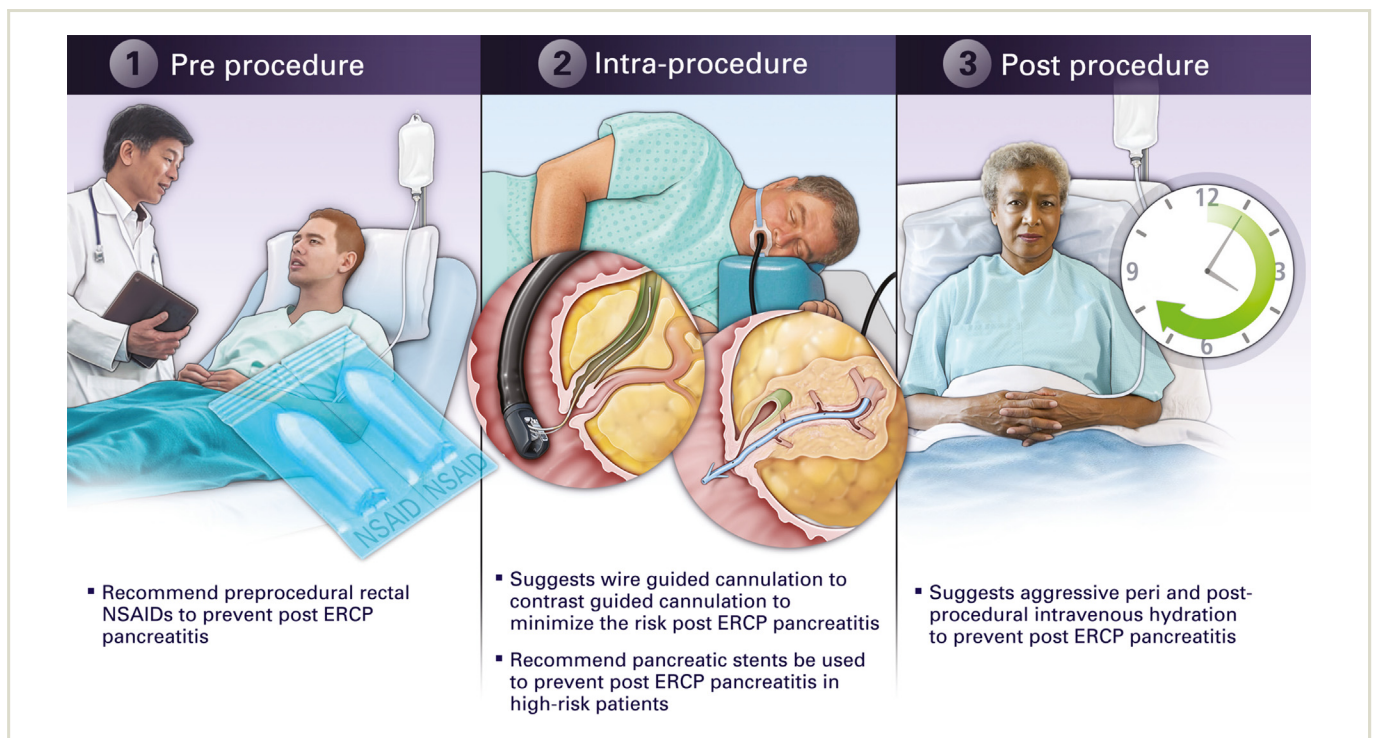ASGE
American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on post-ERCP pancreatitis prevention strategies: summary and recommendations

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GRAPHICAL ABSTRACT

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy using the best available scientific evidence and considering a multitude of variables including, but not limited to, adverse events, patients' values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice.

We recognize that clinical decision-making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgements may, at times, seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the

clinician's experience, local expertise, resource availability, and patient values and preferences.

This document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation, as they were not designed for this purpose.

This clinical practice guideline from the American Society for Gastrointestinal Endoscopy provides an evidence-based approach for strategies to prevent post-ERCP pancreatitis. This document was developed using the Grading of Recommendations Assessment, Development and Evaluation framework. The guideline addresses the role of rectal nonsteroidal anti-inflammatory drugs (NSAIDs), contrast-guided versus wire-assisted cannulation, prophylactic pancreatic stents, and aggressive versus moderate hydration in unselected patients, those without risk factors, to decrease the risk of post-ERCP pancreatitis. Before starting an ERCP, we recommend rectal NSAIDs in all (unselected and high-risk) patients. During an ERCP, we suggest wire-assisted cannulation rather than a contrast-guided approach and placement of prophylactic pancreatic stents in high-risk patients. In the periprocedure period and after ERCP, we suggest aggressive hydration in unselected patients.

ERCP enables minimally invasive treatment of a wide range of pancreaticobiliary conditions with substantially lower morbidity than traditional operative approaches.[1-3] The most feared adverse event (AE) of ERCP is post-ERCP pancreatitis (PEP), which occurs in approximately 8% of average-risk and 15% of high-risk procedures and is the most frequent serious AE of GI endoscopy.[4] Although typically mild, PEP is associated with mortality in 1 in 500 patients and an annual nationwide cost of several hundred million dollars.[4] Investigators have aimed to attenuate this risk.

PEP results from mechanical, thermal, and/or chemical trauma to the pancreatic duct (PD) and papilla. Obstruction because of edema results in intrapancreatic activation of digestive enzymes and injury to the gland.[5,6] The consequent inflammatory cascade mediated by cytokines and chemokines including prostaglandins results in intense inflammation.[7] Local injury is exacerbated by regional pancreatic hypoperfusion[8,9] and intravascular hypovolemia because of capillary leak and resulting in systemic AEs including organ failure associated with severe PEP.[10,11]

Historically, trials of prophylactic agents including corticosteroids, octreotide, and protease inhibitors showed early promise but ultimately disappointing results in larger controlled trials.[12,13] More recently, several strategies have been shown to offer more consistent benefits. These interventions aimed to alleviate mechanical obstruction resulting from papillary trauma (ie, pancreatic stents), inhibit the pancreatitis-related inflammatory cascade (ie, nonste-roidal anti-inflammatory drugs [NSAIDs]), and prevent regional and systemic hypoperfusion that may contribute to injury (ie, aggressive hydration). Despite the proven benefits of these interventions, their use in routine practice in North America remains suboptimal for a variety of reasons.[14-16] Although we have provided previous recommendations on strategies to minimize overall risk of ERCP, this is the first American Society for Gastrointestinal Endoscopy (ASGE) guideline dedicated to providing evidence-based guidance to mitigate the risk of PEP.[17]

METHODS

This document was prepared by the Standards of Practice Committee of the ASGE and was conceptualized and conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The GRADE panel developed recommendations based on certainty in the evidence and the overall balance of benefit and harm, patient values and preferences, cost-effectiveness, and resource utilization.[18,19] Consensus among the panel members was used to determine the wording of the recommendation and, in particular, the direction and strength. Using the GRADE approach, we categorized the recommendations as strong or conditional; "recommend" was used for strong recommendations and "suggest" for conditional recommendations. Further details of the methodology used for this guideline are presented separately, including systematic reviews, evidence profile, and results from all meta-analyses.[20]

These guidelines addressed the following clinical questions using the GRADE format:

1. In unselected patients undergoing ERCP, should rectal NSAIDs be given to prevent PEP?
2. In high-risk patients undergoing ERCP, should rectal NSAIDs be given to prevent PEP?
3. In unselected patients undergoing ERCP, is wire-guided cannulation preferred to contrast-guided cannulation to minimize PEP?
4. In high-risk patients undergoing ERCP, should pancreatic stents be placed to prevent PEP?
5. In unselected patients undergoing ERCP, should aggressive periprocedural and postprocedural intravenous hydration be given to prevent PEP?

Relevant clinical outcomes included PEP, moderately severe/severe PEP, and AEs.

RESULTS AND SUMMARY OF RECOMMENDATIONS

Details of our literature search, data analyses, pooled-effect estimates, evidence profiles, forest plots, and panel deliberation for each outcome can be found in the methodology and technical review document. A summary of our final recommendations is listed in Table 1.

TABLE 1. Summary of recommendations

Timing	GRADE recommendation	General concepts
Preprocedure	Among unselected patients undergoing ERCP, the ASGE recommends preprocedural rectal NSAIDs to prevent PEP (Strong recommendation/Moderate quality of evidence).	• Avoid in patients with recent peptic ulcer disease or renal insufficiency • Can be administered >30 min before or during the procedure • Use indomethacin 100 mg in adults
	For high-risk patients undergoing ERCP, the ASGE recommends preprocedural rectal NSAIDs should be given to prevent PEP (Strong recommendation/Moderate quality of evidence)	• Avoid in patients with recent peptic ulcer disease or renal insufficiency • Can be administered >30 min before or during the procedure
Intraprocedure	In unselected patients undergoing ERCP, the ASGE suggests wire-guided cannulation over contrast-guided cannulation to minimize the risk of PEP (Conditional recommendation/Moderate quality of evidence).	• Cannulate then advance wire • Endoscopist, or experienced operator, to perform wire manipulation • Avoid forceful or repeated wire advancement into the pancreatic duct
	In high-risk patients undergoing ERCP, the ASGE recommends that pancreatic stents be used to prevent PEP in high-risk patients in which the pancreatic duct has been repeatedly or deeply accessed (Strong recommendation/Moderate quality of evidence) and suggests it for high-risk patients as long as pancreatic duct access can be easily achievable (Conditional recommendation/Moderate quality of evidence).	• Use 3F-5F stent (preferably 5F) without internal flange 3-7 cm in length • If wire cannot pass beyond the head, a short stent (2-3 cm) may be used • Get an abdominal x-ray to assess spontaneous stent migration • Remove in 2-4 weeks if needed
Postprocedure	In unselected patients undergoing ERCP, the ASGE suggests aggressive periprocedural and postprocedural intravenous hydration to prevent PEP pancreatitis (Conditional recommendation/Moderate quality of evidence).	• Can be initiated preprocedure or intraprocedure • Avoid in patients with history of congestive heart failure, renal insufficiency, or advanced liver disease • Use lactate Ringer's solution • Periprocedural bolus of 20 mL/kg followed by 3 mL/kg/h for 8 h • May be more feasible for inpatients

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *ASGE*, American Society for Gastrointestinal Endoscopy; *NSAID*, nonsteroidal anti-inflammatory drug; *PEP*, post-ERCP pancreatitis.

Question 1: In unselected patients undergoing ERCP, should rectal NSAIDs be given to prevent PEP?

> **Recommendation 1:** Among unselected patients undergoing ERCP, the ASGE recommends periprocedural rectal NSAIDs should be given to prevent PEP (*Strong recommendation/Moderate quality of evidence*).

Summary of evidence. We performed a systematic review and meta-analysis and identified 18 randomized controlled trials (RCTs) of rectal NSAIDs to prevent PEP in a total of 4817 unselected (ie, with and without risk factors) patients. Outcomes of interest included development of PEP, moderately severe or severe PEP, and the AEs of renal failure and GI hemorrhage (ie, postsphincterotomy bleeding).

Unselected patients were defined as all patients who presented for ERCP without selection based on risk factors. Among all patients, rectal NSAIDs were associated with a significant reduction in the odds of PEP (odds ratio [OR], .49; 95% confidence interval [CI], .37-.65; $I^2 = 38.6\%$). This means that using rectal NSAIDs is associated with a 50% reduction in the risk of PEP. There was a trend toward a reduction of moderately severe and/or severe pancreatitis (OR, .47; 95% CI, .21-1.06; $I^2 = 38.6\%$), but this did not reach statistical significance. There was no difference in postsphincterotomy bleeding (OR, 1.68; 95% CI, .50-5.68; $I^2 = 39\%$), whereas renal failure did not develop in any patient. Most excluded patients had active peptic ulcer disease, ongoing NSAID use, and renal insufficiency (ie, creatinine level >1.4 mg/dL).

A recent study reported that rectal NSAIDs are cost-effective in unselected patients with an incremental cost-effectiveness ratio/quality-adjusted life year (ICER/QALY) of \$33,812.[21] The panel also noted that the overall cost of rectal NSAIDs is small, and the medication is readily available in most settings.

The panel raised concerns about recent extreme increases in the price of rectal NSAIDs, especially in the United States.[22] Over-the-counter formulations of NSAIDs are inexpensive. However, when given in hospital settings, prices seem to be multiplied. Furthermore, the wholesale acquisition cost of rectal indomethacin increased from \$2 to \$340 between 2005 and 2019.[22] Nevertheless, modeling suggests that rectal indomethacin will remain cost-effective

up to a price of \$1134 per suppository.[21] Other NSAIDs, which are not available as rectal preparations on the market, may be formulated from oral medications by compounding pharmacies at substantially lower cost.

A limitation of the data is that the inclusion criteria and study populations were heterogeneous. Unselected patients included mixed high-, medium-, and low-risk patients, and results were not stratified. Although the studies did not select for PEP risk factors, most excluded patients with very-low-risk indications such as biliary stent exchange. Of note, these very-low-risk patients were included in the trial by Levenick et al,[23] which did not demonstrate a protective effect for rectal NSAIDs. Hence, the available literature does not inform the clinical and cost-to-benefit impact of rectal NSAIDS for low-risk patients.

Timing of rectal NSAID administration ranged from 90 minutes before the procedure to the time of arrival in the recovery room.[24] In all but 3 studies they were given before ERCP. We compared efficacy among patients who received the dose $\geq$30 minutes before with those who received the medication closer to or during the procedure and did not identify a difference.

Although ketoprofen and naproxen suppositories have been studied for PEP prevention, the great preponderance of data focuses on rectal indomethacin and diclofenac. Both rectal indomethacin and diclofenac were found to be effective in subgroup analyses. The standard dose for rectal indomethacin and diclofenac is 100 mg. In pediatric patients, the NSAID dose is to be determined by the pediatrician.

Clinical trials excluded patients with peptic ulcer disease and renal insufficiency; therefore, based on the currently available data, such patients may not be good candidates for NSAIDs. In addition, patients with known aspirin or other nonsteroidal allergies should not receive rectal NSAIDs.

In summary, given the significant reduction in PEP, cost-effectiveness, and minimal AEs, the panel made a strong recommendation for use of rectal NSAIDs in unselected patients undergoing ERCP. The overall quality of the evidence was moderate.

Question 2: In high-risk patients undergoing ERCP, should rectal NSAIDs be given to prevent PEP?

> **Recommendation 2:** For high-risk patients undergoing ERCP, the ASGE recommends periprocedural rectal NSAIDs should be given to prevent PEP (*Strong recommendation/moderate quality of evidence*).

Summary of evidence. To address this question, we performed a systematic review and meta-analysis of randomized trials and identified 10 eligible studies with 1008 patients in populations defined by the authors of the RCTs as high risk for PEP. The high-risk status was based on baseline features or technical challenges during ERCP. Outcomes of interest included overall risk of PEP, risk of moderately severe or severe PEP (consensus or revised Atlanta classification), renal failure, and GI bleeding (ie, postsphincterotomy bleeding).

For the outcome of overall risk of PEP, the OR was .49 (95% CI, .30-.83; $I^2 = 56.6\%$) with prophylactic NSAIDs compared with placebo. This means that using rectal NSAIDs is associated with a 50% reduction in the risk of PEP in high-risk patients. There was a trend toward lower risk of moderately severe or severe pancreatitis; however, this did not reach statistical significance (OR, .53; 95% CI, .27-1.05; $I^2 = 11.8\%$). There was no difference in renal failure (OR, .63; 95% CI, .12-3.29; $I^2 = 0$) or bleeding (OR, .82; 95% CI, .40-1.65; $I^2 = 0$) with NSAID use. A recent cost-effectiveness analysis revealed that rectal NSAIDS are cost-effective in high-risk patients.[21]

In several studies a significant proportion of patients also received a pancreatic stent to prevent PEP.[25,26] Thus far, trials to compare whether NSAIDs alone versus NSAIDs combined with pancreatic stents are optimal to prevent PEP in high-risk patients have been underpowered, although a large ongoing multicenter RCT aims to address this question.[27-29]

Additionally, the definition of high-risk conditions continues to evolve as clinical practice patterns change. Sphincter of Oddi dysfunction was the predominant indication in several larger trials of NSAIDs that demonstrated benefit.[22,30] Female gender, age <40 years, and normal bilirubin are predictors of PEP, but with increasing recognition that sphincter of Oddi dysfunction is a suboptimal indication for ERCP, their importance when associated with other pathologies is less clear.[31-33] Difficult, prolonged, and/or traumatic cannulation, particularly if the PD is repeatedly injected or deeply accessed with a guidewire, is a leading risk factor for PEP.[34] Several new techniques and tools such as fully covered self-expanding metal stents have been associated with PEP and will need to be further evaluated in high-quality prospective studies.[35] Over time, the definition of "high risk" will need to be better defined.

Given the evidence of efficacy to prevent PEP, increased cost-effectiveness, and minimal AEs, the panel strongly recommended prophylactic rectal NSAIDs in high-risk patients. The overall quality of the evidence was moderate.

Question 3: In unselected patients undergoing ERCP, is wire-guided cannulation preferred to contrast-guided cannulation to minimize PEP?

> **Recommendation 3:** In unselected patients undergoing ERCP, the ASGE suggests wire-guided cannulation over contrast-guided cannulation to minimize the risk of PEP (*Conditional recommendation/Moderate quality of evidence*).

Summary of evidence. To address the question, we used a Cochrane meta-analysis that was updated by Tse et al[36] in parallel with the development of this guideline. Outcomes of interest included PEP, moderate PEP, and severe PEP as well as bleeding and perforation.

Based on 15 randomized trials reporting on 4426 patients, guidewire-assisted access reduced PEP (relative risk [RR], .50; 95% CI, .31-0.72; $I^2 = 36\%$) relative to contrast-assisted access with no difference in AEs of postsphincterotomy bleeding or perforation. There was no difference in moderate (RR, .76; 95% CI, .38-1.52; $I^2 = 0$) or severe (RR, .69; 95% CI, .27-1.81; $I^2 = 0$) PEP.

In 7 of 15 studies, pancreatic stents were used to prevent PEP at the endoscopist's discretion. PD stents were not permitted in 4 studies. Subgroup analysis revealed that guidewire-assisted approaches reduced PEP among trials that did not permit use of PD stents (RR, .24; 95% CI, .13-0.47; $I^2 = 0$) but not for trials that allowed PD stent use (RR, .78; 95% CI, .42-1.18; $I^2 = 25$). This would suggest that the cannulation technique may not be as relevant if a PD stent is placed. However, by the time an endoscopist has decided to place a PD stent, they have already achieved PD cannulation. Therefore, guidewire-assisted cannulation may still be preferable at the onset of the procedure.

In 5 trials, the guidewire was passed through a sphincterotome already positioned in a duct to confirm whether it was biliary or pancreatic.[37-41] The use of the guidewire minimized the need to inject contrast to confirm catheter location. In our subanalysis, this significantly reduced PEP relative to contrast-assisted approaches (RR, .29; 95% CI, .18-.49; $I^2 = 0$). In 6 trials, the guidewire was first passed into the duct followed by the sphincterotome.[42-47] This approach uses the guidewire to help negotiate access into the duct of interest. In a subanalysis this approach did not reduce the risk of PEP relative to contrast-facilitated access (RR, .66; 95% CI, .39-1.13; $I^2 = 43\%$). Therefore, our data would suggest that guidewire-assisted cannulation is best performed by using the guidewire to confirm location once the cannulatome has been properly positioned inside a duct.[34,48,49] Nevertheless, "positioned in the duct" may be interpreted and explained by endoscopists to refer to the papilla or ampulla rather than the common bile duct or PD. Head-to-head trials that explicitly define and compare these techniques are needed to substantiate these findings.

Cost-effectiveness studies comparing wire- versus contrast-assisted cannulation for PEP prevention are lacking. However, the panel noted that neither technique incurs additional costs, because a guidewire and cannula or sphincterotome are used in most ERCPs. The overall quality of the evidence was moderate.

Despite the evidence cited above, the panel elected to make a conditional, rather than strong, recommendation for this intervention because of several factors:

1. The above-mentioned variation in the definition of guidewire-assessed cannulation.

2. The potential for PD injury, including side-branch perforation, if a guidewire is forcefully or repeatedly introduced into the PD.

During guidewire-associated cannulation, an experienced operator should advance the guidewire into the duct, because skillful manipulation and interpretation of tactile feedback can be critical to avoid guidewire-induced injuries.[50]

Question 4: In high-risk patients undergoing ERCP, should pancreatic stents be placed to prevent PEP?

> **Recommendation 4a:** In patients undergoing ERCP with repeated or deep PD access or performance of ampullectomy, the ASGE recommends PD stents to reduce the risk of PEP (*Strong recommendation/Moderate Quality of evidence*).
>
> **Recommendation 4b:** Otherwise, in high-risk groups, including patients with difficult cannulation, history of PEP, or precut sphincterotomy without fistulotomy technique, the ASGE suggests PD stent placement as long as PD access can be easily achieved (*Conditional recommendation/Moderate quality of evidence*).

Summary of evidence. We performed a systematic review and meta-analysis to assess the benefit of PD stents to prevent PEP in high-risk patients. These populations were classified by the authors of the studies as high risk based on their baseline characteristics and events that occurred during ERCP. The outcomes of interest included the risk of PEP, moderate and severe PEP, and the AEs of bleeding, perforation, and infection.

We included 17 RCTs with a total of 1595 patients. On meta-analysis, PD stents significantly reduced overall PEP in high-risk patients (OR, .35; 95% CI, .26-.46; $I^2 = 14.6\%$). This means that PD stent placement reduced the risk of any PEP by 65% compared with no PD stents. Unlike other interventions, PD stent placement was also associated with reduced occurrence of both moderate (OR, .38; 95% CI, .23-.63; $I^2 = 0$) and severe (OR, .20; 95% CI, .06-.65; $I^2 = 0$) PEP. Overall, 1% of patients (13/1303) randomized to no stent developed severe PEP versus none of the 1292 assigned to prophylactic pancreatic stent.

The protective effect remained significant in subanalyses excluding populations with a high proportion of sphincter of Oddi dysfunction (OR, .37; 95% CI, .27-.49; $I^2 = 12.6$). Pancreatic stents also reduced PEP whether placed as a final additional step of ERCP (OR, .41; 95% CI, .25-.67; $I^2 = 19.2\%$) or used only after the PD had already been inadvertently or intentionally accessed with the guidewire (OR, .31; 95% CI, .18-.53; $I^2 = 0$). There was no difference in incidence of bleeding (OR, .94; 95% CI, .35-2.51; $I^2 = 31\%$), infection (OR, .61; 95% CI, .20-1.92; $I^2 = 0\%$), or perforation (OR, 1.30; 95% CI,

.05-33.3; $I^2 = 56.7\%$). Prophylactic pancreatic stent placement was successful in 97% of procedures (95% CI, 94-100; $I^2 = 74.9\%$) in which it was attempted.

Several studies have shown that PD stents are cost-effective in high-risk populations with an ICER/QALY ranging from $9316 to 11,766.[21,51] Overall, the quality of the evidence was moderate. Based on the evidence above, we concluded that the benefit of prophylactic pancreatic stents in high-risk patients outweighs the risk and cost.

A major concern regarding PD stent placement is the lack of clarity regarding whether prophylactic pancreatic stents should be placed regardless of whether the PD has previously been accessed. In some studies, a prophylactic stent was placed as an additional step at the end of the ERCP, whereas in other trials patients were only randomized to stent versus no stent if the PD had already been intentionally or inadvertently accessed with the guidewire. Many panelists expressed concerns about seeking out the PD for cannulation in high-risk patients unless the PD was already accessed, because this could increase the risk of PEP. By the same reasoning, PD stents were believed to be increasingly advisable in scenarios where the PD had been repeatedly and deeply accessed during the procedure.

The panel also recognized that the contemporary definition of high risk for PEP is different from definitions used in early trials of pancreatic stents, and, indeed, this definition continues to evolve. The benefit of prophylactic pancreatic stents in pediatric patients is also unclear and needs to be prospectively studied.[52]

Most trials in our systematic review used short 5F stents, and a prior network meta-analysis favored this diameter over longer 3F stents.[53] In situations in which the guidewire cannot be passed beyond the head, the panel believed that a short stent was favored to minimize injury. Nevertheless, they recognized that premature PD stent migration increases the risk of PEP.[54] Follow-up imaging is necessary to ensure spontaneous PD stent migration has not occurred and to plan endoscopy with stent removal if the stent is visualized on imaging. A number of panel members noted that imaging can be skipped if a subsequent ERCP is planned for bile duct stent removal or ampullectomy follow-up within a relatively short period of weeks.

A final concern was the declining use of prophylactic pancreatic stents; currently, they are used in <10% of high-risk patients.[15] It is possible that this may reflect concern for technical failure or cost, although this is not valid based on the 97% technical success rate seen in this systematic review and cost-effectiveness analysis. Alternatively, it may reflect uncertainty about incremental efficacy when rectal NSAIDs are used. Nevertheless, this systematic review demonstrates strong evidence for reduction of mild, moderate, and severe pancreatitis with pancreatic stent use in high-risk patients in the absence of NSAID use. Despite increased use of rectal NSAIDs,

the rate of PEP has not decreased, and hospitalization and overall mortality for PEP appear to have increased.[15,16] The increase in prophylactic NSAID use approximates the decrease in prophylactic stent use with a significant group of patients undergoing high-risk procedures still unprotected by either intervention.[15,16] Evidence underscores the need for an increase in the real-world use of rectal NSAIDs and/or pancreatic stents in appropriately skilled hands.

Question 5: In unselected patients undergoing ERCP, should aggressive periprocedural and postprocedural intravenous hydration be given to prevent PEP?

> **Recommendation 5:** In unselected patients undergoing ERCP, the ASGE suggests aggressive periprocedural and postprocedural intravenous hydration to prevent PEP (*Conditional recommendation/Moderate quality of evidence*).

Summary of evidence. A systematic review and meta-analysis was performed to inform the question of whether aggressive hydration prevents PEP in unselected patients. Outcomes included risk of PEP, moderately severe and/or severe PEP, and AEs including fluid overload. Aggressive hydration was defined by most studies as a periprocedural bolus of 20 mL/kg followed by 3 mL/kg/h for 8 hours postprocedure. Lactated Ringer's (LR) solution was used in most studies, whereas normal saline solution and LR solution were used in 1 study.[55]

We identified 12 RCTs that addressed the use of aggressive hydration to prevent PEP, which included a total of 3524 patients. On meta-analysis, aggressive hydration reduced the risk of pancreatitis (OR, .47; 95% CI, .34-.66; $I^2 = 26.3\%$) compared with moderate hydration. There was a trend toward reduction of moderately severe and severe pancreatitis (OR, .60; 95% CI, .34-1.08; $I^2 = 9.0$), but this did not achieve statistical significance. There was no difference in volume overload in subjects receiving aggressive hydration versus control subjects (OR, 1.14; 95% CI, .49-2.67; $I^2 = 0\%$).

A sensitivity analysis that excluded studies that had patients co-managed with rectal NSAIDS and studies that used an infusion protocol different from the 8-hour protocol first proposed by Buxbaum et al[56] did not materially alter outcomes. A recent cost-effectiveness analysis suggested that aggressive hydration is cost-effective in high-risk patients (ICER/QALY of $28,002) but not in unselected patients (ICER/QALY of $139,004), reflecting the model assumption that aggressive hydration requires an additional 24-hour inpatient hospital stay.[21] In regard to equity, aggressive hydration is available in international settings where rectal NSAIDs and pancreatic stents may not be. Additionally, the recently completed FLUYT trial did not show reduced PEP when aggressive hydration was added to NSAIDs but did show a trend toward less severe PEP.[57]

Given the balance of benefits versus harms, the panel suggested aggressive hydration is in order to prevent PEP. LR solution should be used in these patients because most data are based on LR solution and data suggest that LR solution is superior to normal saline solution in treatment of pancreatitis.[58,59] A 20-mL/kg bolus should be give followed by an initial rate of infusion of 3 mL/kg. This intervention is optimal among inpatients who are already staying in-house and would not require observation in the endoscopy unit for 8 hours, which is less practical for most outpatient endoscopy centers given the restraints on postoperative space and staff. For outpatients, a more cost-effective and feasible approach may be to administer more fluid over a shorter 2- to 3-hour period as used in the trial by Brown et al.[60] Nevertheless, shorter hydration protocols have not been adequately studied or shown to have benefit. Although widely available, it is unclear whether aggressive fluids are cost-effective and what their role should be among patients already receiving rectal NSAIDs.[57] Given these considerations, the panel qualified the recommendation as conditional.

FUTURE DIRECTIONS

Our systematic literature reviews highlighted several areas in need of more data to inform PEP prevention. Future studies should address the following:

1. *Role of single-dose NSAIDs in a more generalized population.* Trials of rectal NSAIDs to prevent PEP in high-risk and unselected patients excluded those with a history of peptic ulcer disease, ongoing NSAID use, prior acute or chronic pancreatitis, and renal insufficiency. Studies to define the safety of a single NSAID dose in these patients are needed as well as the specific impact in low-risk patients.

2. *Mechanisms of NSAIDs to prevent PEP.* Although rectal NSAIDs reduce PEP, administration through oral, intravenous, and other routes does not provide consistent benefit.[61,62] Basic and translational studies to better understand the means of action of NSAIDs in pancreatitis prevention could be used to optimize their formulation and dosage.

3. *Specific techniques of wire-assisted cannulation.* Although wire-guided access reduces PEP, comparative trials of the 2 specific guidewire-assisted approaches, guidewire advanced ahead of the sphincterotome to facilitate entry versus guidewire placement only after a sphincterotome is advanced to confirm position in the duct of interest, are needed to define optimal technique. Future studies will need to explicitly define technical methodology, given variations in how access is interpreted and performed among practitioners.

4. *Timing and indications for prophylactic PD stent placement.* There is debate whether to use PD stents in high-risk patients, in whom guidewire access to the PD is otherwise not necessary, versus only when the PD has already been inadvertently or intentionally accessed with the guidewire.[63] Studies are needed to more explicitly define the best scenarios for PD stent use.

5. *Shorter, high-feasibility protocols for aggressive hydration.* Although most studies use 8- to 24-hour infusion protocols for aggressive hydration, this may not be feasible, particularly for outpatients.[21] Further studies on more abbreviated protocols are needed to define safety and efficacy.[60]

6. *Role of combination therapy to prevent PEP.* Studies to define whether combinations of preventative measures perform better than single interventions are needed. Two small trials comparing NSAIDs alone versus NSAIDs with PD stent were not adequately powered to draw conclusions.[27,29] A large ongoing trial aims to inform whether stent and indomethacin performs differently from indomethacin alone.[28] The FLUYT trial did not show reduced PEP for aggressive hydration combined with NSAIDs versus NSAIDs alone, although there was a trend toward less severe PEP.[57] Trials of combination agents may need to be robust to demonstrate the incremental benefit of additional agents used for treatments with demonstrated efficacy.

7. *Standardized definitions of high-, intermediate-, and low-risk populations for PEP.* Consensus definitions of the risk for PEP based on patient and procedural characteristics will facilitate research and clinical use of preventative measures. In addition to high risk, low-risk procedures need to be defined. An "unselected" population that includes patients undergoing scheduled stent exchange[23] is substantially lower risk than a population in which patients have a native papillas.[64] Additionally, from the outset it will be vital to recognize that these definitions will need to be refined as new research and technology impacts clinical practice patterns.[33]

8. *Accurate personalized PEP risk.* Development of a robust PEP calculator informed by gathering high-quality data on granular preprocedural and periprocedural parameters is needed. Input of the specific values on a per-patient basis would yield nuanced risk assessment and better inform decisions on interventions.

SUMMARY AND CONCLUSIONS

This ASGE guideline used the best available evidence to make recommendations for PEP prevention. Several measures can be done preprocedure, intraprocedure, and postprocedure to reduce the risk of PEP. *Pre- or intraprocedure* rectal NSAIDs reduce PEP in unselected patients and those at high risk. *Intraprocedure*, wire-guided cannulation decreases PEP compared with contrast-assisted cannulation, and in high-risk patients, the use of prophylactic

pancreatic stents reduces overall PEP as well as moderate and severe PEP. *Postprocedure*, aggressive hydration reduces PEP in unselected patients undergoing ERCP.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

DISCLOSURE

ACKNOWLEDGMENT

REFERENCES

1. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med 1992;326:1582-6.
2. Speer AG, Cotton PB, Russell RC, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987;2:57-62.
3. Smith AC, Dowsett JF, Russell RC, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bile duct obstruction. Lancet 1994;344:1655-60.
4. Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015;81:143-9.
5. Saluja A, Saluja M, Villa A, et al. Pancreatic duct obstruction in rabbits causes digestive zymogen and lysosomal enzyme colocalization. J Clin Invest 1989;84:1260-6.
6. Ohshio G, Saluja A, Steer ML. Effects of short-term pancreatic duct obstruction in rats. Gastroenterology 1991;100:196-202.
7. Makela A, Kuusi T, Schroder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest 1997;57:401-7.
8. Kusterer K, Enghofer M, Zendler S, et al. Microcirculatory changes in sodium taurocholate-induced pancreatitis in rats. Am J Physiol 1991;260: G346-51.
9. Juvonen PO, Tenhunen JJ, Heino AA, et al. Splanchnic tissue perfusion in acute experimental pancreatitis. Scand J Gastroenterol 1999;34: 308-14.
10. Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. Gastroenterology 2019;156:2008-23.
11. Whitcomb DC, Muddana V, Langmead CJ, et al. Angiopoietin-2, a regulator of vascular permeability in inflammation, is associated with persistent organ failure in patients with acute pancreatitis from the United States and Germany. Am J Gastroenterol 2010;105:2287-92.
12. Andriulli A, Leandro G, Federici T, et al. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. Gastrointest Endosc 2007;65:624-32.
13. Sherman S, Blaut U, Watkins JL, et al. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis? A randomized, prospective, multicenter study. Gastrointest Endosc 2003;58:23-9.
14. Avila P, Holmes I, Kouanda A, et al. Practice patterns of post-ERCP pancreatitis prophylaxis techniques in the United States: a survey of advanced endoscopists. Gastrointest Endosc 2020;91:568-73.
15. Smith ZL, Elmunzer BJ, Cooper GS, et al. 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;115:934-40.

16. Mutneja HR, Vohra I, Go A, et al. Temporal trends and mortality of post-ERCP pancreatitis in the United States: a nationwide analysis. Endoscopy 2021;53:357-66.

17. ASGE Standards of Practice Committee; Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc 2017;85:32-47.

18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

19. Wani S, Sultan S, Qumseya B, et al. The ASGE'S vision for developing clinical practice guidelines: the path forward. Gastrointest Endosc 2018;87:932-3.

20. ASGE Standards of Practice Committee; Buxbaum JL, Freeman M, Amateau SK, et al. American Society for Gastrointestinal Endoscopy guideline on post-ERCP pancreatitis prevention strategies: methodology and review of evidence. Gastrointest Endosc 2023;97:163-83.

21. Thiruvengadam NR, Saumoy M, Schneider Y, et al. A cost-effectiveness analysis for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis in the United States. Clin Gastroenterol Hepatol 2022;20:216-26.

22. Elmunzer BJ, Hernandez I, Gellad WF. The skyrocketing cost of rectal indomethacin. JAMA Intern Med 2020;180:631-2.

23. Levenick JM, Gordon SR, Fadden LL, et al. Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients. Gastroenterology 2016;150:911-7; quiz e19.

24. Li L, Liu M, Zhang T, et al. Indomethacin down-regulating HMGB1 and TNF-alpha to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. Scand J Gastroenterol 2019;54:793-9.

25. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.

26. Mok SRS, Ho HC, Shah P, et al. Lactated Ringer's solution in combination with rectal indomethacin for prevention of post-ERCP pancreatitis and readmission: a prospective randomized, double-blinded, placebo-controlled trial. Gastrointest Endosc 2017;85:1005-13.

27. Sotoudehmanesh R, Ali-Asgari A, Khatibian M, 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;51:915-21.

28. Elmunzer BJ, Serrano J, Chak A, 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;17:120.

29. Koshitani T, Konaka Y, Nakano K, et al. Rectal nonsteroidal anti-inflammatory drugs are equivalent to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography [abstract]. Gastrointest Endosc 2017;85:AB213-A214.

30. Murray B, Carter R, Imrie C, et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003;124:1786-91.

31. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.

32. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311:2101-9.

33. Smith Z, Shah R, Elmunzer B, et al. The next EPISOD: trends in utilization of endoscopic sphincterotomy for sphincter of Oddi dysfunction from 2010-2019. Clin Gastroenterol Hepatol 2022;20:e600-9.

34. Wang P, Li ZS, Liu F, et al. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009;104:31-40.

35. Xia MX, Zhou YF, Zhang M, 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;35:2256-63.

36. Tse F, Liu J, Yuan Y, et al. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database System Rev 2022;3:CD009662.

37. Lella F, Bagnolo F, Colombo E, et al. A simple way of avoiding post-ERCP pancreatitis. Gastrointest Endosc 2004;59:830-4.

38. Mangiavillano B, Mariani A, Glussani A, et al. Guidewire assisted cannulation of the papilla of Vater to reduce the risk of post-ERCP pancreatitis: a prospective randomised study. Endoscopy 2007;39(suppl 1):A373.

39. Artifon EL, Sakai P, Cunha JE, et al. Guidewire cannulation reduces risk of post-ERCP pancreatitis and facilitates bile duct cannulation. Am J Gastroenterol 2007;102:2147-53.

40. Lee TH, Park DH, Park JY, et al. Can wire-guided cannulation prevent post-ERCP pancreatitis? A prospective randomized trial. Gastrointest Endosc 2009;69:444-9.

41. Masci E, Mangiavillano B, Luigiano C, et al. Comparison between loop-tip guidewire-assisted and conventional endoscopic cannulation in high risk patients. Endosc Int Open 2015;3:E464-70.

42. Apostolopoulos P, Alexandrakis G, Liatsos C, et al. Guide wire-assisted selective access to the common bile duct could prevent post-ERCP pancreatitis. Endoscopy 2005;37:A278.

43. Zhang Z, Li D, Liu J, et al. Randomize case-control study on decrease of post-ERCP pancreatitis by selective cannulation of common bile duct guided by guide wire. Chin J Dig Endosc 2007;24:250-3.

44. Bailey AA, Bourke MJ, Williams SJ, et al. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. Endoscopy 2008;40:296-301.

45. Katsinelos P, Paroutoglou G, Kountouras J, et al. A comparative study of standard ERCP catheter and hydrophilic guide wire in the selective cannulation of the common bile duct. Endoscopy 2008;40:302-7.

46. Nambu T, Ukita T, Shigoka H, et al. Wire-guided selective cannulation of the bile duct with a sphincterotome: a prospective randomized comparative study with the standard method. Scand J Gastroenterol 2011;46:109-15.

47. Kobayashi G, Fujita N, Imaizumi K, et al. Wire-guided biliary cannulation technique does not reduce the risk of post-ERCP pancreatitis: multicenter randomized controlled trial. Dig Endosc 2013;25:295-302.

48. Nakai Y, Isayama H, Sasahira N, et al. Risk factors for post-ERCP pancreatitis in wire-guided cannulation for therapeutic biliary ERCP. Gastrointest Endosc 2015;81:119-26.

49. Halttunen J, Meisner S, Aabakken L, et al. Difficult cannulation as defined by a prospective study of the Scandinavian Association for Digestive Endoscopy (SADE) in 907 ERCPs. Scand J Gastroenterol 2014;49:752-8.

50. Buxbaum J, Leonor P, Tung J, et al. Randomized trial of endoscopist-controlled vs. assistant-controlled wire-guided cannulation of the bile duct. Am J Gastroenterol 2016;111:1841-7.

51. Das A, Singh P, Sivak MV Jr, et al. Pancreatic-stent placement for prevention of post-ERCP pancreatitis: a cost-effectiveness analysis. Gastrointest Endosc 2007;65:960-8.

52. Troendle DM, Abraham O, Huang R, et al. Factors associated with post-ERCP pancreatitis and the effect of pancreatic duct stenting in a pediatric population. Gastrointest Endosc 2015;81:1408-16.

53. Afghani E, Akshintala VS, Khashab MA, 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;46:573-80.

54. Kerdsirichairat T, Attam R, Arain M, et al. Urgent ERCP with pancreatic stent placement or replacement for salvage of post-ERCP pancreatitis. Endoscopy 2014;46:1085-94.

55. Park CH, Paik WH, Park ET, et al. Aggressive intravenous hydration with lactated Ringer's solution for prevention of post-ERCP pancreatitis: a prospective randomized multicenter clinical trial. Endoscopy 2018;50:378-85.

56. Buxbaum J, Yan A, Yeh K, et al. Aggressive hydration with lactated Ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol 2014;12:303-7.

57. Sperna Weiland CJ, Smeets X, Kievit W, et al. Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangio-pancreatography pancreatitis (FLUYT): a multicentre, open-label, randomised, controlled trial. Lancet Gastroenterol Hepatol 2021;6:350-8.

58. Lee A, Ko C, Buitrago C, et al. Lactated Ringers vs normal saline resuscitation for mild acute pancreatitis: a randomized trial. Gastroenterology 2021;160:955-7.

59. Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:710-7.

60. Brown R, Meiselman M, Smith Z. High volume lactated Ringer's solution and pancreatitis. Bethesda, MD: National Library of Medicine. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02050048. Accessed November 14, 2022.

61. Cheon YK, Cho KB, Watkins JL, et al. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc 2007;66:1126-32.

62. Park SW, Chung MJ, Oh TG, et al. Intramuscular diclofenac for the prevention of post-ERCP pancreatitis: a randomized trial. Endoscopy 2015;47:33-9.

63. Phillip V, Pukitis A, Epstein A, et al. Pancreatic stenting to prevent post-ERCP pancreatitis: a randomized multicenter trial. Endosc Int Open 2019;7:E860-8.

64. Luo H, Zhao L, Leung J, et al. Routine pre-procedural rectal indometacin versus selective post-procedural rectal indometacin to prevent pancreatitis in patients undergoing endoscopic retrograde cholangiopancreatography: a multicentre, single-blinded, randomised controlled trial. Lancet 2016;387:2293-301.

Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICER/QALY, incremental cost-effectiveness ratio/quality-adjusted life year; LR, lactated Ringer's; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PD, pancreatic duct; PEP, post-ERCP pancreatitis; RCT, randomized controlled trial; RR, relative risk.

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