Annals of Gastroenterology (2024) **37,** 266-279

Update in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Of all the possible complications associated with endoscopic retrograde cholangiopancreatography (ERCP), acute pancreatitis undoubtedly represents the heaviest burden for patients and healthcare professionals. The overall incidence, ranging from 3.5% to around 10%, and annual estimated costs exceeding $150 million in the USA should signal caution for everyone carrying out ERCP. In-depth knowledge of the risk factors and the pharmacological and endoscopic treatment options is required to avoid this adverse event. In this review, we evaluate the relevant data published in the literature since the appearance of the latest recommendations of the leading gastroenterological societies. Thus, we intend to provide a comprehensive and up-to-date overview of the factors to consider and possible interventions applicable before and after the intervention to prevent the development of post-ERCP pancreatitis.

Keywords Post-endoscopic retrograde cholangiopancreatography pancreatitis, prophylaxis, pancreatic stent, nonsteroidal anti-inflammatory drugs, fluid therapy

Ann Gastroenterol 2024; 37 (3): 266-279

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an indispensable tool in managing pancreatobiliary diseases. It was first introduced in 1968, and since then, its utilization has trended from a diagnostic towards a therapeutic approach. The reason behind this change was the intention to reduce the complication rate related to the procedure. The most common serious adverse event following an ERCP is the development of acute pancreatitis.

According to the European Society of Gastrointestinal Endoscopy (ESGE), post-ERCP pancreatitis (PEP) should be diagnosed based on the onset of new or worsening abdominal pain associated with at least 3 times the upper limit of normal serum amylase or lipase levels, more than 24 h after the procedure, and requiring admission or prolongation of planned admission [1]. Two large-volume meta-analyses provided epidemiologic data about PEP. Based on their results, the incidence of PEP varies between 3.47% (95% confidence interval [CI] 3.19-3.75%) and 9.7% (95%CI 8.6-10.7%). As a percentage of all ERCPs performed, the clinical course of pancreatitis is mild in 1.55-5.7%, moderate in 1.52-2.6%, and severe in 0.4-0.5% of cases. The overall PEP-related mortality lies between 0.1-0.7%, and Andriulli *et al* found it to be 3.08% (95%CI 1.65-4.51%) when measured among severe cases [2,3]. Severity grading in these surveys was based on the international consensus criteria formulated by Cotton *et al*. Two decades later, however, several limitations of these criteria were identified [4-6]. Thus, the revised Atlanta classification, devised originally for acute pancreatitis of every etiology, was proposed by the ESGE in its latest guideline to be used in PEP [7].

This review intends to summarize all updates in the prevention of PEP, following a brief overview of its pathophysiology. Papers about the issue published between 1 September 2019 and 21 October 2022 were systematically collected from 3 databases (MEDLINE, Embase, Cochrane Central) and analyzed. The search was actualized in October 2023 and incorporated the new American Association for Gastrointestinal Endoscopy (ASGE) guideline, published online in December 2022.

The main principle to follow in preventing PEP is to avoid any unnecessary ERCP. Therefore, all endoscopists performing ERCP must have complete knowledge of the indications. When the indication is appropriate, other preprocedural

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Conflict of Interest: None

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Received 27 August 2023; accepted 6 December 2023; published online 14 March 2024

DOI: https://doi.org/10.20524/aog.2024.0870

circumstances that can contribute to the development of PEP must be accounted for. Even the most carefully carried out ERCP, in the setting of expert centers, can cause pancreatitis. For this reason, several procedure- and patient-related risk factors have been associated with inflammation of the pancreas following ERCP. The ESGE distinguishes definite and likely risk factors in its current guideline [1] (Table 1). According to this recommendation, patients with at least 1 definite or 2 likely risk factors should be considered high-risk for PEP.

Pathophysiology

Fig. 1 illustrates the processes leading to the inflammation of the pancreas following ERCP. As can be seen, the recommendations of prophylaxis concentrate on managing microcirculatory insufficiency, inhibiting inflammatory pathways related to arachidonic acid metabolism, and securing the integrity of the pancreatic juice outflow tract. However, edema of the pancreatic orifice and proteolytic enzyme activation play an equally important role in the pathophysiological mechanism.

Edema is caused by injury related to accidental or intentional manipulation of the pancreatic orifice during ERCP. It obstructs the pancreatic outflow tract, leading to intraductal pressure elevation and damage to acinar cells. It is well known that more cannulation attempts are associated with a higher incidence of PEP [8]. The next step in the pathophysiological process is the development of circulatory deterioration in the pancreatic microvasculature, which leads to the lowering of intracellular pH and contributes to inflammation severity [9-11]. The acidification activates proteolytic enzymes, which are responsible for pancreatic tissue damage. Finally, intrapancreatic and later extrapancreatic inflammation play a fundamental role in the development of PEP via several pathways. From the perspective of prophylaxis, the hydrolysis of phospholipase A2 and subsequent arachidonic acid metabolism are relevant. Both lead to the progression of acute pancreatitis via the production of pro-inflammatory eicosanoids [12-14].

Only some of the preventive strategies depicted in Fig. 1 have stood the test of time to get incorporated into the current ESGE guideline [1]. Fig. 2 presents the decision-making flowchart proposed by the ESGE.

New strategies of prophylaxis since the updated ESGE guideline

Decompression of pancreatic duct

Epinephrine

Several methods of decreasing intrapancreatic pressure have been studied in recent years. One was the mitigation of edema of the papilla of Vater to restore pancreatic juice outflow. It was proposed that spraying epinephrine on the papilla may reduce tissue swelling. The ESGE 2020 guideline does not recommend its use in light of the controversial results of randomized controlled trials (RCTs) dealing with the subject. Two recent placebo-controlled RCTs investigated the efficacy of the use of epinephrine spray, combined with rectal administration of a non-steroidal anti-inflammatory drug (NSAID), in average- and high-risk patients [15] or unselected patients [16]. The PEP incidence in a multicenter RCT (548 patients) was 3.6% (n=10/275) in the epinephrine groups vs. 5.12% (n=14/273) in the placebo group, P=0.41. A single-center RCT, enrolling 882 patients with naive papilla, resulted in a PEP incidence of 6.4% (n=28/437) and 7.9% (n=35/445) (P=0.401) for the epinephrine and placebo groups, respectively. A meta-analysis enrolled 3 RCTs with 2244 patients and found no beneficial effect from using epinephrine: risk ratio (RR) 1.15, 95%CI 0.62-2.2.

Table 1 Risk factors for post-ERCP pancreatitis according to the ESGE 2019 guideline [2]

Patient-related risk factors	Procedure-related risk factors
Definitive risk factors with OR (95%CI)	
Previous PEP: 3.23 (2.48-4.22) – 8.7 (3.22-23.857)	Difficult cannulation: 1.76 (1.13-2.74) – 14.9 (10.5-21.26)
Suspected sphincter of Oddi dysfunction: 2.04 (1.73-2.33) – 4.37 (3.75-5.09)	Pancreatic guidewire passages >1: 2.1 (1.23-3.51) – 2.77 (1.79-4.3)
Previous pancreatitis: 2.00 (1.72-2.33) – 2.90 (1.87-4.48)	Pancreatic injection: 1.58 (1.21- 2.08) – 2.72 (1.43-5.17)
Female sex: 1.40 (1.24-1.58) – 2.23 (1.75-2.84)	
Likely risk factors with OR (95%CI)	
Nondilated extrahepatic duct: 3.8 (1.88-7.63)	Biliary balloon sphincter dilation: 4.51 (1.51-13.46)
Younger age: 1.59 (1.06-2.39) – 2.87 (1.23-6.69)	Failure to clear bile duct stones: 3.35 (1.33-9.1)
Normal serum bilirubin: 1.89 (1.22-2.93)	Precut sphincterotomy: 2.11 (1.72-2.59) – 3.1 (2.06-4.76)
Absence of chronic pancreatitis: 1.87 (1.00-3.48)	Pancreatic sphincterotomy: 1.23 – 3.07 (1.64-5.75)
End-stage renal disease: 1.7 (1.4-2.1)	Intraductal ultrasound: 2.41 (1.33-4.39)

ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; PEP, post-ERCP pancreatitis; OR, odds ratio; CI, confidence interval

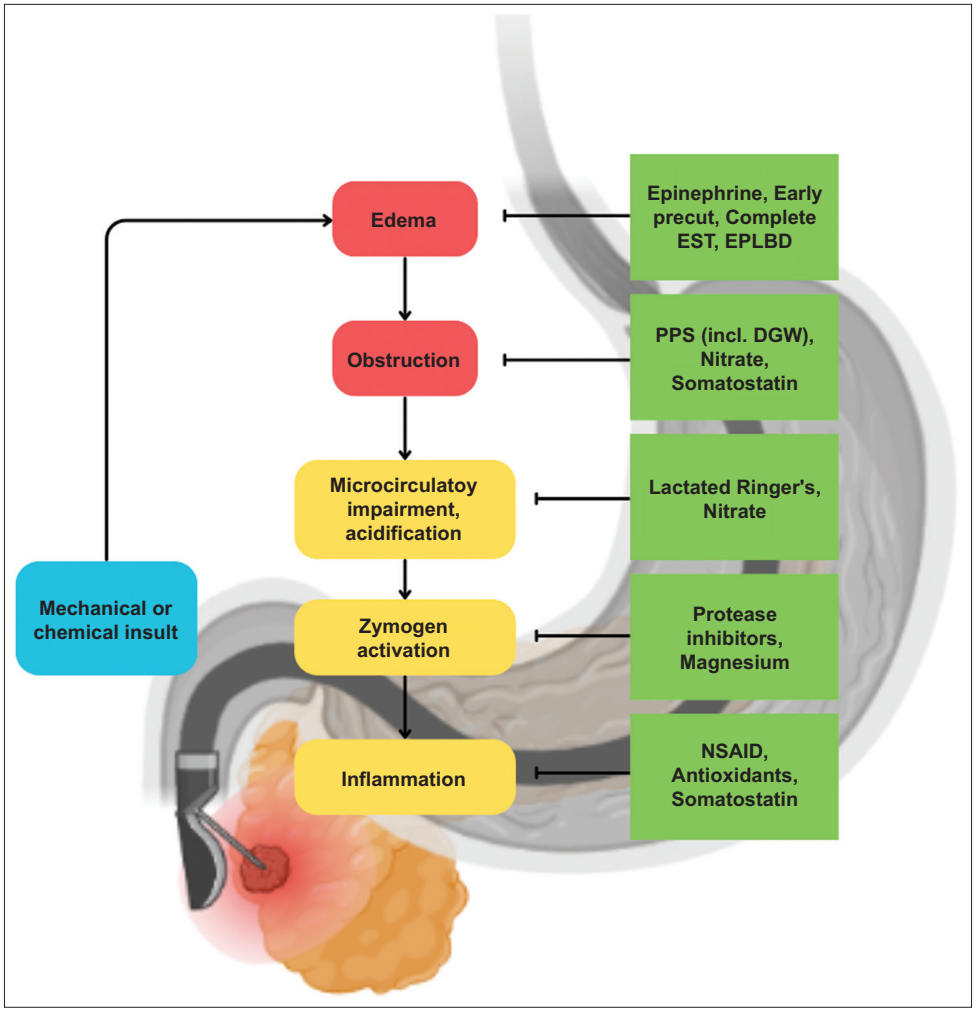

Figure 1 Major pathophysiologic pathways contributing to the development of PEP and possible interventions [41]
PPS, prophylactic pancreatic stent; EST, endoscopic sphincterotomy; EPLBD, endoscopic papillary large balloon dilation; DGW, double-guidewire technique; NSAID, nonsteroidal anti-inflammatory drug

All in all, the use of epinephrine has gained little support in recent years. There has also been an ongoing multicenter, patient-blinded, superiority RCT in Japan investigating the impact of ice water irrigation on the papilla (EUTOPIA trial) for PEP reduction, which is a study worth keeping an eye on [17].

Primary needle-knife precut

Precut or needle-knife sphincterotomy is usually considered a salvage strategy after failed cannulation and is supposed to elevate the risk of PEP. It is not clear, however, whether this supposed increased risk of pancreatitis is due only to the edema caused by the previously failed cannulation attempts or to the needle knife precut. A recent double-blinded, single-center RCT including 303 patients compared the PEP rate after very early precut (defined as after 2 failed cannulation attempts) and primary (i.e., with no previous cannulation attempts) needle knife sphincterotomy. All procedures were performed by 1 expert endoscopist. Primary precut resulted in significantly fewer PEP cases (0.67% vs. 5.2%; P=0.04) and shorter bile duct cannulation time (7.2±1.7 vs. 13.8±2.2 min; P=0.001). However, there was no difference in bleeding or perforation rates [18]. A systematic review and meta-analysis evaluated the results of primary needle knife fistulotomy (NKF) vs. standard biliary cannulation performed by expert endoscopists (582 patients, 3 RCTs, 1 single-arm prospective study). The pooled PEP rate across all 4 studies was 1.5% and, based on the 3 RCTs, NKF was associated with a lower risk of PEP, though not significantly so (odds ratio [OR] 0.22, 95%CI 0.04-1.04), with a moderate level of evidence due to possible selection and performance bias. Pooled complication rates (PEP, perforation, bleeding) were also not different, even when excluding PEP. These results suggest that the PEP rate following primary NKF performed by an expert endoscopist may be lower than after wire-guided cannulation [19]. The results of the 2 studies suggest that primary precut and NKF are associated with a low risk of PEP in expert hands.

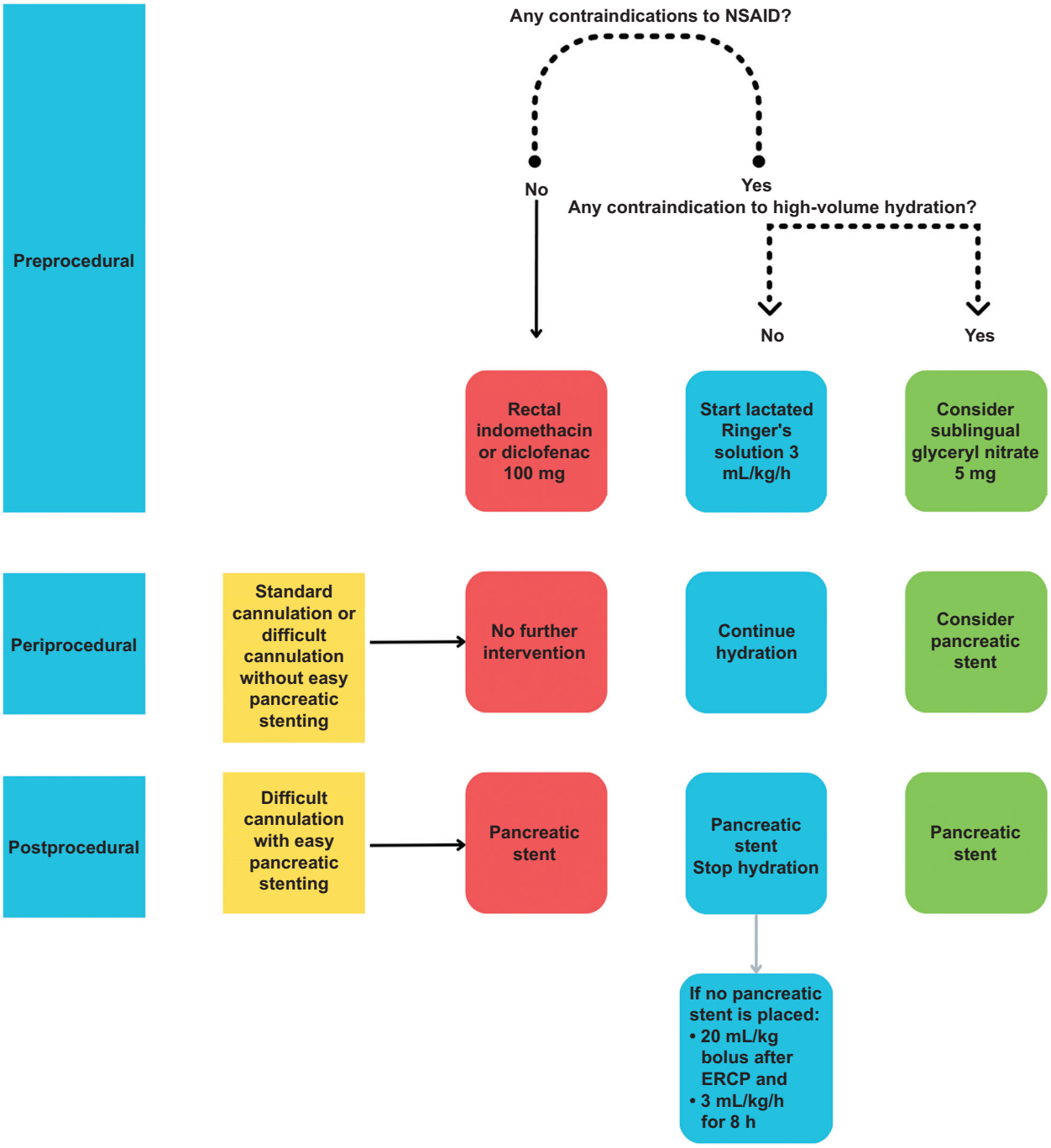

Figure 2 Current strategies used in the prevention of *post-endoscopic retrograde cholangiopancreatography pancreatitis* [2]
NSAID, nonsteroidal anti-inflammatory drug

Sphincterotomy

Another recently published multicenter, non-inferiority RCT (370 patients included, 185 vs. 185 in each group) compared the PEP incidence in unselected patients who needed biliary stenting, with or without endoscopic sphincterotomy [EST]. PEP occurred in 20.6% (n=36/185) in the non-EST group and 3.9% (n=7/185) in the EST group, P<0.001 [20].

It is important to note that this should not lead to re-evaluating the ESGE recommendations, which advise against routine sphincterotomy before placing a biliary plastic stent or uncovered/partially covered metal stents to treat biliary obstruction [21]. This study showed that the PEP risk may be lower with a previous EST, but the guideline also alluded to this. The recommendation against EST was made to prevent bleeding due to unnecessary EST, but the risk of PEP was not shown to be elevated with prior EST.

PPS placement

Another option for pancreatic decompression is the placement of prophylactic pancreatic stents (PPS) [1]. A recent RCT compared the efficacy of PPS placement to rectal diclofenac and the combination of the 2 in average- and high-risk patients [22]. The study was conducted in an equivalent setting, and the PEP rates of the groups were statistically not different. PEP incidences were 2% (n=2/101) vs. 0.9% (n=1/106) vs. 2% (n=2/102) for PPS, NSAID and combination groups, respectively. A network meta-analysis (NMA) by a Hungarian research group (enrolling 21 RCTs with 5535 patients) collated PPS with NSAIDs directly in average- and high-risk patients. Their results showed that PPS placement significantly reduced the risk of severe and moderate PEP in both groups (average-risk: RR 0.07, 95%CI 0.002-0.58, high-risk: RR 0.20, 95%CI 0.051-0.56), whereas NSAIDs showed a trend towards reducing risk, but without statistical significance [23].

A recent multicenter RCT (142 patients) from France added new evidence to the topic of difficult cannulation and the use of PPS. The double-guidewire technique (DGT) had previously been considered to increase the risk of PEP [24]. Laqiuére *et al* evaluated the efficacy and safety of early DGT (n=68) (after 1 guidewire insertion in the pancreatic duct [PD]) compared to PPS deployment applying repeated single guide-wire cannulation attempts (n=74) within 10 min [25]. They found that early DGT was associated not just with higher successful biliary cannulation rates but also with lower PEP incidence (1% vs. 5%). Overall, based on the available evidence, the use of PPS is beneficial in high-risk patients, even compared to NSAIDs as a monotherapy.

Biliary stent placement

Let us continue with the relation between biliary stenting and PEP. Two recent meta-analyses investigated the use of plastic stents or self-expandable metal stents (SEMS) in regard to the risk of PEP. Yang *et al* compared covered self-expandable metal stents (CSEMS) with multiple plastic stents for managing benign biliary strictures, evaluating 6 RCTs with 444 patients overall. The meta-analysis showed that the use of CSEMS was associated with a significantly higher PEP rate (OR 3.34, 95%CI 1.44-7.77), with no difference in stricture resolution rate or pooled complication rate (PEP, abdominal pain, infection, stent occlusion, cholecystitis, and migration). Nevertheless, the number of ERCPs needed for therapy was less with CSEMS, and costs were lower [26].

A multicentric Chinese study investigated PEP incidence retrospectively in 602 patients who received CSEMS for any indication and performed several subgroup analyses according to the baseline and procedural characteristics. The overall risk of PEP was 9.3%, but in cases without PD dilation, the risk of PEP increased to 14.6%, and without prophylaxis, it could rise as high as 18.6% [27]. These results suggest that PEP might appear more often with CSEMS placement than multiple plastic stents, and the risk might be higher in cases with normal PD diameter.

Glyceryl nitrate

A recent RCT (526 patients) compared the combination of glyceryl nitrate with NSAID to PPS placement and placebo in patients with difficult cannulation. The incidence of PEP was 5.1% vs. 12.1% vs. 19.3%, respectively (F=6.445, P=0.011), demonstrating that the combination therapy led to a significantly lower PEP incidence [28]. However, this study suffered from serious flaws that strongly limit its significance. First, allocating patients with difficult cannulation into the placebo arm could be considered unethical according to current standards. Second, there is no data about the ease of PD stent placement in those who were randomized for it, suggesting that it was also mandatory in patients who had no previous cannulation of the duct. This again contradicts international recommendations and raises ethical questions. Furthermore, combining nitroglycerine with an NSAID makes it impossible to measure its effectiveness. Finally, the study exclusively enrolled female patients with difficult cannulation and choledocholithiasis.

An RCT enrolling 585 individuals compared the PEP rate after administration of a combination of naproxen and sublingual isosorbide dinitrate with individual prophylaxis [29]. PEP rates were 14.8% with naproxen, 12.8% with nitrate, and 13.4% with the combination of the two (P=0.845).

The methodological and ethical issues in the study by Wang *et al* and the administration of naproxen instead of diclofenac or indomethacin by Mansour-Ghanaei *et al* make it difficult to relate these results to those cited in the ESGE guideline. All in all, data from recently published RCTs and meta-analyses (Table 2) suggest that glyceryl trinitrate could play a more central role in patient management, but the results are conflicting.

Volume and expertise

Lastly, some recent research has been published about the correlation between ERCP expertise and volume and ERCP outcomes. A Spanish single-center study examined ERCP success and adverse event rates in 3 periods defined by the number of endoscopists included, which was 5 in the first (P1), 4 in the second (P2), and 3 in the third period (P3) (2561 ERCPs, P1: 727, P2: 972, P3: 862). They found that the number of successful ERCPs was significantly greater (81% vs. 91% vs. 87% in P1, 2, 3; P<0.0001) and the frequency of PEP lower (8.5%, 7.3%, 5%; P<0.01) when endoscopists performed a higher annual volume of ERCP [30]. A systematic review and meta-analysis (31 studies) revealed similar results, showing higher procedure success rates among high-volume (HV) endoscopists (OR 1.81, 95%CI 1.59-2.06) and in HV centers (OR 1.77, 95%CI 1.22-2.57), compared to low-volume (LV) endoscopists and centers. Overall adverse events were also more common in LV groups (OR 0.71, 95%CI 0.61-0.82 for endoscopists; OR 0.70, 95%CI 0.51-0.97 for centers). Among individual complications, the bleeding rate was significantly lower in the HV group, whereas the PEP rate was not (OR 0.76, 95%CI 0.53-1.09 for endoscopists; OR 0.84, 95%CI 0.63-1.12

Table 2 Summary of results of network meta-analyses about combination therapies

First author, year of publication [ref.]	Number of studies and patients	Risk group	Analyzed interventions (NSAID: indomethacin or diclofenac)	Results	Comment
			Prophylactic pancreatic stent		
Njei, 2020 [72]	29 RCTs, n=862	Only high-risk	PPS, LR, LR + NSAID, NSAID alone compared with placebo	PPS decreased PEP most effectively compared to placebo on direct comparison. It had the highest SUCRA probability (0.81, 95%CI 0.83 to 0.80]) of being ranked the best prophylactic treatment. On NMA, it was the second-best therapy following the combination of LR and NSAID (B – 1.25, 95%CI –1.81 to –0.69 vs. B – 1.58, 95%CI –3.0 to –0.17)	Every comparison was vs. placebo except for 1 study. Differences may exist in trial design, patient population, intervention (i.e., timing of rectal NSAID administration or operator variability in pancreatic duct stent placement), and outcome assessment, which may limit true comparability between the included studies
Radadiya, 2022 [74]	38 RCTs, n=8980	Average- and high-risk	10 strategies: NSAID + AH, NSAID + nitrate, NSAID alone, PPS, AH, nitrate alone	In high-risk patients, PPS remained the best option (OR 0.25, CrI 0.12-0.42)	Risk of publication bias for PPS (Eggers regression test, $P<0.01$). The limited number of studies evaluating combinations of rectal NSAIDs with AH or sublingual nitrate and reporting positive outcomes may have overestimated efficacy. Limited number of studies for rectal NSAIDs and AH compared with studies of PPS in high-risk patients
Akshintala, 2021 [70]	55 RCTs n=17062	Average- and high-risk	NSAIDs, fluids, PPS, and their combinations	The pairwise comparison proved that the use of PPS of 5-7-Fr reduced PEP rate significantly more than rectal indomethacin alone (OR 0.59, 95%CI 0.41-0.84); moderate confidence)	7 of the 55 RCTs had less than 100 patients. Sensitivity analysis, including only the interventions that had at least 350 patients, had similar results
			Sublingual nitrate + NSAID		
Radadiya, 2022 [74]	38 RCTs, n=8980	Average- and high-risk	NSAID + AH, NSAID + nitrate, NSAID alone, PPS, AH, nitrate alone	Nitrate monotherapy decreased PEP rate by 58% (OR 0.42, 95%CI 0.23-0.75) compared to placebo, a more significant effect than NSAIDs (OR 0.48, 95%CI 0.31-0.74). Lower PEP rates with NSAID + nitrate vs. placebo (OR: 0.51, 95%CI 0.33-0.78, P<0.01)	See above
Du, 2022 [71]	32 RCTs, n=15019	Average- and high-risk	9 strategies with NSAIDs (placebo, alone, nitrate, LR, AH, somatostatin, epinephrine, melatonin)	NSAIDs + sublingual nitrates lowered PEP rate vs. placebo (OR 0.22, 95%CI 0.11-0.39). Only NSAIDs + sublingual nitrates (OR 0.50, 95%CI 0.27-0.89) had a significantly lower PEP rate than NSAIDs alone, with no statistically significant differences observed for the other combinations	

(Contd...)

Table 2 *(Continued)*

First author, year of publication [ref.]	Number of studies and patients	Risk group	Analyzed interventions (NSAID: indomethacin or diclofenac)	Results	Comment
			Sublingual nitrate + NSAID		
Oh, 2021 [73]	24 RCTSs, n=11321	Average- and high-risk	NSAID alone, NSAID + fluid, double dose NSAID, nitrate, somatostatin, epinephrine	Nitrate: mean effect on PEP reduction of -1.94 (95%CI -3.07, -0.81) for combination with diclofenac and -1.53 (95%CI -2.66 to -0.41) with indomethacin	Because predictive intervals crossed the line of no effect, the significance of the results is questionable. The quality of evidence for each outcome was low or moderate
			NSAID + infusion therapy		
Radadiya, 2022 [74]	38 RCTs, n=8980	Average- and high-risk	NSAID + AH, NSAID + nitrate, NSAID alone, PPS, AH, nitrate alone	AH + indomethacin was the best PEP prevention strategy. On direct comparison with placebo, periprocedural AH achieved a 63% reduction in PEP incidence compared with controls (OR 0.37, 95%CI 0.26-0.54). NSAID + AH 84% (OR 0.16, 95%CI (0.03-0.73); $P<0.01$). On NMA, AH + indomethacin remained consistently better than other interventions, except for AH with rectal diclofenac and sublingual glyceryl nitrate with rectal diclofenac or indomethacin	See above
Akshintala, 2021 [70]	55 RCTs n=17062	Average- and high-risk	NSAIDs, fluids, PPS, and their combinations	AH + rectal diclofenac was more efficacious than rectal indomethacin alone (OR 0.49, 95%CI 0.26-0.94) but was not better when compared to diclofenac alone (OR 0.83, 95%CI 0.50-1.36)	See above
Du, 2022 [71]	32 RCTs, n=15019	Average- and high-risk	9 strategies with NSAIDs (placebo, alone, nitrate, LR, AH, somatostatin, epinephrine, melatonin)	Compared to placebo, NSAIDs + aggressive hydration (OR 0.32, 95%CI 0.12-0.71) and NSAIDs + standard hydration (OR 0.34, 95%CI 0.08-1.3) significantly reduced PEP risk. AH did not provide beneficial results to NSAID therapy alone (OR 0.72, CrI 0.28-1.6)	
Oh, 2021 [73]	24 RCTs, n=11321	Average- and high-risk	NSAID alone, NSAID + i.v. fluid, double dose NSAID, nitrate, somatostatin, epinephrine	Compared to placebo, the mean effect on PEP reduction of LR + indomethacin was the largest (-2.33, 95%CI -4.13 to -0.54)	See above
Márta, 2021 [41]	24 RCTs, n=7559	Average- and high-risk	LR, NS -and indomethacin	LR + indomethacin and NS + indomethacin significantly reduced PEP frequency compared to other therapies, with RR >1 and CrI >1 in every comparison. Analysis of fluid volume demonstrated that AH with NSAID was associated with a lower frequency of PEP compared to other treatments	Comparability tests between direct, indirect, and estimated comparisons showed significant differences, meaning that future RCTs can easily change the significance of the results

OR, odds ratio; CI, 95% confidence interval; CrI, 95% credibility interval; RCT, randomized controlled trial; NSAID, nonsteroidal anti-inflammatory drug; AH, aggressive hydration; PPS, prophylactic pancreatic stent; NMA, network meta-analysis; LR, lactated Ringer's solution; NS, normal saline

for centers). The cutoff value to define LV endoscopists or centers varied widely among the included studies, but a sensitivity analysis using 200 procedures as a threshold resulted in similar outcomes [31]. Interestingly, these findings were not confirmed in a pediatric population. A retrospective analysis of prospectively collected multicenter data from 1124 ERCPs showed that the involvement of trainees did not worsen technical success or adverse event rates [32]. These results may have been influenced by possible selection bias because trainees were less often involved in procedures with native papilla. In summary, recent evidence suggests that having ERCP performed by high-volume endoscopists and not just by centers (as stated in the ESGE 2020 guideline) may improve successful cannulation and adverse event rates, including PEP, in an adult population.

Maki *et al* looked for ERCP outcomes among trainees (<2 years of experience) using either angled-tip guidewires (AGW) or straight-tip guidewires (SGW) in a single-center RCT. Their results showed that the selective biliary cannulation rate over 14 min was significantly higher with an AGW than with an SGW (57.8%, n=26/45 vs. 34.3%, n=12/35, P=0.04). At the same time, complications (including PEP) did not differ between the groups [33].

Treating microcirculatory disturbances of the pancreas

At the beginning of the last decade, the need for novel preventive PEP strategies became apparent, as the use of rectal NSAIDs and PPSs could not be implemented for a large group of patients. Aggressive periprocedural hydration (AH) with lactated Ringer's (LR) solution emerged to overcome this issue, as first reported by Buxbaum *et al* [34]. According to the European guideline, its use is now recommended in cases where NSAIDs are contraindicated [1]. The new ASGE guideline suggests aggressive periprocedural and postprocedural intravenous hydration for all patients undergoing ERCP [35], while a recent RCT verified its non-inferiority to NSAIDs when comparing both treatment options individually [36]. Nevertheless, recent studies have questioned the role of AH in the management of PEP.

Aggressive vs. normal volume hydration

A single-center, open-label RCT evaluated PEP reduction in 171 individuals, comparing the combination of diclofenac plus AH with AH and NSAID monotherapy. The incidence of PEP was 10.5% (n=6/57) vs. 14% (n=8/57) vs. 15.8% (n=9/57) for the 3 groups, respectively (P=0.70) [37]. The long-awaited FLUYT trial compared NSAIDs (diclofenac or indomethacin) in combination with AH or with normal hydration in average- and high-risk patients [38]. The PEP rate was 8% (n=30/388) for the AH group, and 9% (39/425) for the control group (P=0.53), and the study showed that adding AH to a routine rectal NSAID did not reduce PEP incidence compared to NSAIDs with restricted fluid therapy. In another double-blind RCT, with the same study design, the incidence of PEP was 3.6% in the AH group and 13.9% in the control group (P=0.021) [39]. On the other hand, the results of Sperna *et al* are more generalizable, given their multicenter design, large sample size, and the application of international standards in treatment designs.

Meta-analyses investigating fluid therapy drew favorable conclusions regarding AH. Radadiya *et al* (9 RCTs, n=2094) also compared AH with standard hydration, but their results instead suggest that AH is associated with a lower incidence of PEP compared to standard hydration (5.1%, n=108/969 vs. 11.1%, n=57/1125) and reduces the risk of PEP significantly (OR 0.44, 95%CI 0.28-0.69). They found no difference in the risk of fluid overload (OR 1.29, 95%CI 0.16-10.69) [40]. However, only 3 (1 unpublished) of the 7 included studies reporting on adverse events provided useable information for the meta-analysis, as the other 4 included too many zero events in both arms. Another NMA demonstrated significantly lower PEP frequency with the combination of AH and indomethacin than normal volume hydration plus indomethacin (RR 18, 95% credibility interval 1.3-6.4e+02) [41]. However, the authors themselves acknowledged severe limitations of their results because the comparability tests between direct, indirect, and estimated comparisons showed significant differences, thus indicating that a future RCT might lead to different results than those estimated by the network.

Fluid type

Regarding the fluid type, administration of LR is recommended for its favorable effect on preventing acidosis, thus alleviating pancreatic enzyme activation. This was put in question by a recent RCT performed on high-risk patients who received fluid therapy according to the ESGE guideline. The PEP rate was 4% (n=3/72) in the LR group vs. 11% (n=7/64) in the normal saline (NS) group (P=0.131). The non-significant difference means that Patel *et al* failed to show the dominant role of LR in fluid therapy, though the study did not reach the estimated sample size, creating a need for further studies [42]. The role of LR also became questionable following the FLUYT trial, but while the latter compared AH with LR to maintenance NS, Patel *et al* compared AH with LR to AH with NS.

Attenuation of proteolytic enzyme activation

Protease inhibitors

Several drugs have been associated with an inhibition effect on the pancreatic enzyme cascade. Protease inhibitors have been considered potential candidates, as they could theoretically prevent PEP by inhibiting the cleavage of trypsinogen to trypsin in pancreatic acinar cells, thus preventing the activation of various injurious pancreatic digestive enzymes. Nafamostat mesylate (NM) has shown promising results in reducing PEP, but not in high-risk patients [43-46]. Thus, protease inhibitors failed to show any potential advantage over conventional drugs,

and because of their high prices, ESGE does not recommend their use.

A recent multicenter RCT from Japan (441 patients) showed a PEP rate of 9% (n=25/292) with NM vs. 10% (n=15/149) in the control group, P=0.60. The frequency of PEP with pre-ERCP NM administration was 12% (n=17/144) vs. 5% (n=8/148) for NM applied post-ERCP (P=0.06). Once again, NM failed to show lower PEP rates in high-risk patients (P=1.00) [47]. A meta-analysis of 13 RCTs enrolling 3718 participants concluded that gabexate mesylate was associated with a significantly lower PEP incidence compared to placebo (RR 0.66, 95%CI 0.49-0.89) [48]. These latest results of another RCT and a meta-analysis investigating the role of protease inhibitors are controversial; thus, the topic is still open for further research.

Magnesium

Magnesium has been associated with the potential to antagonize pathologic calcium signaling in acute pancreatitis, which would otherwise lead to premature activation of elastase and trypsin in pancreatic acini [12]. In addition, magnesium may be able to relax the sphincter of Oddi and promote intestinal motility, thus accelerating the intestinal transit of pancreatic enzymes [49,50]. A recently published RCT addressed the potential therapeutic effect of magnesium by comparing it with placebo in patients undergoing ERCP with AH and rectal NSAID administration. The overall PEP rate was 8.9% (n=12/135) for magnesium vs. 12.6% (n=17/135) for the placebo group (P=0.33), but in high-risk patients, it was 11% (n=8/74) vs. 27% (n=16/60), respectively (P=0.017) [51]. This result suggests that magnesium may be beneficial for high-risk patients.

Treating local pancreatic inflammation

Murray and his colleagues provided the first evidence of successful PEP prevention by conducting an RCT in which rectal diclofenac was administered directly after ERCP [52]. The utilization of NSAIDs as a prophylactic agent against PEP has become a boiling issue since Elmunzer *et al* published their results [53], which have been verified by other high-quality clinical trials and meta-analyses [8,54-57]. There had been some controversy as to whether rectal NSAIDs should be suggested only for high-risk [56], or also for low-risk patients [57], but now their application has become widely accepted for all patients and has even been incorporated into all official guidelines [1,35].

Dosage

This did not mean an end to investigations with NSAIDs, as some still unanswered questions have been explored, e.g., the ongoing debate about dosage options. The current standard is 100 mg for both indomethacin and diclofenac. Fogel and colleagues randomly allocated patients to receive the standard dose or 200 mg of indomethacin. PEP occurred in 5% (n=28/515) vs. 5% (28/522) of patients, respectively (P=1.0) [58]. Katoh *et al* demonstrated that low-dose diclofenac (50 mg) turned out to be not superior to placebo in PEP reduction (5.4%, n=8/147 vs. 3.3%, n=5/150, P=0.286) or mitigation of severity (9.3%, n=8/86 vs. 4.7%, n=4/85, P=0.37) [59].

Timing

The issue of the timing of drug administration was addressed by a secondary analysis of the previously mentioned FLUYT trial, but only with data from the patients who received NSAIDs alone (409 patients). PEP occurred in 7.5% (n=26/346) of patients receiving NSAIDs before ERCP and in 17.5% (n=11/63) of the post-ERCP group (P=0.02) [60]. This was also verified by 2 meta-analyses [61,62]. Compared to placebo, Yang *et al* (23 RCTs, 9382 patients) found pre-ERCP diclofenac (OR 0.25, 95%CI 0.14-0.46) and pre-ERCP indomethacin (OR 0.44, 95%CI 0.32-0.62) performed the best. Liu *et al* compared NSAIDs to placebo only and their results are consistent with those of Yang *et al*, with the PEP risk being significantly lower for pre-ERCP NSAIDs (RR 0.49, 95%CI 0.39-0.62). Nevertheless, some severe limitations of the study narrow its clinical implications.

Combination therapies with NSAIDs

A recent RCT (120 patients) compared the combination of normal saline infusion (after ERCP, at a rate of 10 mL/kg/h for 2 h) with rectal indomethacin to indomethacin alone. The PEP rate was significantly higher in the indomethacin group than in the combination group (8.3%, n=5/60 vs. 0%, n=0/60, P=0.022) [63].

In summary, no evidence has challenged the role of NSAIDs and their timing of administration or dosage. As mentioned before, according to direct and indirect comparisons in meta-analyses, NSAID-based combination therapy, preferably with AH, maybe the most effective prevention strategy.

NSAIDs in selected patients

A retrospective case-control study (n=2000) measured PEP incidence in patients with known or suspected primary sclerosing cholangitis after diclofenac administration (n=1000) compared to placebo (n=1000). The PEP rate was 4.9% vs. 6.2%, respectively (P=0.241) [64]. ERCP of patients in the diclofenac group was judged to be more difficult, probably because the patients had more advanced stages of the disease. Based on the results of this study and of a previous one from their institute, the authors concluded that in low PEP risk units, administration of diclofenac may no longer be necessary. They did not limit this conclusion only to patients with primary sclerosing cholangitis. Troendle *et al* evaluated the PEP rate in a small pediatric population (n=58), comparing intravenous ibuprofen (n=29) to placebo (n=29), and no significant

difference [65] was found between them. However, the study's low sample size limits generalizability.

Somatostatin analogs

Octreotide has also been the subject of recent studies. In a recent RCT (376 patients) by Norouzi *et al*, the efficacy of its combination with an NSAID (indomethacin) was compared with individual NSAID prophylaxis. It did not show any additive effect as regards PEP reduction, as there was no significant difference between the treatment groups [66]. On the other hand, Zhou *et al* (RCT, 124 patients) found a significantly lower PEP rate with the use of octreotide combined with intramuscularly delivered diclofenac compared to the administration of diclofenac alone 5% (n=3/62) vs. 16% (n=10/62) [67]. The larger sample size may endow the findings of Norouzi *et al* with more significance, but the controversial results require more standardized prospective trials in the future.

Antioxidants

An Iranian RCT (280 patients completed the study) investigated the effect of adding melatonin to indomethacin on PEP development. The frequency of PEP in those who received melatonin was 9.3% (n=13/140) vs. 15.6% (n=19/140), respectively (P=0.034) [68]. The results mean that the antioxidant effect of melatonin may be beneficial in preventing PEP. Still, the emphasis of the interpretation should be on the possible additive effect of melatonin on rectal NSAIDs.

Calcineurin inhibitors

Calcineurin inhibitors can inhibit the production of inflammatory end-products of zymogen activation. Tacrolimus was studied in a small pilot prospective trial (n=99), where it decreased the rate of PEP from 15.7% to 8.3% compared to placebo, though the change was not significant (P=0.24) [69].

Meta-analyses investigating combination therapies

Six network meta-analyses were identified that compared the efficacy of single and combination therapies on PEP reduction, and they highlighted 3 therapeutic modalities: PPS, a combination of sublingual nitrate plus NSAIDs, and a combination of fluid therapy with NSAIDs [41,70-74]. Table 2 gives a brief overview of their most relevant findings. Their results are also incorporated into our conclusions.

Concluding remarks

Prevention of acute pancreatitis is still one of the most challenging tasks for physicians who are caring for patients undergoing ERCP. Fig. 3 represents the most relevant aspects of the individual PEP prophylaxis used in everyday practice.

PPS placement is a cornerstone of PEP prophylaxis in high-risk patients and recent studies strengthened this. However, we are waiting for the results of Elmunzer *et al*, who are about to assess the non-inferiority of rectal indomethacin alone to its combination with PPS in high-risk individuals. There is also an ongoing RCT from Hong Kong comparing rectal NSAID to PPS (NCT03713879).

The amount of intravenous fluid therapy was investigated by large, multicenter RCTs, which advocated against the use of AH. These results were further supported by the multicenter, international, open-label WATERFALL trial, which had to be stopped after the first interim analysis because the incidence of fluid overload was unacceptably high in patients receiving AH [75]. It did not focus explicitly on PEP but on all acute pancreatitis cases; nevertheless, its results could be extrapolated to PEP because the fluid regimen in the AH group was the same as in the ESGE 2020 guideline. On the other hand, 1 smaller RCT and 2 meta-analyses (1 NMA) found AH to be beneficial in PEP reduction, with no significant increase in risk of complications. Notably, the new ASGE guideline suggests AH for all patients, given the balance of benefits vs. harm [35]. Regardless of the controversy, we suggest not using AH in patients receiving rectal NSAIDs, given the risk of fluid overload, as there is no clear evidence supporting its benefit in PEP prevention, and most of the meta-analyses arguing for AH faced some severe limitations.

NSAIDs as a fundamental part of the prophylaxis was fortified by recent studies. A current issue with the drugs came under the spotlight, however, which expounded the costs. The price of NSAIDs has risen in the USA in the past years, a trend that could cause concern if it spreads widely [76]. This cost trend has not yet become a significant issue in other parts of the world. Hopefully, it will stay that way because the beneficial effects of NSAIDs are clearly established, and the price of a prolonged hospital stay exceeds by far the price of rectal NSAIDs. This was proven by a cost-effectiveness analysis showing that rectal indomethacin was the most cost-effective strategy in average-risk (vs. LR, nitrate, and no treatment) and high-risk patients (vs. LR, nitrate, PPS, and no treatment) [77].

In conclusion, fluid therapy, NSAIDs, and PPS placement have remained the backbone of PEP prevention. However, the combination of fluid therapy and rectal NSAIDs seems to be more effective than single therapy, and evidence suggests that a standard dose of infusion will be sufficient. In addition, the use of PPS might not be restricted just to high-risk patients (Fig. 3). In addition, the use of advanced cannulation techniques, such as DGT or early/primary precut, in cases of difficult biliary access can also reduce the risk of PEP. Finally, a higher volume of ERCP procedures performed by endoscopists and centers seems to be associated with a lower PEP incidence. More well-powered randomized clinical trials are generally needed to gain a better understanding of the role of the different treatment options in the prophylaxis of PEP.

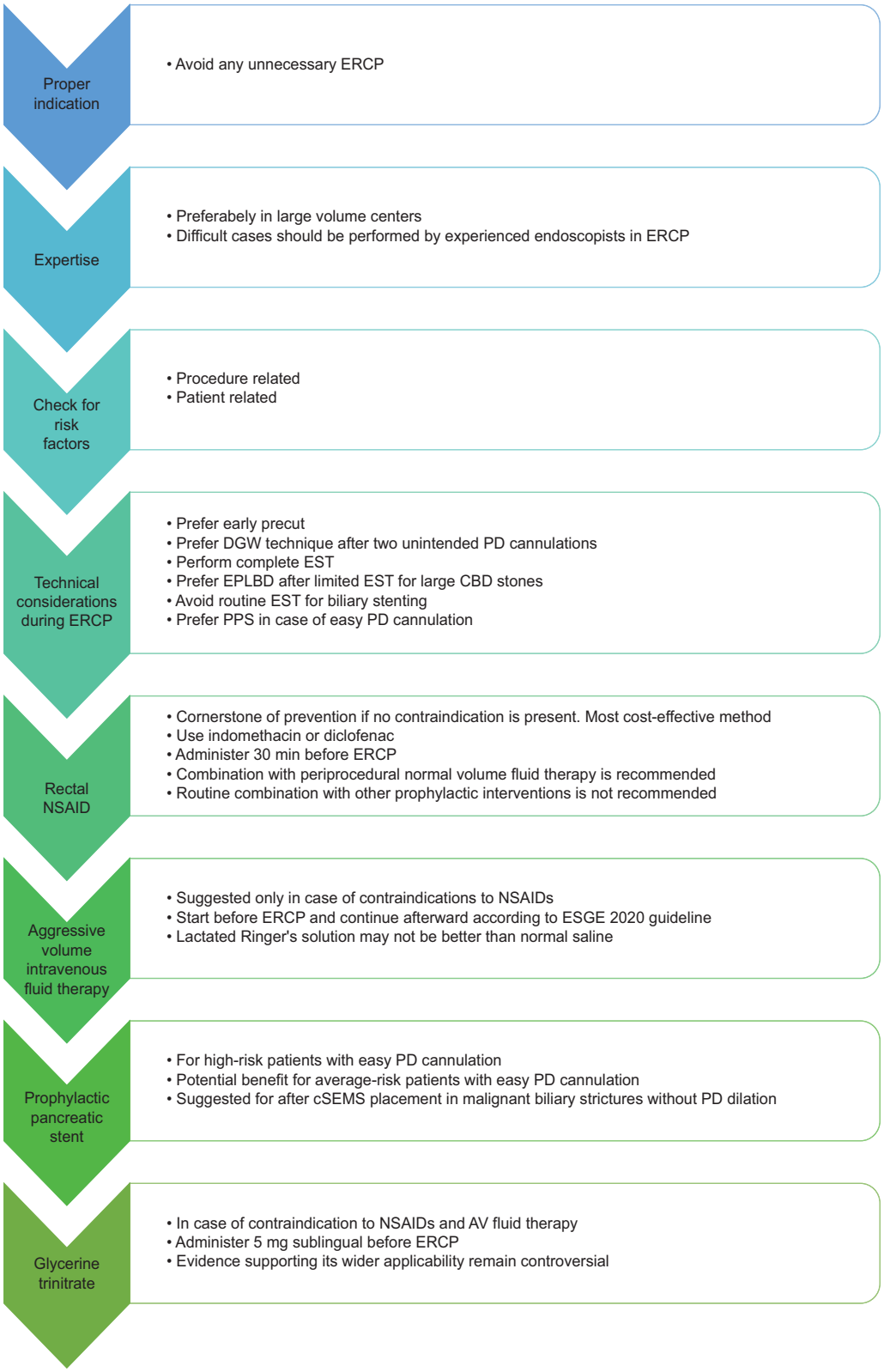

Figure 3 The authors recommentations for PEP prophylaxis in light of recent publications
ERCP, endoscopic retrograde cholangiopancreatography; PPS, prophylactic pancreatic stent; EST, endoscopic sphincterotomy; EPLBD, endoscopic papillary large balloon dilation; DGW, double-guidewire technique; NSAID, nonsteroidal anti-inflammatory drug; PD, pancreatic duct; AV, aggressive volume; cSEMS, fully covered self-expendable metal stent; PEP, post-ERCP pancreatitis

Acknowledgments

We want to thank Katalin Márta and Péter Hegyi for their contribution to our work, by allowing us to use a figure from their publication. We also acknowledge the contribution to our work of the Editorial Board of Endoscopy Journal and the Permissions-Team of the publisher Thieme by permitting us to use a figure and data from their publication.

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