<ul style="list-style-type: none"> • Organ failure that resolves within 48 h (transient organ failure) OR • Local or systemic complications without persistent organ failure 	<ul style="list-style-type: none"> • Persistent organ failure (>48 h) (single or multiple organ failure)

2. Risk Factors

The risk factors related to PEP have been investigated in many studies and systematic reviews, and some patient-related risk factors (e.g., female, previous PEP, previous pancreatitis, and sphincter of Oddi dysfunction) and procedure-related risk factors (e.g., difficult cannulation, pancreatic injection, precut sphincterotomy, and non-prophylactic pancreatic duct stent) have been confirmed [6–11]. The presence of multiple factors can have a cumulative effect. Typically, patients without the above risk factors were defined as low-risk. High-risk patients were identified as patients who met one or more of the above risk factors [12]. In addition, there are a number of other risk factors that we need to consider, for example the research of Deenadayalu VP et al. showed that obesity increases the risk of PEP (OR = 1.143; $p = 0.002$) [13], and other earlier studies also found that using pancreatotoxic drugs (including estrogen, azathioprine, valproic acid, mesalazine, morphine derivatives, and prednisone) in the preoperative period of ERCP significantly increased the risk of PEP (OR = 3.7, $p = 0.04$) [14]. However, the use of BMI and drugs is not involved in the recent meta-analysis because of the lack of relevant clinical studies. In addition, several studies [15–17] have shown that the incidence of PEP progressively decreases with age and middle-aged people have a higher incidence and mortality. The pathophysiology behind that observance remains unclear. One explanation could be reduced levels of pancreatic enzyme secretion or more advanced atrophy of the pancreas in older patients [16,17].

Because of the high incidence of PEP in high-risk patients, early identification and the implementation of therapeutic strategies for high-risk patients is critical to avoid the occurrence of PEP [18,19]. Additionally, further investigations of novel risk factors of PEP are highly warranted. The risk factors of PEP are shown in Table 2.

Table 2. Risk factors for PEP.

Risk Factors	Odds Ratios
Patient-related risk factors	
•Female sex [14,15]	1.40–2.23
•Previous pancreatitis [14,15]	2.00–2.90
•Previous PEP [14,15]	2.90–8.50
•Suspected SOD [14,15]	2.04–4.37
•Intraductal papillary mucinous neoplasm (IPMN) [15]	3.01
Patient-related likely risk factors	
•Age [9,11,13]	1.60–3.97
•Obesity [16]	1.143
•Taken potent pancreatotoxic drugs [17]	3.70

Table 2. Cont.

Risk Factors	Odds Ratios
Procedure-related risk factors	
•Difficult cannulation [14,15]	3.49–14.9
•Pancreatic injection [14,15]	1.58–2.72
•Precut sphincterotomy [14,15]	2.11–3.10
•Non-prophylactic pancreatic duct stent [10,14]	1.84–2.10
•Difficult cannulation [14,15]	3.49–14.9
Procedure-related likely risk factors	
•Trainee involvement [9]	1.5
•Extent of pancreatogram [13]	9.516

3. Prevention

The prevention of PEP has been studied for decades, and some breakthroughs have been made in pharmacological and technological prevention measures which are discussed below in detail (Figure 1).

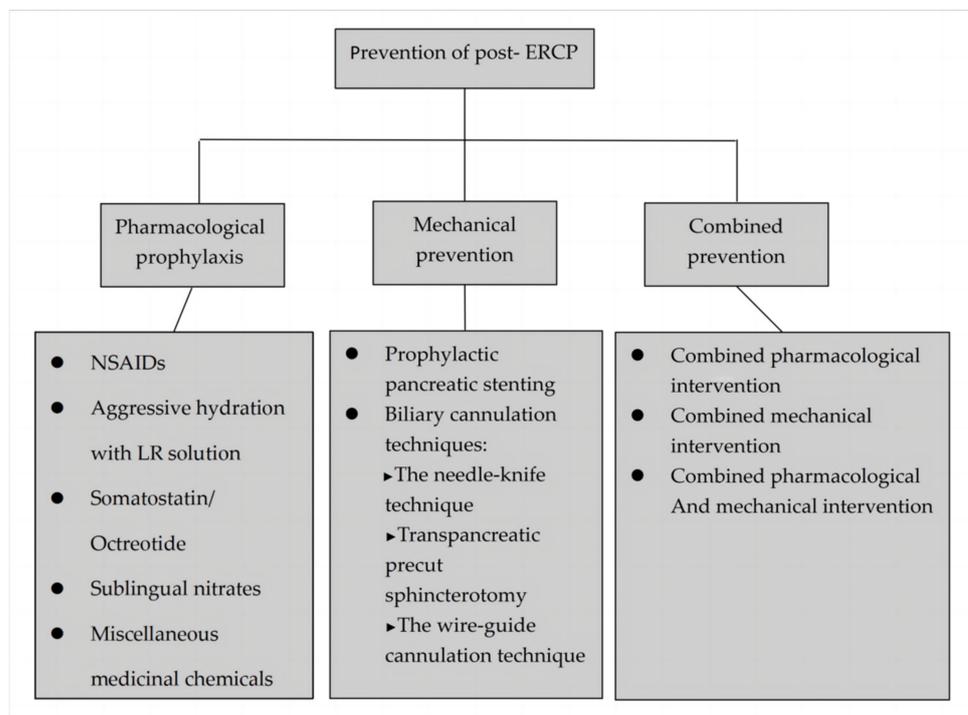


Figure 1. Methods for prevention of post-ERCP pancreatitis.

3.1. Pharmacological Prophylaxis

Pharmacological prophylaxis was routinely given to patients who performed ERCP. As an ideal strategy for the prevention of PEP, medication also should have the following advantages: (1) effective and safe; (2) easily available and simple to use; (3) inexpensive. Numerous drugs to prevent PEP have been studied, including nonsteroid anti-inflammatory drugs (NSAIDs), nitroglycerin, somatostatin, octreotide, gabexate, steroids, heparin, allopurinol, etc.

3.1.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

As an inexpensive, safe, and easily administered drug, NSAIDs have been the most attractive agents against PEP in the past decade. NSAIDs are potent inhibitors of prostaglandins, phospholipase A2, and neutrophil-endothelial interaction, which might prevent

PEP by inhibiting synthesis of prostaglandin and interrupting the inflammatory cascade of pancreatitis [20–22]. A large meta analysis [23] (6 RCTs, 1300 patients) further confirmed the efficacy of NSAIDs for preventing PEP (OR: 0.46, 95% CI: 0.32–0.65, $p < 0.0001$). At present, there are four common routes of NSAIDs administration including intravenous injection, intramuscular injection, oral administration, and rectal suppositories. Furthermore, rectal NSAIDs administration is the most widely used due to its advantages of less gastrointestinal irritation and rapid absorption [21]. In addition, compared with other routes, rectal NSAIDs administration indicates a better clinical response in the prevention of PEP. Diclofenac and indomethacin are the main NSAIDs which have been studied and applied in clinics widely. In 2008, Elmunzer et al. [24] performed a meta-analysis (four RCTs, 912 patients) which demonstrated that rectal NSAIDs may significantly reduce the incidence of PEP (RR = 0.36, 95% CI: 0.22–0.60). However, data recruited from only four RCTs are too small to be entirely convincing. Numerous studies have shown that rectal NSAIDs have less side effects, which shows their own unique advantage. Traditionally, clinicians often use 100 mg of rectal diclofenac or rectal indomethacin immediately before ERCP in all patients without contraindications to NSAID administration.

Furthermore, Ding et al. [25] (10 RCTs, 2269 patients) found that the rectal route of NSAIDs administration seems to be more effective than other routes. A recent meta analysis has confirmed the effects of rectal NSAIDs; however, controversy still remains in the prevention of moderate to severe PEP. The study by Yang et al. [26], (12 RCTs, 3989 patients) showed that NSAIDs reduce the risk of moderate to severe PEP (RR = 0.44, 95% CI: 0.28–0.69, $p < 0.01$). In contrast, the study of Li et al. [27] (9 RCTs, 1883 patients) revealed that NSAIDs had no effect on the development of moderate to severe pancreatitis (RR = 0.79, 95% CI: 0.52–1.18). Thus, the effectiveness of NSAIDs for PEP prevention needs to be further evaluated. Beyond that, with gradual intense study, there are some major problems that demand discussion and emphasis, such as dosages of NSAIDs, type and timing of administration, etc. The most frequent dosage of diclofenac or indomethacin was 100 mg, which was mostly based on clinical experience. However, there is still no confirmed information about the appropriate dosage to prevent PEP. Some studies have applied certain reference values to observe the efficacy in prevention of PEP. A retrospective study [28] in Japan showed that 50 mg rectal diclofenac had superiority over the 25 mg dose in preventing PEP, which suggested that the effectiveness of NSAIDs for PEP may be dose-dependent. The latest trial [29] showed that 200 mg rectal indomethacin had no superiority over the standard 100 mg regimen in preventing PEP, which suggested that more NSAID doses are not always better. In addition, the timing of administration of rectal NSAIDs is equally important. Although Yang et al.'s subgroup analyses showed that the timing of administration (pre-or post-ERCP) and NSAID type (indomethacin or diclofenac) could not affect rectal NSAIDs' preventive effects, more relevant research results are still lacking. This is a reminder that although remarkable achievements have been made in NSAIDs, there are still many issues to be resolved and additional experimental investigations are needed.

3.1.2. Somatostatin/Octreotide

Somatostatin and its synthetic analogue octreotide decreases pancreatic enzyme secretion by inhibiting cholecystokinin (CCK) and secretin. Earlier studies have shown that they can decrease the secretion of pancreatic enzymes, and reduce intraductal pressure and possibly proteolysis [30–33]. Although somatostatin and octreotide have been extensively investigated for the chemoprophylaxis of PEP, early studies have shown conflicting results regarding the preventive effect of somatostatin or octreotide on PEP [34–36].

In 2007, a meta-analysis [34] that included 16 trials compared the administration of somatostatin to controls for the incidence of pancreatitis. While pancreatitis occurred in 7.3% of controls compared with 5.3% of patients treated with somatostatin, this difference was not statistically significant (OR = 0.73; 95% CI: 0.54–1.006). However, a meta-analysis by Rudin et al. [36] (7 RCTs, 3130 patients) reported conflicting results showing that long-

term somatostatin infusion significantly reduced the incidence of PEP. Similarly, in 2008, a systematic review (15 trials, 2621 patients) also did not find any benefit in favor of treatment with octreotide (OR = 0.78, 95% CI: 0.57–1.08, $p = 0.49$) [35]. In contrast, a meta-analysis by Zhang et al. [37] (17 RCTs, 2784 patients) showed that a sufficient dose (≥ 0.5 mg) of octreotide (OR = 0.45, 95% CI: 0.28–0.73, $p = 0.001$) was more effective in preventing PEP than a dose of <0.5 mg octreotide (OR = 1.23, 95% CI: 0.80–1.91, $p = 0.35$). These different results let us speculate that the preventive effect of somatostatin or octreotide may correlate directly with the dose. Furthermore, this speculation was confirmed in subsequent research. A meta-analysis of Omata et al. [38] (17 RCTs, 3818 patients) revealed that high doses of somatostatin or octreotide have a significant effect on the prevention of PEP. In recent years, several subgroup analyses have shown that when a long-term infusion or high-dose somatostatin therapy is used, the incidence of PEP is significantly reduced [39–41]. Thus, in accordance with current research, using high doses of somatostatin or octreotide to prevent PEP seems to be a viable option.

3.1.3. Sublingual Nitrates

Glyceryl trinitrate (GTN) as a nitric oxide donor can relax the sphincter of Oddi (SOD) and decrease SOD pressure [42]. It has been used to induce papillary dilation so far in clinicals. GTN for the prevention of PEP was confirmed in the earlier meta-analysis [43–45]. The most common adverse events were headache and transient hypotension, noted more frequently in trials with sublingual or intravenous delivery. Compared with other therapeutic agents that might possibly be used to reduce the frequency of PEP, the GTN has a number of advantages such as feasibility, low cost, and mild side effects.

In 2013, Ding et al. [46] performed a meta-analysis (12 RCTs, 2649 patients), which showed that the incidence of PEP was significantly reduced by GTN treatment (RR = 0.67, 95% CI: 0.52–0.87). However, GTN administration did not decrease the incidence of moderate to severe PEP (RR = 0.70, 95% CI: 0.42–1.15). After subgroup analyses, they suggested that the advantage of sublingual GTN (RR = 0.47) was greater than topical and transdermal application (RR = 1.00, RR = 0.78, respectively). The latest studies, combining NSAIDs with sublingual nitrates to prevent PEP have also achieved good results. Hence, ESGE (2019) also suggested administration of 5 mg sublingual GTN before ERCP in patients for the prevention of PEP (weak recommendation, moderate quality evidence). Further clinical trials are still required to explore the effectiveness of nitroglycerin in the prevention of PEP.

3.1.4. Aggressive Hydration with Lactated Ringer's Solution

As the pancreatic inflammatory response causes vasodilation with intravascular volume depletion and organ hypoperfusion, perioperative aggressive hydration has attracted immense attention. Perioperative aggressive hydration can maintain pancreatic microperfusion, which can effectively delay the pancreatic inflammation and ultimately reduce the incidence of PEP [4,47]. The evidence supporting aggressive hydration fluid type to prevent PEP is unclear. Most studies have used Lactated Ringer's (LR) solution as the preferred hydration fluid. The possible reason is that intravenous hydration with normal saline can potentiate acidosis and activate pancreatic enzymes. However, LR solution has more pH-balanced properties, which can prevent hyperchloremic metabolic acidosis [48]. The total amount of fluid used for aggressive hydration is 35–45 mL/kg, administered within 8–10 h.

The meta-analysis by Wu et al. [49] (3 RCTs, 722 patients) showed that the aggressive hydration treatment reduced the incidence of PEP (OR = 0.29; 95% CI: 0.16–0.53) and slightly shortened the length of hospital stay. The latest meta-analysis (9 RCTs, 2094 patients), including two RCTs from the above study, confirmed the previous result [50]. At the same time, the risk analysis showed that aggressive hydration reduced the risk of PEP (OR = 0.44, 95% CI: 0.28–0.69, $p = 0.0004$). The studies of hydration with Lactate Ringer's solution are showed in Table 3. However, the side effects of aggressive hydration are also obvious.

Hydration volume overload may aggravate the circulatory system burden resulting in a higher incidence of peripheral edema. Furthermore, the study of Grunwald et al. [51] showed that an increase in the amount of IV fluids administered during ERCP may increase the risk of PEP. In addition, the latest randomized prospective multicenter trial by De-Madaria et al. [52] regarding early aggressive hydration in the management of acute pancreatitis demonstrated that early aggressive fluid resuscitation resulted in a higher incidence of fluid overload without improvement in clinical outcomes of pancreatitis patients (adjusted RR, 2.85; 95% CI: 1.36–5.94, $p = 0.004$). Therefore, fluid overload risk should be taken into account in aggressive fluid resuscitation. Furthermore, more research is needed before the routine use of aggressive hydration to prevent PEP.

Table 3. The project of hydration with Lactate Ringer’s solution.

First Author	Country	Study Design	
		The Aggressive Hydration (AH) Group	The Standard Hydration (SH) Group
Buxbaum et al. [49,50]	USA	3.0 cc/kg/h during the procedure, a bolus of 20 cc/kg immediately after ERCP, followed by a post-ERCP rate of 3.0 cc/kg/h for 8 h	1.5 cc/kg/h during ERCP and for 8 h after ERCP without a bolus
Shygan-Nejad et al. [50]	Iran	3.0 cc/kg/h during ERCP, a bolus of 20 mL/kg right after ERCP and 3.0 cc/kg/h of lactated Ringer solution for 8 h	1.5 cc/kg/h during ERCP and the following 8 h
Choi et al. [49,50]	Korea	10 cc/kg before ERCP, 3.0 cc/kg/h during and for 8 h after ERCP, and a post-ERCP bolus of 10 cc/kg	1.5 cc/kg/h during and for 8 h after ERCP
Park et al. [50]	Korea	20-mL/kg bolus and 3 cc/kg/h for 8 h after ERCP	1.5 cc/kg/h during and for 8 h after ERCP
Shaygan-Nejad et al. [49,50]	Iran	3 mL/kg/h during ERCP, 3 mL/kg/h for 8 h after the procedure to 20 mL/kg	1.5 mL/kg/h during and for 8 h after procedure

3.1.5. Miscellaneous Medicinal Chemicals

Some potentially effective drugs have also been used to prevent PEP, but the results were not very satisfactory. Hereby, we have mentioned a brief summary of other drugs.

Corticosteroid is an anti-inflammatory hormone that may reduce inflammatory response during the initial steps of autodigestive cascade and relieve exudation or edema [53]. Previous studies showed that corticosteroid is able to increase the activity of C1-antiprotease inhibitor [54], inhibiting synthesis of phospholipase A2 [55,56]. It is suggested that corticosteroid may be used to prevent PEP. However, in 1999, a controlled prospective study [57] (535 patients) showed that the advantage of hydrocortisone is similar to placebo in preventing PEP (the incidence of PEP: 5.7% vs. 4.9%). Later, a larger study [58] (1115 patients) arrived at a similar conclusion that prophylactic orally administered corticosteroid did not reduce the frequency or severity of PEP. In 2008, Zheng et al. [59] performed a meta-analysis (7 RCTs, 2632 patients) indicating that there were no beneficial effects of corticosteroid on PEP (OR = 1.13, 95% CI: 0.89–1.44, $p = 0.32$). Thus, the use of corticosteroids for preventing PEP is not recommended.

Nifedipine is a widely used calcium channel inhibitor that acts on L-type calcium channels and may reduce the basal pressure of the sphincter of Oddi and the contraction amplitude and duration of the sphincter [60]. However, nifedipine has not been effective in current clinical studies. In 2002, Prat et al. [61] performed a double-blind randomized trial (nifedipine 76 patients, placebo 79 patients), which not only failed to demonstrate

that nifedipine has a significant effect in preventing PEP (The rate of PEP: 13.2% vs. 17.7%, $p = 0.4$; respectively), but also showed that nifedipine did not reduce the frequency of difficult cannulation (OR = 3.78, 95% CI: 1.25–11.45). So far, there have been no clinical trials to support the benefits of nifedipine in preventing PEP.

Lidocaine has been shown to minimize the increase in cholecystokinin (CCK) after the diversion of the pancreatic-biliary stream [62,63]. However, the preventive effect of PEP is not significant [64].

There is evidence that heparin has anti-inflammatory effects [65,66]. However, low-dose heparin was ineffective in two previous clinical trials [67,68].

Allopurinol is a structural isomer of hypoxanthine, which has the effect of inhibiting xanthine oxidase. Allopurinol may prevent capillary injury, which is an early event regulated by oxygen-derived free radicals in the pathogenesis of acute pancreatitis [69]. However, several studies confirmed that prophylactic allopurinol was not useful for preventing PEP. In 2008, Bai et al. performed a meta-analysis [70] (4 RCTs, 1730 patients), which showed that the RR of allopurinol was 0.86 (95% CI: 0.42–1.77, $p = 0.68$), and the subgroup analyses showed that doses of allopurinol did not affect the results. In the same year, a larger meta-analysis [71] (6 RCTs, 1 554 patients) confirmed that prophylactic allopurinol was not effective in reducing the incidence of PEP (RR=0.74, 95% CI: 0.37–1.48, $p = 0.40$). The most recent study [72] (RR = 0.75, 95% CI: 0.39–1.42) confirmed this result again, so this option is not recommended.

Protease inhibitors can inhibit the activation of proteolytic enzymes and play an important role in the recognized pathogenesis of PEP [73]. Several clinical trials have shown that gabexate mesylate or ulinastatin seems to be effective in preventing PEP [74–79]. However, a subsequent meta-analysis showed that protease inhibitors had no significant effect on preventing PEP (OR: 0.65–0.67) [80,81]. It even did not have any beneficial effects on hyperamylasemia and abdominal pain after ERCP. As protease inhibitors are expensive and less effective, these agents may not be practical in routine clinical use.

3.2. Mechanical Prevention

Some mechanical preventive measures during the ERCP have also achieved good results. Below, we will mainly introduce the measures of handling difficult cannulation and prophylactic pancreatic stenting.

3.2.1. Prophylactic Pancreatic Stenting

Pancreatic duct (PD) stent placement is a substitute drainage pathway, which can maintain the patency of pancreatic drainage. PD stents are commonly made of polyethylene, which is sometimes mixed with vinyl or other softer materials, and typically have side holes [82–84]. In addition, clinicians have been updating PD stents to make it easily deployable without causing stent-induced ductal or parenchymal pancreatic damage. An early meta-analysis [85] (3 RCTs, 258 patients) showed that the risk of PEP in patients with PD stent was significantly reduced (OR = 0.18, 95% CI: 0.07–0.47, $p = 0.001$). However, the sample size of the three studies included was too small to allow a proper conclusion regarding the effects of treatment. Two subsequent meta-analyses (8 RCTs, 680 patients [86]; 14 RCTs, 1 541 patients [87], respectively) confirmed that pancreatic stent placement after ERCP reduced the risk of PEP (RR = 0.32, $p < 0.001$ and RR = 0.39; $p < 0.001$, respectively).

In 2015, Fan et al. performed a larger meta-analysis [83] (15 RCTs, 1606 patients), which had more comprehensive data compared to the previous studies. The meta analysis showed that pancreatic stent placement after ERCP had a significantly lower incidence of PEP (OR = 0.35, 95% CI: 0.25–0.49, $p < 0.00001$). Furthermore, the subgroup analysis demonstrated that it could effectively decrease the incidence of complications and shorter hospital stay in high-risk patients. A recent meta-analysis [88] (11 RCTs, 1475 patients) obtained the same results (OR = 0.32, 95% CI: 0.23–0.45). Although pancreatic-stent placement decreases the incidence of PEP, this endoscopic maneuver also has been related to complications and

additional costs. A cost-effectiveness analysis [89] showed that the use of prophylactic pancreatic stenting only for high-risk patients was the most cost-effective strategy.

At present, there is a controversy about the optimal size and length of the PD stent. Clinically, 3–5 Fr pancreatic stents have been used most widely, which may result in less ductal irritation and may spontaneously dislodge more frequently than larger-diameter ones. Some clinical trials [84,90,91] have shown that when placing a PD stent to prevent PEP, using small-caliber stents (3 Fr, 4 Fr, or 5 Fr) can minimize PD injury and promote spontaneous dislodgment. However, placing small luminal diameter stents is technically more difficult, as it can occlude early resulting in the compromise of pancreatic duct drainage, and leading to an increase in the risk of pancreatitis. In 2011, Zolotarevsky et al. [92] reported that the placement of a 5-Fr compared with a 3-Fr PS for PEP prophylaxis was easier and faster and required fewer wires. The most recent meta-analysis [93] showed that 5-Fr stents were superior to 3-Fr in preventing PEP. Therefore, for prophylactic pancreatic stenting, we suggest the use of a short 5-Fr pancreatic stent in high-risk patients.

3.2.2. Biliary Cannulation

Selective biliary intubation is the initial step to successfully enter the biliary tract during ERCP. Even an experienced endoscopist may fail in 10–15% cases [94]. Some studies [95–97] have indicated that every new attempt to cannulate through the papilla or repeat cannulation of the pancreatic duct increases the risk of PEP. Repeated cannulation attempts may result in ductal injury or injury to the ampulla. At the same time, in the standard contrast agent injection method, the inadvertent injection of a contrast agent into the pancreatic duct may cause chemical damage to the pancreas. Therefore, several supplementary techniques have been developed to overcome the difficult cannulation, including the needle-knife technique, the double guide-wire technique, and the technique trans pancreatic sphincterotomy (TPS) [98,99].

3.2.3. Needle-Knife Precut Sphincterotomy

The needle-knife technique was first described in the early 1980s, including needle-knife papillotomy (NKP) and needle-knife fistulotomy (NKF) [100,101]. Initial studies have found this technique to be an independent risk factor for the development of PEP [102–104], but it is more likely that the increased risk of PEP stems from the prolonged cannulation attempts with resultant papillary edema, stressing the importance of implementing alternative techniques earlier rather than later to reduce the incidence of PEP [105–107]. In 2014, a systemic review and meta-analysis by Choudhary et al. [108] suggested that needle-knife fistulotomy significantly lowered the risk of PEP (OR = 0.27, 95% CI: 0.09–0.82; $p = 0.02$) by an absolute risk reduction of 5%. Therefore, NKF has been recommended as the preferred technique for difficult biliary cannulation by current guidelines [12]. Although needle-knife precut sphincterotomy greatly increases the efficiency of biliary cannulation [109], the technique also carries the risk of postoperative complications (including bleeding, perforation, and cholangitis), ideally performed by experienced endoscopists [110].

3.2.4. Transpancreatic Precut Sphincterotomy (TPS)

TPS was first described by Goff in 1995. As the technical accessibility is not so complicated and the incision depth is easier to control, TPS may be a simple way to find the way to bile duct compared with needle-knife sphincterotomy [111]. A retrospective study in Taiwan [112] showed that TPS had an acceptable success rate (83.0% vs. 74.2%, $p = 0.34$) and a similar PEP rate (16.1% vs. 6.4%, $p = 0.17$) compared with needle-knife therapy. Although there is no evidence that TPS is superior to needle-knife therapy, it is relatively easier for young endoscopists to learn this technique. In a word, it is a promising operative approach.

3.2.5. The Wire-Guide Cannulation (WGC) Technique

The WGC technique is an alternative to the standard contrast agent injection method, which can increase the success rate and reduce the risk of PEP [113–115]. The guidewire

technology uses a soft-tipped guidewire to cannulate the bile duct, which is believed to potentially limit papillary trauma and need for precut sphincterotomies. In addition, this technique avoids the injection of a contrast medium into PD and prevents submucosal injection in the papilla, further reducing the risk of pancreatitis [116,117].

In 2009, a meta-analysis [118] (5 RCTs, 1762 patients) showed that the use of the guide wire-assisted cannulation technique not only increased the primary cannulation rate (OR = 2.05, 95% CI: 1.27–3.31), but also reduced the need for the precut technique (the guide wire-assisted cannulation technique compared with the standard-method: 10.3 vs. 14.7%, respectively). Furthermore, the guide wire to achieve deep biliary cannulation significantly reduced the risk of PEP (RR = 0.23, 95% CI: 0.13–0.41).

In 2013, Tse et al. [119] performed a larger meta-analysis (12 RCTs, 3450 patients) and reached similar conclusions that the guide wire assisted cannulation technique and resulted in a greater primary cannulation rate (RR = 1.07, 95% CI: 1.00–1.15), fewer precut sphincterotomies (RR = 0.75, 95% CI: 0.60–0.95), and a significant reduction in PEP (RR = 0.51, 95% CI: 0.32–0.82).

According to current studies, the use rate of WGC cannulation is increasing when performing ERCP. In addition, the double-guidewire technique (DGT) also seems to be a good cannulation measure [120–122]. It has been postulated that the DGT can increase the success rate of cannulation and reduce the risk of PEP [123,124]. Although the current research results are controversial in some aspects [125,126], in 2020, the ESGE recommended the DGT with prophylactic pancreatic stenting to address difficult biliary cannulation [12].

4. Combined Prevention

Combined prevention has actually been extensively used in high-risk patients. Clinicians generally use rectal NSAIDs and prophylactic pancreatic stenting to prevent PEP in high-risk patients, and the treatment effect is obvious. However, for low-risk patients, prophylactic pancreatic stenting is not an efficient and cost-effective approach. Therefore, we think that PEP-related risk factors should be used to stratify risk among patients better before the procedure, which would help physicians decide on preventative measures, such as drug prophylaxis or PD stenting.

For low-risk patients, clinicians emphasize the use of pharmacological treatment to prevent PEP, which is generally accepted for their obvious advantages such as good efficacy and a cheaper price. Based on the current research, we found that the use of rectal NSAIDs alone cannot completely prevent PEP and the use of other drugs only, such as GTN and somatostatin/ octreotide, also have some limitations. Thus, we suggest the combination of multiple drugs to prevent PEP in low-risk patients.

So far, the combined prevention of multiple drugs has shown effective results in the latest clinical trials, which is a good start. The result confirms further investigations are worthy and needed. In 2014, Sotoudehmanesh et al. [127] performed a randomized, double-blind controlled trial (300 patients) to evaluate the efficacy of the combination of indomethacin and sublingual nitrates compared with indomethacin alone to prevent PEP. The experimental results were pleasantly surprising. Rectal indomethacin plus sublingual nitrate significantly reduced the incidence of PEP compared with indomethacin alone (6.7% vs. 15.3%, RR = 0.39, 95% CI: 0.18–0.86, $p = 0.016$). In addition, adding drugs did not increase drug-related adverse effects. The latest trial [128] (886 patients) obtained similar results that rectal diclofenac plus sublingual nitrate significantly reduced the incidence of PEP compared with diclofenac alone (5.6% vs. 9.5%, RR = 0.59, 95% CI: 0.37–0.95, $p = 0.03$). Although some patients developed hypotension and headache in the combined group, they were significantly relieved after simple treatment. Furthermore, the relative benefit of additional sublingual nitrate had a tendency to decline according to the number of risk factors for PEP. Due to it being simple, inexpensive, and well tolerated, the combination of rectally administered NSAIDs and sublingual nitrate should be an ideal pharmacologic prophylaxis in low-risk patients (moderate quality evidence).

In addition, there are other drug combinations being studied. The study of Katsinelos et al. [129] (540 patients) demonstrated that the preventive effect of rectal diclofenac plus somatostatin was better than that of rectal diclofenac alone (low quality evidence). In the multivariate analysis, pretreatment with diclofenac plus somatostatin significantly reduced the risk of PEP (OR = 0.423, 95% CI: 0.201–0.889, $p = 0.023$). Hajalikhani et al. [130] compared the preventive effects of diclofenac and aggressive hydration by LR ($n = 107$) with diclofenac alone ($n = 112$). Although the results showed that there was no significant difference between them (0.9% vs. 2.7%, $p = 0.622$), the serum levels of pancreatic enzymes in the combination group were significantly lower than those of diclofenac alone group at 2 h, 8 h, and 24 h after ERCP ($p < 0.001$ at all levels). The author believes that this result may be caused by the low overall PEP rate and the small sample size of the trial. A previous randomized, double-blind trial [131] (192 high risk patients) showed that LR plus indomethacin had a lower PEP rate (6% vs. 21%, $p = 0.04$) and a lower readmission rate (2% vs. 13%; $p = 0.03$) compared with normal saline plus placebo. Although these results cannot confirm the superiority of NSAIDs plus LR, they showed that the combination of NSAIDs and aggressive hydration to prevent PEP is feasible. Excitingly, the latest network meta-analysis [132] (24 studies, 11,321 patients) showed that indomethacin plus LR solution, followed by diclofenac plus nitrate and indomethacin plus normal saline, are the most efficacious combinations of pharmacological agents for the prevention of PEP (low quality evidence).

These experimental results undoubtedly bring confidence to the combination of drugs to prevent PEP. However, it is not the case that increasing the type of drug use can greatly improve the preventive effect. For example, a latest meta-analysis of rectal indomethacin plus topical epinephrine to prevent PEP (3 RCTs, 2244 patients) showed that this combination had no more advantage than rectal indomethacin alone (RR = 1.15, 95% CI: 0.62–2.2) [133]. This is an indication that the combination of drugs to prevent PEP is not simply adding drugs to improve the preventive effect. There are many questions to be considered in combined prevention, including which drugs should be combined, whether the dose of combined drug should be changed, whether the adverse drug reactions of the combined drug are obvious, etc. At present, there are few large-scale clinical trials in this area, and we hope that more large-sample studies can be published. Clinically, effective drug combinations use are worthy of promotion in low-risk patients.

For high-risk patients, factors that promote the occurrence of PEP are diverse and complex, combining drugs with mechanical prophylaxis to prevent PEP in high-risk patients is necessary, with PD stenting being the recommended option (Table 4).

At present, the most commonly used mechanical prophylaxis to prevent PEP in high-risk patients is PD stenting, which is recommended in most patients with difficult cannulation, suspected sphincter dysfunction, history of post-ERCP pancreatitis, or in those with other risk factors. Most of the studies of PD stenting to prevent PEP were conducted before the routine use of pharmacological prophylaxis including indomethacin (high quality evidence). In addition to this, an atraumatic and efficient method of cannulation needs to be used in difficult intubation cases, such as the WGC technique, TPS, or needle-knife precut sphincterotomy. Until further evidence are available, it is advisable to combine pharmacological with mechanical prophylaxis in high-risk cases (moderate quality evidence).

Table 4. Summary of benefit of various pharmacological agents and mechanical measures for prevention of PEP.

Shows Consistent Benefit ^a	Possible Benefits/ Unclear ^b	No Benefit ^c
Pharmacological agents		
Rectal NSAIDs	Gabexate mesilate	Corticosteroid
Glyceryl trinitrate	Somatostatin/ Octreotide	Nifedipine
Aggressive hydration with Lactated Ringer's solution	Ulinastatin	Lidocaine

Table 4. Cont.

Shows Consistent Benefit ^a	Possible Benefits/ Unclear ^b	No Benefit ^c
	Allopurinol gabexate mesylate	Heparin
Mechanical measures		
Prophylactic pancreatic stenting The wire-guide cannulation (WGC) technique	Needle-knife precut sphincterotomy Transpancreatic precut sphincterotomy (TPS)	
Combined prevention		
Rectal NSAIDs plus prophylactic pancreatic stenting Rectal NSAIDs plus sublingual nitrates	Rectal NSAIDs plus somatostatin Lactated Ringer's solution plus indomethacin The double-guidewire technique (DGT) with prophylactic pancreatic stenting	Rectal indomethacin plus topical epinephrine

^a Multiple RCTs and/or meta-analyses show a consistent and significant reduction in the incidence or severity of PEP. ^b Some RCTs show a benefit. Insufficient published experience to define a clear role in PEP. ^c Published trials demonstrate no statistical advantage over the placebo, or increased incidence of PEP.

5. Conclusions

With the development and application of ERCP, the burden caused by its complications is undoubtedly the most important contraindication in the implementation of ERCP. With the aim of reducing the incidence of PEP, the development of a combined prevention is necessary and inevitable. The purpose of this review was to describe current research on the prevention of PEP and to value the reasonable combination of multiple drugs and mechanical measures in the prevention of PEP. We expect that future updates and more high-quality studies will identify the optimal combination regimen that reduces the incidence of PEP.

Author Contributions: Y.Z. and Y.F. drafted and edited the manuscript. Y.Z., Y.L., and Y.F. provided critical revisions of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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