



American Society for Gastrointestinal Endoscopy guideline on post-ERCP pancreatitis prevention strategies: methodology and review of evidence



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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) 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 belp 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 because they were not designed for this purpose.

Postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common serious adverse event of GI endoscopy, occurring in approximately 8% of all endoscopic retrograde cholangiopancreatography (ERCP) procedures.¹ PEP is fatal in 0.2% of cases and results in an annual cost of several hundred million dollars each year.¹ Therefore, the American Society for Gastrointestinal

Endoscopy (ASGE) aimed to develop evidence-based guidelines for the prevention of PEP based on GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.^{2,3} In formulating these guidelines, we conducted extensive literature reviews, including formal systematic reviews of the literature and metaanalyses. To make all the information that we collected and analyzed readily assessable, this guideline is presented in 2 documents.

METHODS

The aim of this document is to describe the methodology used in this process and to provide a detailed review of the evidence used to inform the guideline. It details the formulation of clinical questions, literature searches, data analyses, panel composition, evidence profiles, and other considerations such as cost effectiveness, patient preferences, and health equity. For each clinical question, this document includes outcomes of interest, pooled effect estimates, and evidence that was considered by the panel in making final recommendations. A separate publication provides a summary of the main findings and final recommendations of the ASGE Standards of Practice (SOP) Committee for strategies to prevent PEP.

Formulation of clinical questions

The panel addressed 5 questions relevant to the prevention of PEP by using GRADE methodology (Table 1). For these questions we followed the PICO format: P, population in question; I, intervention; C, comparator; and O,

TABLE 1. List of PICO quest	ions addressed			
Population	Intervention	Comparator	Outcomes	Rating
1. Unselected patients undergoing ERCP	Rectal NSAIDs	No rectal NSAIDs	 Post-ERCP pancreatitis Severe post-ERCP pancreatitis Adverse events 	Critical Important
2. High risk for PEP	Rectal NSAIDs	No rectal NSAIDs	 Post-ERCP pancreatitis Severe post-ERCP pancreatitis Adverse events 	Critical Important
3. Unselected patients undergoing ERCP	Wire guided cannulation	Contrast guided cannulation	 Post-ERCP pancreatitis Severe post-ERCP pancreatitis Adverse events 	Critical Important
4. High risk for PEP	Pancreatic stents	No pancreatic stents	 Post-ERCP pancreatitis Severe post-ERCP pancreatitis Adverse events 	Critical Important
5. Unselected patients undergoing ERCP	Aggressive peri- and postprocedural hydration	Standard hydration	 Post-ERCP pancreatitis Severe post-ERCP pancreatitis Adverse events 	Critical Important

NSAIDs, Nonsteroidal anti-inflammatory drugs; PEP, post-ERCP pancreatitis; PICO, P, population in question; I, intervention; C, comparator; O, outcomes of interest.

outcomes of interest. For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "critical" to "important" through a consensus process.

Literature search and study selection criteria

For each PICO question, we searched for existing systematic reviews of available randomized controlled trials (RCTs). We performed systematic reviews and metaanalyses (SRMAs) to address the PICO questions 1 and 2 and 4 and 5. PICO question 3 was addressed with a Cochrane systematic review and meta-analysis, which was updated for this guideline.⁴

A health sciences librarian developed the search strategy and searched the following databases on March 25, 2021, for PICOs 1 and 2; on March 24, 2021, for PICOs 4 and 5, and on March 23, 2021, for PICO 6. This included PubMed (coverage 1946–present), Embase and Embase Classic (coverage 1947–present), Cochrane Library (coverage 1898–present), and Web of Science (coverage 1900– present). Filters were applied to include only RCTs published in English on human subjects. The updated systematic review by Tse et al⁴ (PICO 3) included a search through February 26, 2021.

A combination of subject headings (when available) and keywords was used and is provided in Appendix 1. Cross-referencing (snowballing) and forward searches of the citations from articles fulfilling the inclusion criteria and other pertinent articles were performed with the use of Web of Science. Only RCTs were included in the literature search. Citations were imported into EndNote x9.2 (Clarivate Analytics, Philadelphia, Penn, USA), and duplicates were removed by use of the Bramer method and uploaded into Covidence (Melbourne, Australia) for screening.⁵

Data extraction and statistical analysis

Two or more independent reviewers (S.Z., J.S., A.C., R.D., J.B.) performed data extraction for all of the systematic reviews and meta-analyses by using Covidence (Melbourne, Australia). Summary statistics included odds ratios (ORs) for PICOs 1 and 2 and 4 and 5; risk ratios (RRs) for PICO 3; and proportions for PICO 4. Pooled effects were calculated by the use of random-effects models, given the anticipation of heterogeneity among the source studies Statistical heterogeneity was quantified by the use of the I^2 statistic, and other potential sources of heterogeneity were assessed by performing subgroup and sensitivity analyses. Studies were weighted on the basis of size. Publication bias was assessed with funnel plots. Statistical analyses were performed with STATA 14.2 (College Station, Tex, USA).

Panel composition and conflict of interest management

On November 13, 2021, we assembled a panel of stakeholders to review evidence and make recommendations. The panel consisted of the lead author (J.B.); a content expert independent of the SOP committee (M.F.); a GRADE methodologist (N.F.); SOP committee members with expertise in methodology, systematic reviews, and meta-analysis; and the committee chair (B.Q.). A patient representative (T.T.) from the National Organization for Transplant Enlightenment (N.O.T.E.) was also included. Per ASGE policy, members were asked to disclose conflicts of interests (https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/default-source/about-asge/ mission-andgovernance/asge-conflict-of-interest-anddisclosure-policy.pdf). Panel members who received funding for any technologies or companies associated with any of the PICOs or who had other relevant conflicts

GRADE quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

TABLE 2. GRADE categories of quality of evidence

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

of interest were asked to declare this before the discussion and did not vote on the final recommendation addressing that specific PICO question.

The GRADE approach was used to determine the quality of the evidence and confidence in the estimated effects. The following domains were addressed: bias of individual studies, imprecision, inconsistency, indirectness, and publication bias. Certainty was categorized into 1 of 4 levels: high, moderate, low, and very low (Table 2). The Evidence profiles were generated by use of the GRADEpro/GDT applications (https://gdt.guidelinedevelopment.org/app).

RESULTS

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

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

We performed an SRMA of RCTs among unselected patients. Unselected patients were defined by the authors of the source studies as those without specific risk factors for PEP. A search through March 25, 2021, yielded 738 citations, which were all screened by 2 independent reviewers (Appendix 1, available online at www.giejournal.org). Eighteen RCTs fulfilled the inclusion criteria and compared rectal nonsteroidal anti-inflammatory drugs with placebo in 4554 patients (Supplementary Table 1, available online at www.giejournal.org). Fourteen of the trials were fulltext publications, and the remainder were abstracts. The most frequently used NSAID was diclofenac (56%), followed by indomethacin, (36%), ketoprofen, (4%), and naproxen, (4%). The most frequent exclusion criteria for NSAID use were acute pancreatitis, NSAID allergy, renal insufficiency (ie, creatinine level >1.4 mg/dL), and active peptic ulcer disease. The consensus criteria were used to diagnose PEP in 14 of the studies, limiting the ability to perform subanalyses addressing diagnostic criteria.⁶

Risk of PEP

On the basis of the random-effects model, prophylactic rectal NSAIDs were associated with significantly lower odds of the development of PEP in unselected patients when compared with placebo (OR, 0.49; 95% CI, 0.37-0.65; $I^2 = 38.6\%$) (Fig. 1; Supplementary Fig. 1A, available online at www.giejournal.org). There was no significant difference in postsphincterotomy bleeding (OR, 1.68; 95% CI, 0.50-5.68; $I^2 = 39\%$) (Supplementary Figs. 1B, 2A, available online at www.giejournal.org). No renal failure occurred in either group.

Risk of moderately severe to severe PEP

Prophylactic rectal NSAIDs were associated with a statistically nonsignificant trend toward lower occurrence of moderately severe and severe pancreatitis (OR, 0.47; 95% CI, 0.21-1.06; P = -.52; $I^2 = 0$) (Supplementary Figs. 1C, 2B, available online at www.giejournal.org). In most of the studies, severity was graded by the consensus criteria (Supplementary Table 1).

Sensitivity analyses

Rectal NSAIDs remained protective in subanalysis restricting to full-text documents (Supplementary Fig. 3A, available online at www.giejournal.org). NSAIDs were given before ERCP in all but 3 studies. Stratified meta-analysis revealed that NSAIDs remained protective regardless of exact timing (≥30 minutes vs <30 minutes before ERCP or intraprocedure) and type of NSAID (indomethacin, diclofenac) (Supplementary Table 1, Supplementary Fig. 3B, C, D, and E). Dose-response analysis was limited, given that only 2 studies used a dose >100 mg and 4 studies used a



OR of Post ERCP Pancreatitis with Prophylactic Rectal NSAIDs in Unselected Patients

Figure 1. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients. *CI*, Confidence interval; *NSAIDs*, nonsteroidal antiinflammatory drugs; *OR*, odds ratio.

dose <100 mg; a subanalyses of studies that used only a specific 100-mg dose revealed consistent results (Supplementary Fig. 3F).

Certainty in the evidence

For the main outcome of PEP, there was a nonserious risk of bias (Table 3). The included studies concealed allocation and followed proper random sequence generation; furthermore, funnel plots were symmetric, indicating an absence of serious publication bias (Supplementary Fig. 1A, 4, available online at www.giejournal.org). The certainty was downgraded to moderate, given the inconsistency suggested by the high I^2 (Fig. 1). Whereas the I^2 was low for renal insufficiency and bleeding, the certainty was downgraded to moderate for imprecision indicated by wide confidence intervals (Supplementary Figs. 1C, 5A, 2B, 5B, available online at www.giejournal.org). The certainty

for the outcome of moderately severe and severe PEP was low, given the wide confidence intervals and asymmetric funnel plot (Supplementary Figs. 1A, 2A) suggesting possible publication bias.

Other considerations

Cost-effectiveness analyses indicate that for average-risk patients, the incremental cost per quality-adjusted life year (QALY) was \$33,812/QALY, which was significantly less than the willingness-to-pay threshold of \$100,000/QALY.⁷ Over the past 15 years, the approximate wholesale acquisition cost of rectal indomethacin has increased from \$2 in 2005 to \$340 in 2019.⁸ Nevertheless, a sensitivity analysis indicates that rectal indomethacin would remain cost effective for prophylaxis of PEP in an average-risk patient to the threshold of \$1134.⁷ NSAIDs that are not available as rectal formulations on the market, however, may be

TABLE 3. Evidence profile for population, intervention, comparator, outcomes 1: rectal NSAIDs versus placebo to prevent PEP in unselected patients

		Cer	tainty assessm	ent			No. of	patients	Ef	fect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal NSAIDs	None	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Overall rate of PEP												
18	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	167/2288 (7.3%)	306/2272 (13.5%)	OR 0.50 (0.30 to 0.83)	62 fewer per 1000 (from 90 fewer to 20 fewer)	⊕⊕⊕⊖ Moderate	Critical
Moderately sever	re and severe	PEP										
8	Randomized trials	Not serious	Not serious	Not serious	Serious†	Publication bias strongly suspected‡	8/1577 (0.5%)	24/1569 (1.5%)	OR 0.5 (0.2 to 1.1)	8 fewer per 1000 (from 12 fewer to 2 more)	⊕⊕⊖⊖ Low	Critical
Renal insufficient	cy											
18	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	0/2288 0.0%)	0/2272 (0.0%)	Not estimable		⊕⊕⊕⊖ Moderate	Critical
Bleeding (define)	1											
18	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	15/2288 (0.7%)	9/2272 (0.4%)	OR 1.7 (0.5 to 5.7)	3 more per 1000 (from 2 fewer to 18 more)	⊕⊕⊕⊖ Moderate	Critical

CI, Confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PEP, post-ERCP pancreatitis.

*High I².

+Low number of events.

‡Funnel plot,

formulated from oral medications by compounding pharmacies at significantly lower cost. In regard to patient preferences, there is little published information. Patient representatives on the guideline panel viewed rectal NSAIDs favorably.

Discussion

NSAIDs are potent inhibitors of prostaglandin synthesis and phospholipase A2 activity.^{9,10} The cardinal role of these mediators in the pancreatitis inflammatory cascade is the basis for the use of NSAIDs to prevent PEP. Although they were originally trialed for high-risk patients undergoing pancreatography or sphincter of Oddi evaluation, the low cost and favorable risk profile of NSAIDs has led to their use in unselected patients.¹¹ Although the initial studies of rectal indomethacin to prevent PEP for unselected patients had favorable results, several trials, including the doubleblind trial by Levenick et al,¹⁴ did not show a significant benefit.¹²⁻¹⁴ Additionally, NSAID administration by nonrectal routes such as intramuscular or intravenous administration does not reliably confer a protective effect.¹⁵⁻¹⁷

Nevertheless, a meta-analysis of the 18 randomized trials on the topic indicates a decrease in the overall risk of PEP in unselected patients. These results are in agreement with those from a trial of 2600 patients randomized to universal preprocedure indomethacin versus risk-stratified postprocedure indomethacin by Luo et al.¹⁸ In this trial the rate of PEP in unselected patients given preprocedure indomethacin was 4% compared with 8% in patients who received only postprocedure indomethacin if stratified to have higher risk. The risk of PEP with universal preprocedure NSAIDs was significantly lower in both high-risk patients—6% versus 12% (P = .0057)—and those at average risk: 3% versus 6% (P = .0003).

Given that the overall incidence of PEP in the control group of RCTs of unselected patients was 9.7% (95% CI, 8.6%-10.7%) and mortality was 0.7% (95% CI, 0.5%-0.9%), the panel recognized that the benefit of prevention is high. Inasmuch as rectal indomethacin does confer a protective effect in unselected patients and is cost effective, feasible, and associated with only minimal discomfort and adverse effects, the GRADE panel recommended its use in this population.

Nevertheless, the efficacy of NSAIDs in the prevention of moderate and severe pancreatitis was not statistically significant in the systematic review of the literature. This may be a consequence of the rarity of this event and the principle that the studies were not powered to detect more severe PEP. Similarly, there was no difference in adverse events, including postsphincterotomy bleeding, although the rarity of these events similarly diminished the power to detect differences.

Additionally, the panel recognized that the source studies excluded many patients, including those with ongoing NSAID use, abnormal renal function, aspirin or NSAID allergy, and a history of peptic ulcer disease, which are features common in the adult population. The inclusion criteria also varied, with most studies excluding patients undergoing ERCP for "very low risk" indications such as biliary stent exchange. Interestingly, these patients were included in the negative study by Levenick et al.¹⁴ Hence, studies are needed to specifically measure the impact of NSAIDs in patients at low risk for PEP.

Overall, rectal NSAID use is associated with a 50% relative reduction in the rate of PEP and is therefore recommended for all patients undergoing ERCP unless there is a contraindication such as renal insufficiency or active peptic ulcer disease. This also assumes that the price will not exceed the threshold of cost effectiveness.

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

Recommendation 2: For high-risk patients undergoing ERCP, the ASGE recommends that periprocedural rectal NSAIDs be given to prevent post-ERCP pancreatitis (*strong recommendation/moderate quality of evidence*).

A systematic review and meta-analysis were performed to address the main outcomes of interest for this clinical question and including PEP, moderately severe or severe PEP, postsphincterotomy bleeding, and acute renal failure in populations that were defined by the authors of the RCTs as high risk for PEP (Supplementary Table 2). After a systematic literature search (Appendix 1), 270 manuscripts and conference abstracts were screened by 2 investigators (J.S., A.C.). We identified 10 RCTs comparing NSAIDs with placebo in 2006 patients. One trial included 2 randomized comparisons in which patients in both the NSAID and control groups were given either normal saline solution or lactated Ringer's solution.¹⁹ Two trials of rectal NSAIDs in unselected patients presented a subgroup analysis reporting the risk of PEP specifically for high-risk subgroups.^{20,21} The designation of high risk was based on the authors' definition of their study population. The earlier published trials predominantly enrolled patients with suspected sphincter of Oddi dysfunction, whereas difficult cannulation was the more common indication among recent studies (Supplementary Table 2, available online at www.giejournal.org). All but 1 study used a 100mg dose of rectal diclofenac or indomethacin.

Risk of PEP

Based on the random-effects model, there was a significant reduction in post-ERCP pancreatitis in high-risk patients treated with rectal NSAIDs compared with placebo (OR, 0.50; 95% CI, 0.30-0.83; $I^2 = 56.6\%$) (Fig. 2; Supplementary Fig. 6A, available online at www.giejournal.org). There were no significant differences in renal failure (OR, 0.63; 95% CI, 0.12-3.29; $I^2 = 0$) (Supplementary Fig. 5B) or postsphincter-

otomy bleeding (OR, 0.82; 95% CI, 0.40-1.65; $I^2 = 0$) (Supplementary Fig. 6B).

Risk of moderately severe and severe PEP

There was a statistically nonsignificant trend toward reduction in the odds of moderately severe/severe post-ERCP pancreatitis (OR, 0.53; 95% CI, 0.27-1.05; P = .035; $I^2 = 10.7\%$) (Supplementary Fig. 6C).

Sensitivity analyses

Exclusion of the studies that used a lower dose did not have an impact on the results (Supplementary Table 3, Supplementary Fig. 7A, available online at www. giejournal.org). Similarly, exclusion of the 1 study that was published only as an abstract did not alter the findings (Supplementary Fig. 7B). There was a trend (not statistically significant) toward protection whether given before or after ERCP (Supplementary Fig. 7C and D). Whereas subanalyses restricted to indomethacin demonstrated significant protection in high-risk patients, a statistically significant protective effect was not found in studies restricted to diclofenac (Supplementary Fig. 7E and F).

Certainty in the evidence

The randomized trials used to inform this question used random sequence generation and concealed allocation (Supplementary Fig. 8, available online at www. giejournal.org). Funnel plots were symmetric, and the trials appeared to be low risk for detection and attrition bias (Supplementary Fig. 5C and D). Certainty for the main outcome of PEP was rated down to moderate for imprecision, given an $I^2 = 59\%$ (Table 4). For the outcome of moderately severe/severe pancreatitis, postsphincterotomy bleeding, and renal failure, the certainty was also rated as moderate, given the imprecision suggested by wide confidence intervals.

Other considerations

Analyses revealed that for high-risk patients, rectal NSAIDs were cost effective. Sensitivity analyses indicated that rectal NSAIDs remained cost effective for high-risk patients to a threshold of \$6069 per suppository. The patient representatives on the panel expressed that rectal NSAIDs were a favorable prophylactic strategy.

Discussion

In randomized trials of patients with risk factors for PEP, the prevalence of PEP in control groups was 14.7% (95% CI, 8.6%-10.7%), with moderate and severe disease occurring in 3.9% (95% CI, 2.6%-5.3%) and 0.4% (95% CI, 0.2%-0.6%), respectively.¹ A systematic review of randomized trials indicates a 2-fold reduction in PEP, and given its association with prolonged hospitalization, morbidity, and mortality, this represents a substantial health benefit. Rectal NSAIDs are strongly favored in high-risk patients



OR of Post ERCP Pancreatitis in High Risk Patients with Prophylactic NSAIDs

Figure 2. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients. CI, Confidence interval; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

because of their moderate cost, simplicity of placement, and association with minimal inconvenience.

Nevertheless, the panel recognized several topics that merit further consideration and future research.

The definition of high risk has continued to evolve with evidence-based practice patterns and technology. Female gender, age <40 years, and normal bilirubin are predictors of PEP.²² However, inasmuch as practice patterns increasingly reflect the recognition that ERCP for suspected sphincter of Oddi dysfunction (SOD) is a suboptimal indication, the primacy of these factors is less clear.²³⁻²⁵ Increasingly, trauma associated with prolonged cannulation attempts, repeated deep pancreatic guidewire passage, and pancreatic injection are associated with PEP.²⁶ Precut sphincterotomy is less strongly associated with PEP if performed early, suggesting that its role as a risk factor may in part be as a surrogate of prolonged cannulation.²⁷ Fully covered self-expanding metal biliary stents, which expand treatment options for benign biliary disease, may be associated with increased PEP.²⁸ Hence, the highrisk population in which rectal NSAIDs show the greatest

benefit (ie, sphincter of Oddi dysfunction) may not fully reflect contemporary clinical practice.^{11,29} The observed heterogeneity in the main outcome may be related to differences in the definition of the high-risk population (ie, SOD predominant enrollment in some studies vs difficult cannulation in others).

Additionally, in most trials of NSAIDs to prevent PEP, pancreatic duct (PD) stents were used in an uncontrolled manner at the discretion of the endoscopist. In the largest trial of NSAIDs in post-ERCP pancreatitis by Elmunzer et al,²⁹ PD stents were placed in >80% of patients in both groups. Therefore, the true efficacy of NSAIDs alone (ie, discrete from PD stent) to prevent PEP is unclear. Given that PEP results at least in part from physical trauma to the duct, it is controversial whether pharmacologic therapy such as NSAIDs alone may be as effective as strategies involving physical duct decompression by use of a stent. The 2 randomized trials that directly compared NSAIDs plus pancreatic stents versus NSAIDs without PD stents were underpowered to detect a difference or noninferiority.^{30,31} An ongoing multicenter randomized controlled

TABLE 4.	Evidence profile fo	r population,	intervention,	comparator,	outcomes	2: rectal	NSAIDs [•]	versus p	olacebo to	prevent P	EP in high	-risk
patients												

			Certainty ass	sessment			No. of	patients	Ef	fect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal NSAIDs	None	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Overall P	EP											
10	Randomized trials	Not serious	Serious*	Not serious	Not serious	None	80/1008 (7.9%)	152/1022 (14.9%)	OR 0.50 (0.30 to 0.83)	68 fewer per 1000 (from 99 fewer to 22 fewer)	⊕⊕⊕⊖ Moderate	Critical
Moderate	ly severe and s	evere PEP										
9	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	21/998 (2.1%)	46/1017 (4.5%)	OR 0.5 (0.2 to 1.0)	22 fewer per 1000 (from 36 fewer to 0 fewer)	⊕⊕⊕⊖ Moderate	Critical
Renal ins	ufficiency											
10	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	2/1008 (0.2%)	4/1022 (0.4%)	OR 0.6 (0.1 to 3.3)	2 fewer per 1000 (from 4 fewer to 9 more)	⊕⊕⊕⊖ Moderate	Critical
Bleeding												
10	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	15/1008 (1.5%)	19/1022 (1.9%)	OR 0.8 (0.4 to 1.7)	4 fewer per 1000 (from 11 fewer to 13 more)	⊕⊕⊕⊖ Moderate	Critical

CI, Confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PEP, post-ERCP pancreatitis.

*High *l*².

+Low number of events.

trial of stents and rectal indomethacin versus indomethacin alone in high-risk patients aims to address this question.³²

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

Recommendation 3: In unselected patients undergoing ERCP, the ASGE suggests wire-guided cannulation over contrast-guided cannulation to minimize the risk of post-ERCP pancreatitis (*conditional recommendation/moderate quality of evidence*).

We used an existing Cochrane meta-analysis on this topic by Tse et al,⁴ which was updated in parallel with the development of this guideline. The authors systematically reviewed the literature from inception through February 26, 2021, and identified 15 RCTs reporting on 4426 patients assigned to guidewire-assisted versus contrast-guided cannulation. Whereas contrast-guided ERCP was defined as a procedure in which contrast material was injected at the level of the papilla followed by introduction of the wire, guidewireassisted ERCP had a more heterogeneous definition.³³ Wire-guided cannulation includes 2 techniques: a) the guidewire leads and is then followed by the cannulating catheter; and b) the cannulating catheter is first advanced into a duct followed by a guidewire to confirm the desired duct (pancreatic vs biliary).

Risk of PEP

A meta-analysis of 15 studies demonstrated that the wire-guided technique significantly reduced PEP compared with contrast-guided access (relative risk [RR], 0.5; 95% CI, 0.36-0.72; $I^2 = 36\%$) (Fig. 3). The unweighted pooled rate of PEP in the wire-guided group was 3.7% versus 7.7% in the contrast-guided group. There was no difference in postsphincterotomy bleeding (RR, 0.87; 95% CI, 0.49-1.54; $I^2 = 0\%$) (Supplementary Fig. 9, available online at www.giejournal.org) or perforation (RR, 0.93; 95% CI, 0.11-8.23; $I^2 = 46\%$) (Supplementary Fig. 10, available online at www.giejournal.org).

Risk of moderate and severe PEP

There was a significant reduction in mild PEP with the wire-guided approach (RR, 0.47; 95% CI, 0.26-0.83; $I^2 =$ 49%) but no reduction in moderate PEP (RR, 0.76; 95% CI, 0.38-1.52; $I^2 = 0\%$) (Supplementary Fig. 11, available online at www.giejournal.org) or severe PEP (RR, 0.69; 95% CI, 0.27-1.81; $I^2 = 0\%$) (Supplementary Fig. 12, available online at www.giejournal.org). Sensitivity and subgroup analyses

The authors stratified the main analysis by whether studies permitted a PD duct stent. Although there was significantly reduced PEP for the wire-guided approach among trials that did not permit the use of a PD stent (RR, 0.24; 95% CI, 0.13-0.47; $I^2 = 0\%$), there was no

GW		С			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Apostolopoulos 2005	1	67	6	63	2.4%	0.16 [0.02 , 1.27]	
Artifon 2007	5	150	18	150	7.9%	0.28 [0.11 , 0.73]	
Bailey 2008	16	215	13	215	11.0%	1.23 [0.61 , 2.50]	_ _ _
Gruchy 2007	4	241	6	135	5.6%	0.37 [0.11 , 1.30]	_ _
Katsinelos 2008	9	167	13	165	9.5%	0.68 [0.30 , 1.56]	
Kawakami 2012	8	199	6	201	7.2%	1.35 [0.48 , 3.81]	_ _ _
Kobayashi 2013	10	163	10	159	9.1%	0.98 [0.42 , 2.28]	
Lee 2009	3	150	17	150	5.9%	0.18 [0.05 , 0.59]	
Lella 2004	0	200	8	200	1.4%	0.06 [0.00 , 1.01]	← →────
Mangiavillano 2007	2	100	6	100	3.9%	0.33 [0.07 , 1.61]	
Mangiavillano 2011	2	46	4	42	3.6%	0.46 [0.09 , 2.37]	
Masci 2015	8	160	19	160	9.8%	0.42 [0.19 , 0.93]	
Nambu 2011	2	86	5	86	3.8%	0.40 [0.08 , 2.01]	
Savadkoohi 2012	6	65	12	78	8.3%	0.60 [0.24 , 1.51]	_ _
Zhang 2007	12	342	16	171	10.7%	0.38 [0.18 , 0.77]	
Total (95% CI)		2351		2075	100.0%	0.51 [0.36 , 0.72]	•
Total events:	88		159				•
Heterogeneity: Tau ² = 0	0.15; Chi ² =	21.72, df	= 14 (P =	0.08); l ² =	= 36%		0.01 0.1 1 10
Test for overall effect: 2	Z = 3.81 (P =	= 0.0001)					Favors GW Favors C

Test for subgroup differences: Not applicable

Figure 3. Relative risk of post-ERCP pancreatitis with wire-guided cannulation. *CI*, Confidence interval. Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.

difference in PEP for wire-guided studies that permitted a PD stent (RR, 0.78; 95% CI, 0.52-1.18; $I^2 = 25\%$) (Supplementary Fig. 13, available online at www. giejournal.org).

We performed a subanalysis of studies identified in the systematic review stratifying by whether the investigators used a guidewire "leading" or "following" strategy (Supplementary Figs. 14A, B, available online at www. giejournal.org). Six studies used the guidewire-leading approach, 5 used the guidewire-following approach, and the remaining 4 used both or did not specify their approach. We found that the guidewire-following approach (RR, 0.29; 95% CI, 0.18-0.49; $I^2 = 0\%$) reduced PEP relative to contrast-guided ERCP, but the guidewire-leading approach did not (RR, 0.66; 95% CI, 0.39-1.13; $I^2 = 43\%$).

Certainty in the evidence

The certainty in the main outcome of PEP was rated down to moderate because of the serious risk of bias (Table 5, Supplementary Fig. 15, available online at www. giejournal.org). The latter was a consequence of the absence of blinding but also unclear random sequence generation and concealment of allocation in some studies (Supplementary Fig. 15). For the outcome of moderately severe and severe PEP, the certainty of evidence was low, given the serious risk of bias and inconsistency. Given the imprecision and serious risk of bias, the certainty of the outcomes of postsphincterotomy bleeding was low. The certainty of the outcome of perforation was very low, given the serious risk of bias, imprecision, and inconsistency.

Other considerations

Cost-effectiveness data are lacking for the comparison of wire versus contrast-guided access. Although some cost is incurred by using different wires and accessories such as locking devices, this cost is potentially offset by the greater cost of PEP with contrast-guided methods.³⁴ The patient representative had no strong opinions regarding discomfort or preference for wire-guided versus contrastguided cannulation but valued the reduced risk of PEP with the former strategy.

Discussion

Our updated Cochrane systematic review and metaanalysis indicates that wire-guided cannulation attenuates the risk of post-ERCP pancreatitis versus the contrastguided approach.⁴ It minimizes the risk associated with hydrostatic, chemical, and potential allergic injury associated

			Certainty asse	essment			No. o	f patients	E	ffect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Wire-guided cannulation	Contrast-guided cannulation	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Overall ra	te of PEP											
15	Randomized trials	Serious*	Not serious	Not serious	Not serious	None	88/2351 (3.7%)	159/2075 (7.7%)	RR 0.5 (0.4 to 0.7)	38 fewer per 1000 (from 46 fewer to 23 fewer)	⊕⊕⊕⊖ Moderate	Critical
Moderate	PEP											
12	Randomized trials	Serious*	Not serious	Not serious	Serious†	None	14/1999 (0.7%)	19/1820 (1.0%)	RR 0.8 (0.4 to 1.5)	2 fewer per 1000 (from 6 fewer to 5 more)		Critical
Severe PE	P											
12	Randomized trials	Serious*	Not serious	Not serious	Serious†	None	7/1999 (0.4%)	11/1820 (0.6%)	RR 0.7 (0.3 to 1.8)	2 fewer per 1000 (from 4 fewer to 5 more)		Critical
Bleeding												
7	Randomized trials	Serious*	Not serious	Not serious	Serious†	None	23/1117 (2.1%)	24/1005 (2.4%)	RR 0.9 (0.5 to 1.5)	2 fewer per 1000 (from 12 fewer to 12 more)		Critical
Perforatio	'n											
8	Randomized trials	Serious*	Serious	Not serious	Serious†	None	5/1316 (0.4%)	4/1206 (0.3%)	RR 0.9 (0.1 to 8.2)	0 fewer per 1000 (from 3 fewer to 24 more)		Critical

Cl, Confidence interval; PEP, post-ERCP pancreatitis; RR, risk ratio.

*Performance bias.

†Low number of events.

with the introduction of iodinated contrast material into the PD.³⁵ The risk associated with pancreatic injection accrues with the number, force, and volume of injection(s) as well as the anatomic extent of introduction (head versus tail).^{36,37} Given that wire-guided cannulation provides substantial health benefit and does not require appreciable cost or patient inconvenience, the panel felt that the balance of effects favor wire-guided versus contrast-guided cannulation.

Nevertheless, the panel qualified their recommendation as conditional given several concerns. Foremost, the approach to wire-guided cannulation among the individual RCTs was heterogenous. In 5 trials, the wire was passed through a cannulating catheter already positioned in a duct to confirm whether it was biliary or pancreatic.^{35,38-41} This minimized the need to inject contrast. In our subanalysis, this significantly reduced PEP relative to contrastguided approaches. In 6 trials the wire was first passed into the duct followed by the cannulating catheter (Supplementary Fig. 14).⁴²⁻⁴⁷ This approach uses the wire to help negotiate access into the duct of interest. In subanalysis this approach did not reduce the risk of PEP relative to contrast facilitated access. The panel expressed

concern that repeated wire introduction may be associated with post-ERCP pancreatitis.³⁷ Additionally, there is a risk of fistulation and traumatic injury with forceful and deep advancement of the guidewire into the PD.^{26,48} Direct interpretation of tactile feedback from wire advancement has been proposed to explain why endoscopist versus assistant-controlled cannulation reduced PEP in a randomized trial.⁴⁹ Additionally, in 4 of the trials, either both approaches were used or the methods were not specified.⁵⁰⁻⁵³ The benefit of wire-guided cannulation was not demonstrated among studies in which PD stents were used. Another concern was that nearly all these studies were carried out in expert centers. The panel recognized that the threshold to place a PD stent after inadvertent guidewire introduction into the PD is variable among endoscopists. Additionally, there are numerous variations in how these techniques are interpreted and performed among practitioners. To define the role of wire-guided cannulation more clearly, the specific technical approaches need to be more explicitly defined in future studies.

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



OR of Post ERCP Pancreatitis with Prophylactic Pancreatic Duct Stent

Figure 4A. Odds ratios of post-ERCP pancreatitis with prophylactic pancreatic duct stent. CI, Confidence interval; OR, odds ratio.

Recommendation 4:

- a) In patients undergoing ampullectomy, or if the PD is repeatedly or deeply accessed, the ASGE recommends PD stents to reduce the risk of post-ERCP pancreatitis (*strong recommendation/moderate quality of evidence*).
- b) Otherwise, in high-risk groups, including patients with difficult cannulation, history of PEP, or precut sphincterotomy, the ASGE suggests PD stent placement as long as PD access can be easily achieved (*conditional recommendation/moderate quality of evidence*).

To address this question, a de novo systematic review and meta-analysis of pancreatic stents to prevent PEP was performed. Our search yielded 1668 citations, of which 116 articles were selected for full text review. Seventeen randomized trials of prophylactic stents to prevent PEP in high-risk populations met the inclusion criteria and compared their use versus no stent in 2595 patients. Two of the studies included consecutive patients, but by the nature of the procedures (pancreatography and juice aspiration, pancreatic cytology) and the authors' assessment, they were composed of high-risk patients.^{54,55} Strategies to verify stent passage and remove PD stents varied. Imaging to confirm spontaneous passage was performed within 2 weeks, or endoscopy for assessment and removal within 4 weeks. The sizes and lengths of stents used also varied, although 5F stents were used in the great majority of studies, limiting the ability to perform stratified analyses.

Risk of PEP

Prophylactic PD stents significantly reduced the risk of PEP (OR, 0.35; 95% CI, 0.26-0.46; $I^2 = 14.6\%$) (Fig. 4A, Supplementary Fig. 16A, available online at www. giejournal.org). There was no difference in bleeding (OR, 0.94; 95% CI, 0.35-2.51; $I^2 = 31.1\%$) (Supplementary



OR of Moderately Severe/Severe PEP with Prophylactic Pancreatic Duct Stent

Figure 4B. Odds ratios of moderately severe/severe post-ERCP pancreatitis with prophylactic pancreatic duct stent. CI, Confidence interval; OR, odds ratio.

Figs. 17A, 16B, available online at www.giejournal.org), infection (OR, 0.61; 0.20-1.92; $I^2 = 0\%$) (Supplementary Figs. 17B, 16C), or perforation (OR, 1.30; 95% CI, 0.05-33.3; $I^2 = 56.7\%$) (Supplementary Figs. 17C, 16D). Prophylactic PD stent placement was successful in 97% (95% CI, 94-100; $I^2 = -74.9\%$) of procedures in which it was attempted (Supplementary Fig. 17D).

Risk of moderately severe and severe PEP

Prophylactic PD stent placements were also associated with a reduced risk of moderately severe PEP (OR, 0.38; 95% CI, 0.23-0.63; $I^2 = 0\%$) (Fig. 4B, Supplementary Fig. 16E) and severe pancreatitis (OR, 0.20; 95% CI, 0.06-0.66; $I^2 = 0\%$) (Fig. 4C, Supplementary Fig. 16F). Across the RCTs, 13 of 1303 patients (1%) treated without stents experienced moderate or severe PEP versus none of the 1292 patients treated with prophylactic PD stents.

Sensitivity and subgroup analyses

Several subanalyses were performed to address differences in patient population and technique.

Before 2005, studies of prophylactic PD stent placement include a high proportion of patients with SOD (Supplementary Table 4, available online at www. giejournal.org). More recently, trials of prophylactic PD stent placement have included few patients with SOD. A subanalysis excluding studies with majority SOD patients revealed that PD stents protected against PEP (Supplementary Fig. 18A, available online at www.giejournal.org). Additionally, in some studies prophylactic stents were 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 wire (Supplementary Table 5, available online at www.giejournal.org). PD stents reduced



OR of Severe Post ERCP Pancreatitis with Prophylactic Pancreatic Duct Stent

Figure 4C. Odds ratios of severe post-ERCP pancreatitis with prophylactic pancreatic duct stent. CI, Confidence interval; OR, odds ratio.

PEP both among patients in whom prophylactic stents represented an additional step (Supplementary Fig. 18B) and among cases in which it was used only after wire access had been achieved (Supplementary Fig. 18C).

A subanalysis excluding the 2 studies that technically enrolled "unselected patients" did not materially alter the results, with significant reduction of PEP with pancreatic stents in this subgroup (Supplementary Fig. 18D).

Certainty of Evidence

Although the included studies were randomized trials, there was a serious risk of bias, given the absence of blinding (performance bias) and asymmetric funnel plots (publication bias); therefore, we rated down the overall certainty of the main outcome of PEP prevention to moderate (Table 6; Supplementary Fig. 19, available online at www.giejournal.org). The other outcomes including

moderately severe/severe pancreatitis, severe pancreatitis, and adverse events were rated down to low certainty, given the serious risk of bias and the imprecision, given the wide confidence intervals (Table 6).

Other considerations

A recent cost-effectiveness analysis demonstrated that pancreatic stent placement is cost effective (Incremental Cost Effectiveness Ratio [ICER] = \$9316/quality-adjusted life year [QALY]).⁷ This concorded with an earlier cost-effectiveness study, which demonstrated an ICER of \$11, 766/year of life saved for high-risk patients.⁵⁶ The patient representatives reported value in the prevention of pancreatitis, especially severe PEP, although they acknowledged the inconvenience of subsequent radiography to evaluate stent migration and potentially upper endoscopy to remove the prophylactic stent.

		Certa	inty assessment			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Overall rate of PEP						
17	Randomized trials	Serious*	Not serious	Not serious	Not serious	None
Moderate and severe PEP						
17	Randomized trials	Serious*	Not serious	Not serious	Serious	None
Severe PEP		<u> </u>				
0	Randomized trials	Serious*	Not serious	Not serious	Serious†	None
Bleeding		<u> </u>	<u> </u>	<u> </u>	<u> </u>	
7	Randomized trials	Serious*	Not serious	Not serious	Serious†	None
Infection						
7	Randomized trials	Serious*	Not serious	Not serious	Serious†	None
Perforation						
7	Randomized trials	Serious*	Serious	Not serious	Serioust	None

Cl, Confidence interval; OR, odds ratio; PEP, post-ERCP pancreatitis; PD, pancreatic duct.

*Performance bias, possible publication bias.

[†]Low number of events

[‡]High /².

Discussion

In animal models, PD obstruction results in the intrapancreatic activation of digestive enzymes and subsequent local and systemic manifestation of pancreatitis.^{57,58} It is proposed that direct injury and edema related to accidental and intentional manipulation of the pancreatic orifice during ERCP results in transient duct obstruction and subsequently PEP. PD stents maintain a drainage route in the event that obstructive papillary edema results, and they enable consistent clearance of pancreatic enzymes and juice.^{59,60} Our systematic review and meta-analysis revealed a significant decrease in PEP without an increase in adverse events. The panel discussed that given the widely valued effect of PEP resuscitation with the low rate of adverse events, the balance of effects favored the intervention of prophylactic pancreatic stent placement. Although some cost was associated with stent placement and radiography/upper endoscopy for evaluation and removal, formal analysis indicated that PD stent placement is cost effective.

Additionally, the panel underscored that although NSAIDs (PICOS 1-2) and aggressive hydration (see PICO 5) also prevent PEP overall, only PD stent placement significantly reduced moderately severe and severe pancreatitis. Whereas this may reflect a very high baseline risk of patients treated with PD stents, these patients had similar features to high-risk cohorts in studies of NSAIDs. The effect remained significant in subanalysis excluding studies

primarily in SOD, a population who are at very high risk, and represents a diminishing component of patients undergoing ERCP.^{22,24} Furthermore, none of the 1292 patients randomized to PD stents experienced severe disease.

Nevertheless, although pancreatic stents reduce PEP, it is unclear specifically when and how they should be used. In some studies in our systematic review, PD stents were placed at the end of the procedure as an additional step, such as after ampullectomy.⁶¹ In other studies, a PD stent was used only after the PD had already been inadvertently accessed with the guidewire.⁶²⁻⁶⁴ In scenarios in which the PD has not already been accessed, intentional attempts to place a PD stent, especially if unsuccessful, may be associated with greater injury.^{65,66} We attempted to address this concern by using a subgroup analysis of trials that used PD stent placement as an additional step or done only in patients who had an existing pancreatic guidewire in place. On the basis of limited information, both approaches appeared protective. Nevertheless, there was concern about intentionally seeking out the PD to place a stent in scenarios in which PD access is not otherwise needed. Given the need to better define the specific timing and approach to stent placement, the panel qualified the recommendation as conditional. This was balanced by concern about an increasing risk of pancreatitis with repeated or deep PD access.^{48,62} In the latter scenario, the panel strongly recommended PD stents, given

TABLE 6. Continue	d				
No. of	patients		Effect		
PD stent	None	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
		· · · · · · · · · · · · · · · · · · ·			
98/1284 (7.6%)	247/1291 (19.1%)	OR 0.4 (0.3 to 0.5)	105 fewer per 1000 (from 125 fewer to 86 fewer)	$ \bigoplus \bigoplus \bigoplus \bigcirc \bigcirc \\ Moderate $	Critical
24/1284 (1.9%)	63/1291 (4.9%)	OR 0.4 (0.2 to 0.6)	29 fewer per 1000 (from 39 fewer to 19 fewer)	⊕⊕⊖⊖ Low	Critical
0/963 (0.0%)	10/980 (1.0%)	OR 0.25 (0.10 to 0.80)	8 fewer per 1000 (from 9 fewer to 2 fewer)	⊕⊕⊖⊖ Low	Critical
5/782 (0.6%)	8/781 (1.0%)	OR 0.9 (0.3 to 2.5)	1 fewer per 1000 (from 7 fewer to 15 more)	⊕⊕⊖⊖ Low	Critical
20/782 (2.6%)	18/781 (2.3%)	OR 0.6 (0.2 to 1.9)	9 fewer per 1000 (from 18 fewer to 20 more)	⊕⊕⊖⊖ Low	Critical
3/782 (0.4%)	2/781 (0.3%)	OR 1.2 (0.0 to 37.0)	1 more per 1000 (from – to 84 more)	⊕○○○ Very low	Important

the compelling efficacy and minimal downside. The technical strategies used in the source studies were often not explicitly defined, and trials are needed to inform this concern.⁵⁹

Given that most randomized trials of pancreatic stent versus no stent to prevent PEP used 5F stents, our systematic review did not address this concern. However, the results of a prior network meta-analysis favor 5F vis-à-vis 3F stents.⁶⁷ In situations in which the wire cannot pass beyond the head of the pancreas, the panel thought that a short stent was favored. Nevertheless, they recognized that very early migration or removal affords little protection from PEP.68,69 The optimal timing of imaging (or endoscopy) to evaluate stent migration is also needed. Whereas the evidence supports investigation within 2 weeks, several endoscopists on the panel routinely investigate PD stents during subsequent ERCP for biliary stent evaluation. However, to avoid injury to the PD from the stent, this should be done within a relatively short period of weeks. The efficacy and impact of pancreatic stents is also not well defined in the pediatric population.⁷⁰ Additionally, as described in the discussion for PICO 2, the definition of high risk for PEP has changed as novel research and technology have influenced practice patterns. Therefore, the population most likely to benefit from prophylactic pancreatic stents needs to be reappraised over time.

A final consideration is that pancreatic stents are used in <10% of high-risk cases despite compelling evidence of their efficacy.^{71,72} The reluctance to use pancreatic stents may result from concern for failure or apprehension regarding cost and repeated procedures. The decreased use of pancreatic stents approximates the increased use of NSAIDs.^{71,73} Furthermore, neither intervention is used in a substantial portion of patients undergoing high-risk ERCP, and the overall rate of PEP, mortality, and need for hospitalization for PEP appears to be rising.^{71,73} The data in this systematic review of the literature, including 97% success of placement and compelling reduction in PEP of all levels of severity, underscore that the real-world use in appropriately skilled hands must be increased.

Question 5: In unselected patients undergoing ERCP, is aggressive peri- and post-procedural intravenous hydration favored to prevent PEP?

Response 5: In unselected patients undergoing ERCP, the ASGE suggests aggressive peri- and post-procedural intravenous hydration to prevent post-ERCP pancreatitis (*conditional recommendation/moderate quality of evidence*).

To address this clinical question, we performed an SRMA of RCTs that compared aggressive versus standard fluids to prevent PEP. The search yielded 584 citations and abstracts, which were screened by 2 reviewers. After evaluation of 46 full-text articles, 12 RCTs were identified that met the inclusion criterion, comparing 3400 patients treated with aggressive versus standard hydration. One trial included 2 randomized comparisons in which patients were given either aggressive resuscitation with lactated Ringer's solution or normal saline solution. In most trials, aggressive hydration was defined as a bolus of 20 mL/kg



OR of Post ERCP Pancreatitis with Aggressive vs Standard Hydration

Figure 5. Odds ratios of post-ERCP pancreatitis with aggressive hydration. CI, Confidence interval; OR, odds ratio.

of fluid followed by a rate of 3 mL/kg and standard hydration as no bolus and a rate of 1.5 mL/kg after the procedure.

Risk of PEP

Aggressive hydration significantly reduced the overall risk of PEP (OR, 0.47; 95% CI, 0.34-0.66; $I^2 = 26.3\%$) (Fig. 5; Supplementary Fig. 20A, available online at www. giejournal.org). There was no difference in the risk of volume overload between the 2 groups (OR, 1.14; 95% CI, 0.49-2.67; $I^2 = 0\%$) (Supplementary Figs. 20B, 21A, available online at www.giejournal.org).

Risk of severe PEP

There was no significant difference in moderately severe or severe pancreatitis with aggressive hydration (OR, 0.60; 95% CI, 0.34-1.08; P = .36; $I^2 = 9.0$) (Supplementary Figs. 20C, 21B, available online at www.giejournal.org).

Sensitivity and subgroup analyses

Eight trials were published as full-text manuscripts. Exclusion of the abstracts did not alter the results (Supplementary Fig. 22A, Supplementary Table 6, available online at www. giejournal.org). All but 2 small trials required the presence of a native papilla for inclusion. Exclusion of these trials did not alter the protective effect of aggressive hydration for PEP in subanalysis (Supplementary Fig. 22B, available online at www.giejournal.org). Most of the trials used a bolus followed by an 8-hour infusion; however, 1 study used a 2.5hour protocol, and another used a 24-hour infusion (Supplementary Table 7, available online at www.giejournal. org).^{74,75} Exclusion of these 2 trials did not materially affect the main outcome (Supplementary Fig. 22C).^{74,75} Two of the studies treated patients in both aggressive and moderate hydration groups with rectal NSAIDs; a subanalysis excluding the trials did not materially alter the primary outcome (Supplementary Fig. 22D).

			Certainty as	sessment			No. of p	atients	Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aggressive IV hydration	Standard IV hydration	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Overall r	ate of PEP											
13	Randomized trials	Serious†	Not serious	Not serious	Not serious	None	96/1755 (5.5%)	188/1769 (10.6%)	OR 0.5 (0.4 to 0.8)	50 fewer per 1000 (from 61 fewer to 19 fewer)	⊕⊕⊕⊖ Moderate	Critical
Moderate	e and severe P	ΈP										
10	Randomized trials	Serious*	Not serious	Not serious	Serious†	None	32/1546 (2.1%)	54/1562 (3.5%)	OR 0.6 (0.3 to 1.2)	14 fewer per 1000 (from 24 fewer to 7 more)	⊕⊕⊖⊖ Low	Critical
Volume	overload											
9	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	12/1273 (0.9%)	10/1286 (0.8%)	OR 1.5 (0.3 to 9.0)	4 more per 1000 (from 5 fewer to 58 more)	⊕⊕⊕⊖ Moderate	Critical

Cl, Confidence interval; IV, intravenous; OR, odds ratio; PEP, post-ERCP pancreatitis.

*Lack of blinding.

†Low number of events

Certainty of evidence

Although the studies were randomized, there was a serious risk of bias, given that the studies were not blinded and some asymmetry was noted in the funnel plot; therefore, the certainty for the main outcome was rated down to moderate (Table 7; Supplementary Fig. 23, available online at www.giejournal.org). Given the serious risk of bias and also of imprecision, suggested by wide confidence intervals, the certainty of evidence for the other outcomes was low.

Other considerations

Recent cost-effectiveness studies indicate that for average-risk patients the ICER/QALY was \$139,004, which exceeds the 2020 threshold of \$100,000. Although aggressive hydration was not cost effective for average-risk patients, it was cost effective for high-risk patients with ICER/QALY of \$28,002. The patient representative on the panel valued the reduction in post-ERCP pancreatitis but expressed a preference to avoid increased length of hospitalization.

Discussion

Aggressive hydration is recommended for the management of acute pancreatitis in general, given cohort studies correlating adequate systemic hydration with reduced necrosis, organ failure, and mortality.⁷⁶⁻⁷⁸ Given the high incidence of pancreatitis after ERCP, prophylactic administration of fluids was proposed as a preventative measure.^{79,80} Our systematic review and meta-analysis demonstrated that aggressive hydration reduced the incidence of PEP relative

to standard hydration without significant risk of increased volume overload. The panel discussed that there is a substantial desirable effect of reduced PEP without increased adverse events. The patient advocate expressed value in PEP reduction. An additional advantage is that intravenous fluids are inexpensive and widely available, whereas rectal NSAIDs cannot be obtained in many countries, and pancreatic stent placement may necessitate repeated radiography or endoscopic procedures.⁷⁴

Nevertheless, in terms of resource utilization, it is unclear whether aggressive hydration is cost effective, and the patient advocate was concerned about increased hospital stay.

In the recent analysis by Thiruvengadam et al,⁷ aggressive hydration was cost effective for high-risk but not average-risk patients undergoing ERCP. Although the SRMA technically enrolled unselected patients, the predefined inclusion criteria for nearly all trials included the presence of a native papilla. The requirement for firsttime cannulation increased the risk level of these procedures to moderate or high.⁸¹ Additionally, the recent costeffectiveness analysis assumed that aggressive hydration required an additional 24-hour stay for fluid administration, which was the dominant cost in the models.⁷ However, only 1 of the trials of fluids to prevent PEP mandated a fluid protocol requiring greater than 8 hours.⁷⁴ Additionally, several studies were restricted to inpatients; thus, the assumption that prophylactic aggressive hydration required a 24-hour hospital stay may not apply. For outpatients a more practical approach may be to administer more fluid over a shorter 2- to 3-hour period, as used in the trial by Brown et al.⁷⁵

Another pertinent consideration is the role of aggressive fluids in the setting of concomitant rectal NSAIDs. In a recent multicenter randomized trial, aggressive hydration did not significantly reduce PEP among patients receiving prophylactic rectal NSAIDs.⁸¹ However, the sample size calculation assumed the same degree of PEP reduction for fluids added to NSAIDs as for NSAIDs versus placebo. A smaller incremental effect might be more likely for a treatment added to a proven therapy. Additionally, patients in the moderate arm received substantial intravenous fluids. Aggressive hydration was also associated with a trend toward less moderately severe/severe pancreatitis. In a small study, the combination of rectal indomethacin and 3 L of intravenous fluids was associated with a lower rate of PEP than rectal indomethacin without any fluids.⁸² Additional studies of aggressive hydration with concomitant rectal NSAIDs as well as other combinations for PEP prophylaxis are needed.

Given the uncertainty regarding cost effectiveness and the role of fluids in the context of widespread rectal NSAID use, the GRADE panel qualified the recommendation as conditional. Whereas aggressive hydration may be easily implemented in the care of inpatients, its role for outpatients is undefined. It is less feasible in patients at low risk for PEP, given the associated cost, patient value, and operational challenges associated with prolonged recovery. However, outpatients with significant baseline and procedural risk factors for PEP likely benefit from PEP, although additional study regarding the timing and amount of fluid administration is needed.

HEALTH DISPARITIES AND EQUITY

The panel addressed health equity and feasibility for each of the PICOs. It was acknowledged that many patients have reduced access to high-quality medical care and specific medications and therapies. Members of the panel addressed the fact that in several countries, rectal NSAIDs are not available. In these scenarios, aggressive hydration may be of particular importance. Additionally, the availability of and technical expertise with wire-guided cannulation and pancreatic stents may be greater at tertiary centers than in community health centers. Recent work suggests that the clinical characteristics associated with increased PEP risk vary by race.⁸³ For example, low body weight is associated with post-ERCP pancreatitis in African American men. Further definition of these specific risk factors has implications for the use of preventative measures in specific populations.

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

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; ERCP, endoscopic retrograde cholangiopancreatography; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICER, incremental cost-effectiveness ratio; NSAIDS, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PD, pancreatic duct; PEP, post-ERCP pancreatitis; QALY, quality-adjusted life year; RCT, randomized controlled trial; RR, risk ratio; [RR], relative risk; SOD, sphincter of Oddi dysfunction; SOP, standards of practice; SRMA, systematic review and meta-analysis.

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APPENDIX 1. PREVENTION OF POST-ERCP PANCREATITIS SEARCH STRATEGIES

Search strategies for population, intervention, comparator, and outcomes (PICOs) questions 1 and 2: NSAIDs Ovid MEDLINE ALL

Database: Ovid MEDLINE ALL Search Date: March 25, 2021

Number of Results: 147

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP.tw,kf. or exp cholangiopancreatography, endoscopic retrograde/
- 2. (endoscop* adj2 retrograd* adj2 (cholangiopancreatograph* or cholangio-pancreatograph*)).tw,kf.
- 3. exp Sphincterotomy, Endoscopic/
- 4. ((endoscop* adj3 sphincterotom*) or EST).tw,kf.
- 5. papillotom*.tw,kf. or exp papillotomy/
- 6. rendezvous.tw,kf.
- 7. or/1-6

NSAIDs

- 8. (non steroid\$ antiinflammatory agent\$ or non steroid\$ anti inflammatory agent\$ or nsaid\$).tw,kf. or exp Anti-Inflammatory Agents, Non-Steroidal/ or Anti-Inflammatory Agents, Non-Steroidal.nm.
- 9. (indomethacin* or indometacin*).tw,kf. or exp Indomethacin/
- 10. diclofenac*.tw,kf.
- 11. naproxen*.tw,kf.
- 12. (lornoxicam* or chlortenoxicam*).tw,kf.
- 13. Parecoxib*.tw,kf.
- 14. or/8-13

Post-ERCP Pancreatitis

- 15. pancreatitis.tw,kf. or exp pancreatitis/
- 16. 7 and 14 and 15

Randomized Controlled Trials/Humans

- 17. randomized controlled trial.pt.
- 18. controlled clinical trial.pt.
- 19. random*.mp.
- 20. trial.ab.
- 21. groups.ab.
- 22. or/17-21
- 23. 16 and 22
- 24. exp animals/ not humans/
- 25. 23 not 24
- 26. Limit 25 to English language

Embase

Database: Embase.com

Search Date: March 25, 2021

Number of Results: 314

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP:ti,ab,kw OR 'endoscopic retrograde cholangiopancreatography'/exp
- 2. (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)):ti,ab,kw
- 3. 'endoscopic sphincterotomy'/exp
- 4. ((endoscop* NEAR/3 sphincterotom*) OR EST):ti,ab,kw
- 5. papillotom*:ti,ab,kw OR 'endoscopic papillotomy'/ exp
- 6. rendezvous:ti,ab,kw
- 7. #1 OR #2 OR #3 OR #4 OR #5 OR #6

NSAIDs

- 8. (non steroid\$ antiinflammatory agent\$ OR non steroid\$ anti inflammatory agent\$ OR nsaid\$):ti,ab,kw OR 'nonsteroid antiinflammatory agent'/exp OR "Anti-Inflammatory Agents, Non-Steroidal":tn
- 9. (indomethacin* OR indomethacin):ti,ab,kw OR 'indometacin'/exp
- 10. diclofenac*:ti,ab,kw
- 11. naproxen*:ti,ab,kw
- 12. (lornoxicam* OR chlortenoxicam*):ti,ab,kw
- 13. Parecoxib*:ti,ab,kw
- 14. #8 OR #9 OR #10 OR #11 OR #12 OR #13

Post-ERCP Pancreatitis

- 15. Pancreatitis:ti,ab,kw OR 'pancreatitis'/exp
- 16. #7 AND #14 AND #15

Randomized Controlled Trials/Humans

- 17. 'randomized controlled trial'/de
- 18. 'controlled clinical trial'/de
- 19. random*:ti,ab,tt
- 20. 'randomization'/de
- 21. 'intermethod comparison'/de
- 22. placebo:ti,ab,tt
- 23. (compare:ti,tt OR compared:ti,tt OR comparison: ti,tt)
- 24. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
- 25. (open NEXT/1 label):ti,ab,tt
- 26. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
- 27. 'double blind procedure'/de
- 28. (parallel NEXT/1 group*):ti,ab,tt
- 29. (crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
- 30. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
- 31. (assigned:ti,ab,tt OR allocated:ti,ab,tt)
- 32. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt

- 33. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
- 34. 'human experiment'/de
- 35. Trial:ti,tt
- 36. #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
- 37. (((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
- 38. ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
- 39. ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
- 40. ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
- 41. (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
- 42. 'random field*':ti,ab,tt
- 43. ('random cluster' NEAR/4 sampl*):ti,ab,tt
- 44. (review:ab AND review:it NOT trial:ti,tt)
- 45. ('we searched':ab AND (review:ti,tt OR review:it))
- 46. 'update review':ab
- 47. (databases NEAR/5 searched):ab
- 48. ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cat:s:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
- 49. ('animal experiment'/de NOT ('human experiment'/ de OR 'human'/de))
- 50. #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
- 51. #36 NOT #50
- 52. #16 AND #51
- 53. #52 AND English:la

Cochrane Library

Database: Cochrane Library (Cochrane Reviews [CDSR] and Cochrane Central Register of Controlled Trials [CENTRAL])

Search Date: March 25, 2021

Number of Results: 201

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. (ERCP OR EST):ti,ab OR [mh "cholangiopancreatography, endoscopic retrograde"]
- 2. (endoscop* NEAR retrograd* NEAR (cholangiopancreatograph* OR cholangio-pancreatograph*)):ti,ab
- 3. [mh "Sphincterotomy, Endoscopic"]
- 4. (endoscop* NEAR sphincterotom*)
- 5. (papillotom* OR rendezvous)
- 6. #1 OR #2 OR #3 OR #4 OR #5

NSAIDs

- 7. (non steroid\$ antiinflammatory agent\$ OR non steroid\$ anti inflammatory agent\$ OR nsaid\$):ti,ab OR [mh "Anti-Inflammatory Agents, Non-Steroidal"]
- 8. (indomethacin* OR indometacin*):ti,ab or [mh Indomethacin]
- 9. diclofenac*:ti,ab
- 10. naproxen*:ti,ab
- 11. (lornoxicam* OR chlortenoxicam*):ti,ab
- 12. Parecoxib*:ti,ab
- 13. #7 OR #8 OR #9 OR #10 OR #11 OR #12

Post-ERCP Pancreatitis

14. Pancreatitis:ti,ab OR [mh pancreatitis] 5. #

15. #6 AND #13 AND #14

Web of Science

Science Citation Index Expanded (SCI-EXPANDED) –1900-present

Conference Proceedings Citation Index- Science (CPCI-S) –1993-present

Database: Web of Science (Clarivate)

Search Date: March 25, 2021

Number of Results: 162

Limits: randomized controlled trials, English language, human studies

ERCP

1. TS = (ERCP) OR TS = (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)) OR TS = (endoscop* NEAR/3 sphincterotom*) OR TS = (EST OR papillotom* OR rendezvous)

NSAIDs

 TS = (non steroid\$ antiinflammatory agent\$ OR non steroid\$ anti inflammatory agent\$ OR nsaid\$) OR TS = (indomethacin* OR indomethacin OR diclofenac* OR naproxen* OR lornoxicam* OR chlortenoxicam* OR parecoxib*)

Post-ERCP Pancreatitis

3. TS = (pancreatitis)

Randomized Controlled Trials/Humans

- 4. TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))
- 5. #1 AND #2 AND #3 AND #4
- 6. #5 AND LANGUAGE: (English)

Sample Articles

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.e1.

Radadiya D, Devani K, Arora S, et al. Peri-procedural aggressive hydration for post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis prophylaxsis: meta-analysis of randomized controlled trials. Pancreatology 2019;19:819-27.

Yang C, Zhao Y, Li W, et al. Rectal nonsteroidal antiinflammatory drugs administration is effective for the prevention of post-ERCP pancreatitis: an updated meta-analysis of randomized controlled trials. Pancreatology 2017;17:681-8.

Mazaki T, Mado K, Masuda H, et al. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol 2014;49:343-55.

Search strategies for population, intervention, comparator, and outcomes (PICOs) question 3: Wire-guided versus contrast-guided cannulation

PICOs question 3 was addressed with a Cochrane systematic review and meta-analysis, which was updated for this guideline. $^{\!\!\!\!\!^4}$

Search strategies for population, intervention, comparator, and outcomes (PICO) question 4: Prophylactic pancreatic stent placement

Database: Ovid MEDLINE ALL

Search Date: March 24, 2021

Number of Results: 277

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP.tw,kf. or exp cholangiopancreatography, endoscopic retrograde/
- 2. (endoscop* adj2 retrograd* adj2 (cholangiopancreatograph* or cholangio-pancreatograph*)).tw,kf.
- 3. exp Sphincterotomy, Endoscopic/
- 4. ((endoscop* adj3 sphincterotom*) or EST).tw,kf.
- 5. papillotom*.tw,kf. or exp papillotomy/
- 6. rendezvous.tw,kf.

7. or/1-6

Prophylactic Pancreatic Stent Placement

8. exp stents/ or "Prostheses and Implants"/

- 9. (stent* or prosthesi?s or prosthet* or endoprosthes?s).tw,kf.
- ("fully?covered SEMS?" or FC?SEMS? or FCSEMS? or SEM or SEMs or SEMT or SEMTs or "fully?covered SEPS?" or FC?SEPS? or FCSEPS? or SEP or SEPs or SEPT or SEPTs).tw,kf.
- 11. (uncovered SEMS? or UCSEMS? or uncovered SEPS? or UCSEPS?).tw,kf.
- 12. (multi-stent* or multistent*).tw,kf.

- 13. ((pancrea* or "pancreatic duct" or PD) adj2 stent*).tw,kf.
- 14. or/8-13

Post-ERCP Pancreatitis

- 15. pancreatitis.tw,kf. or exp pancreatitis/
- 16. 7 and 14 and 15

Randomized Controlled Trials/Humans

- 17. randomized controlled trial.pt.
- 18. controlled clinical trial.pt.
- 19. random*.mp.
- 20. trial.ab.
- 21. groups.ab.
- 22. or/17-21
- 23. 16 and 22
- 24. exp animals/ not humans/
- 25. 23 not 24
- 26. Limit 25 to English language

Embase

Database: Embase.com

Search Date: March 24, 2021

Number of Results: 859

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP:ti,ab,kw OR 'endoscopic retrograde cholangiopancreatography'/exp
- 2. (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)):ti,ab,kw
- 3. 'endoscopic sphincterotomy'/exp
- 4. ((endoscop* NEAR/3 sphincterotom*) OR EST):ti,ab,kw
- 5. papillotom*:ti,ab,kw OR 'endoscopic papillotomy'/ exp
- 6. rendezvous:ti,ab,kw
- 7. #1 OR #2 OR #3 OR #4 OR #5 OR #6

Prophylactic Pancreatic Stent Placement

- 8. 'stent'/exp OR 'prostheses and orthoses'/de
- 9. (stent* OR prosthesi?s OR prosthet* OR endoprosthes?s):ti,ab,kw
- 10. ("fully?covered SEMS?" OR FC?SEMS? OR FCSEMS? OR SEM OR SEMs OR SEMT OR SEMTS OR "fully? covered SEPS?" OR FC?SEPS? OR FCSEPS? OR SEP OR SEPs OR SEPT OR SEPTs):ti,ab,kw
- 11. (uncovered SEMS? OR UCSEMS? OR uncovered SEPS? OR UCSEPS?):ti,ab,kw
- 12. (multi-stent* OR multistent*):ti,ab,kw
- 13. ((pancrea* OR "pancreatic duct" OR PD) NEAR/2 stent*):ti,ab,kw
- 14. #8 OR #9 OR #10 OR #11 OR #12 OR #13

Post-ERCP Pancreatitis

- 15. Pancreatitis:ti,ab,kw OR 'pancreatitis'/exp
- 16. #7 AND #14 AND #15

Randomized Controlled Trials/Humans

17. 'randomized controlled trial'/de

- 18. 'controlled clinical trial'/de
- 19. random*:ti,ab,tt
- 20. 'randomization'/de
- 21. 'intermethod comparison'/de
- 22. placebo:ti,ab,tt
- 23. (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
- 24. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
- 25. (open NEXT/1 label):ti,ab,tt
- 26. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
- 27. 'double blind procedure'/de
- 28. (parallel NEXT/1 group*):ti,ab,tt
- 29. (crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
- 30. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
- 31. (assigned:ti,ab,tt OR allocated:ti,ab,tt)
- 32. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
- 33. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
- 34. 'human experiment'/de
- 35. Trial:ti,tt
- 36. #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
- 37. (((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
- 38. ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
- 39. ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
- 40. ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
- 41. (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
- 42. 'random field*':ti,ab,tt
- 43. ('random cluster' NEAR/4 sampl*):ti,ab,tt
- 44. (review:ab AND review:it NOT trial:ti,tt)
- 45. ('we searched':ab AND (review:ti,tt OR review:it))
- 46. 'update review':ab
- 47. (databases NEAR/5 searched):ab
- 48. ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR

sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)

- 49. ('animal experiment'/de NOT ('human experiment'/ de OR 'human'/de))
- 50. #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
- 51. #36 NOT #50
- 52. #16 AND #51
- 53. #52 AND English:la

Cochrane Library

Database: Cochrane Library (Cochrane Reviews [CDSR] and Cochrane Central Register of Controlled Trials [CENTRAL])

Search Date: March 24, 2021

Number of Results: 262

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. (ERCP OR EST):ti,ab OR [mh "cholangiopancreatography, endoscopic retrograde"]
- 2. (endoscop* NEAR retrograd* NEAR (cholangiopancreatograph* OR cholangio-pancreatograph*)):ti,ab
- 3. [mh "Sphincterotomy, Endoscopic"]
- 4. (endoscop* NEAR sphincterotom*)
- 5. (papillotom* OR rendezvous)
- 6. #1 OR #2 OR #3 OR #4 OR #5

Prophylactic Pancreatic Stent Placement

- 7. [mh stents] OR [mh "Prostheses and Implants"]
- 8. (stent* OR prosthesi?s OR prosthet* OR endoprosthesis OR endoprostheses):ti,ab
- 9. ("fully*covered SEMS*" OR FC*SEMS* OR FCSEMS* OR SEM OR SEMS OR SEMT OR SEMTS OR "fully*covered SEPS*" OR FC*SEPS* OR FCSEPS* OR SEP OR SEPS OR SEPT OR SEPTs):ti,ab
- 10. (uncovered SEMS* OR UCSEMS* OR uncovered SEPS* OR UCSEPS*):ti,ab
- 11. (multi-stent* OR multistent*):ti,ab
- 12. ((pancrea* OR "pancreatic duct" OR PD) NEAR/2 stent*):ti,ab
- 13. #7 OR #8 OR #9 OR #10 OR #11 OR #12

Post-ERCP Pancreatitis

14. Pancreatitis:ti,ab OR [mh pancreatitis]

15. #6 AND #13 AND #14

Web of Science

Science Citation Index Expanded (SCI-EXPANDED) –1900-present

Conference Proceedings Citation Index- Science (CPCI-S) –1993-present

Database, Web of Science

Database: Web of Science (Clarivate) Search Date: March 24, 2021

Number of Results: 270

Limits: randomized controlled trials, English language, human studies

ERCP

 TS = (ERCP) OR TS = (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)) OR TS = (endoscop* NEAR/ 3 sphincterotom*) OR TS = (EST OR papillotom* OR rendezvous)

Prophylactic Pancreatic Stent Placement

2. TS=(stent* OR prosthesi?s OR prosthet* OR endoprosthesis OR endoprostheses OR "fully*covered SEMS*" OR FC*SEMS* OR FCSEMS* OR SEM OR SEMs OR SEMT OR SEMTS OR "fully*covered SEPS*" OR FC*SEPS* OR FCSEPS* OR SEP OR SEPs OR SEPT OR SEPTs OR uncovered SEMS* OR UCSEMS* OR uncovered SEPS* OR UCSEPS* OR multi-stent* OR multistent*) OR TS=((pancrea* OR "pancreatic duct" OR PD) NEAR/2 stent*)

Post-ERCP Pancreatitis

3. TS = (pancreatitis)

Randomized Controlled Trials/Humans

- 4. TS = (randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))
- 5. #1 AND #2 AND #3 AND #4
- 6. #5 AND LANGUAGE: (English)

Search strategies for population, intervention, comparator, and outcomes (PICOs) question 5: Aggressive peri- and post-procedural intravenous hydration

Ovid MEDLINE ALL

Database: Ovid MEDLINE ALL

Search Date: March 23, 2021

Number of Results: 105

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP.tw,kf. or exp cholangiopancreatography, endoscopic retrograde/
- 2. (endoscop* adj2 retrograd* adj2 (cholangiopancreatograph* or cholangio-pancreatograph*)).tw,kf.
- 3. exp Sphincterotomy, Endoscopic/
- 4. ((endoscop* adj3 sphincterotom*) or EST).tw,kf.
- 5. papillotom*.tw,kf. or exp papillotomy/
- 6. rendezvous.tw,kf.
- 7. or/1-6

Aggressive Peri- and Post-Procedural Intravenous Hydration

- 8. exp Fluid Therapy/ or exp Infusions, Intravenous/ or exp Injections, Intravenous/
- 9. Dehydration/
- 10. Exp Saline Solution/
- 11. (hydrat* or dehydrat* or rehydrat* or saline or (fluid* adj6 therap*) or (fluid* adj6 balance*) or

(fluid* adj6 manag*) or (intravenous adj3 (hydrat* or fluid* or saline or sodium OR infusion* OR infuse* OR inject*)) or hypodermoclys*).tw,kf.

12. or/8-11

Post-ERCP Pancreatitis

- 13. pancreatitis.tw,kf. or exp pancreatitis/
- 14. 7 and 12 and 13

Randomized Controlled Trials/Humans

- 15. randomized controlled trial.pt.
- 16. controlled clinical trial.pt.
- 17. random*.mp.
- 18. trial.ab.
- 19. groups.ab.
- 20. or/15-19
- 21. 14 and 20
- 22. exp animals/ not humans/
- 23. 21 not 22
- 24. Limit 23 to English language
- Embase

Database: Embase.com

- Search Date: March 23, 2021
- Number of Results: 228

Limits: randomized controlled trials, English language, human studies

ERCP

- 1. ERCP:ti,ab,kw OR 'endoscopic retrograde cholangiopancreatography'/exp
- 2. (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)):ti,ab,kw
- 3. 'endoscopic sphincterotomy'/exp
- 4. ((endoscop* NEAR/3 sphincterotom*) OR EST):ti,ab,kw
- 5. papillotom*:ti,ab,kw OR 'endoscopic papillotomy'/ exp
- 6. rendezvous:ti,ab,kw
- 7. #1 OR #2 OR #3 OR #4 OR #5 OR #6

Aggressive Peri- and Post-Procedural Intravenous Hydration

- 8. 'fluid therapy'/exp or 'intravenous drug administration'/exp or 'intravenous drug administration'/exp
- 9. 'dehydration'/exp
- 10. 'sodium chloride'/exp
- 11. (hydrat* OR dehydrat* OR rehydrat* OR saline OR (fluid* NEAR/6 therap*) OR (fluid* NEAR/6 balance*) OR (fluid* NEAR/6 manag*) OR (intravenous NEAR/3 (hydrat* OR fluid* OR saline OR sodium OR infusion* OR infuse* OR inject*)) OR hypodermoclys*):ti,ab,kw
- 12. #8 OR #9 OR #10 OR #11

Post-ERCP Pancreatitis

- 13. Pancreatitis:ti,ab,kw OR 'pancreatitis'/exp
- 14. #7 AND #12 AND #13

Randomized Controlled Trials/Humans

- 15. 'randomized controlled trial'/de
- 16. 'controlled clinical trial'/de

- 17. random*:ti,ab,tt
- 18. 'randomization'/de
- 19. 'intermethod comparison'/de
- 20. placebo:ti,ab,tt
- 21. (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
- 22. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
- 23. (open NEXT/1 label):ti,ab,tt
- 24. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
- 25. 'double blind procedure'/de
- 26. (parallel NEXT/1 group*):ti,ab,tt
- 27. (crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
- 28. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
- 29. (assigned:ti,ab,tt OR allocated:ti,ab,tt)
- 30. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
- 31. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
- 32. 'human experiment'/de
- 33. Trial:ti,tt
- 34. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
- 35. (((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
- 36. ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
- 37. ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
- 38. ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
- 39. (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
- 40. 'random field*':ti,ab,tt
- 41. ('random cluster' NEAR/4 sampl*):ti,ab,tt
- 42. (review:ab AND review:it NOT trial:ti,tt)
- 43. ('we searched':ab AND (review:ti,tt OR review:it))
- 44. 'update review':ab
- 45. (databases NEAR/5 searched):ab
- 46. ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR

sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)

- 47. ('animal experiment'/de NOT ('human experiment'/ de OR 'human'/de))
- 48. #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
- 49. #34 NOT #48
- 50. #14 AND #49
- 51. #50 AND English:la

Cochrane Library

Database: Cochrane Library (Cochrane Reviews [CDSR] and Cochrane Central Register of Controlled Trials [CENTRAL])

Search Date: March 23, 2021

Number of Results: 160

Limits: N/A

ERCP

- 1. (ERCP OR EST):ti,ab OR [mh "cholangiopancreatography, endoscopic retrograde"]
- 2. (endoscop* NEAR retrograd* NEAR (cholangiopancreatograph* OR cholangio-pancreatograph*)):ti,ab
- 3. [mh "Sphincterotomy, Endoscopic"]
- 4. (endoscop* NEAR sphincterotom*):ti,ab
- 5. (papillotom* OR rendezvous):ti,ab
- 6. #1 OR #2 OR #3 OR #4 OR #5

Aggressive Peri- and Post-Procedural Intravenous Hydration

- 7. [mh "Fluid Therapy"] OR [mh "Infusions, Intravenous"] OR [mh "Injections, Intravenous"]
- 8. [mh Dehydration]
- 9. [mh "Saline Solution"]
- (hydrat* OR dehydrat* OR rehydrat* OR saline OR (fluid* NEAR/6 therap*) OR (fluid* NEAR/6 balance*) OR (fluid* NEAR/6 manag*) OR (intravenous NEAR/3 (hydrat* OR fluid* OR saline OR sodium OR infusion* OR infuse* OR inject*)) OR hypodermoclys*):ti,ab
- 11. #7 OR #8 OR #9 OR #10

Post-ERCP Pancreatitis

12. Pancreatitis:ti,ab OR [mh pancreatitis]

13. #6 AND #11 AND #12

Web of Science

Science Citation Index Expanded (SCI-EXPANDED) -1900-present

Conference Proceedings Citation Index- Science (CPCI-S) –1993-present

Database: Web of Science (Clarivate)

- Search Date: March 23,
- Number of Results: 91

Limits: randomized controlled trials, English language,

human studies

ERCP

1. TS = (ERCP) OR TS = (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangiopancreatograph*)) OR TS = (endoscop* NEAR/ 3 sphincterotom*) OR TS = (EST OR papillotom* OR rendezvous)

Aggressive Peri- and Post-Procedural Intravenous Hydration

2. TS=(hydrat* OR dehydrat* OR rehydrat* OR saline OR (fluid* NEAR/6 therap*) OR (fluid* NEAR/6 balance*) OR (fluid* NEAR/6 manag*) OR (intravenous NEAR/3 (hydrat* OR fluid* OR saline OR sodium OR infusion* OR infuse* OR inject*)) or hypodermoclys*)

Post-ERCP Pancreatitis

3. TS = (pancreatitis)

Randomized Controlled Trials/Humans

- 4. TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))
- 5. #1 AND #2 AND #3 AND #4
- 6. #6 AND LANGUAGE: (English)

Web of Science RCT filter: https://ent.cochrane.org/ sites/ent.cochrane.org/files/public/uploads/rct_filters.pdf



Supplementary Figure 1A. Funnel plot of post-sphincterotomy bleeding in unselected patients with prophylactic NSAIDs. *NSAID*, nonsteroidal anti-inflammatory drug.



Supplementary Figure 1C. Funnel plot of moderately severe/severe post-ERCP pancreatitis in unselected patients with prophylactic NSAIDs. *NSAID*, nonsteroidal anti-inflammatory drug.



Supplementary Figure 1B. Funnel plot of post-sphincterotomy bleeding in unselected patients with prophylactic NSAIDs. *NSAID*, nonsteroidal anti-inflammatory drug.

Author	Year	OR (95% CI)	% Weight
Levenick	2016	0.67 (0.19, 2.41)	43.98
Patai	2015	3.06 (0.82, 11.42)	42.70
Ucar	2016	• 5.21 (0.24, 111.24)	13.32
Alcivar-Leon	2017	(Excluded)	0.00
Arain	2013	(Excluded)	0.00
Dobronte	2014	(Excluded)	0.00
Hosseini	2016	(Excluded)	0.00
Katoh	2020	(Excluded)	0.00
Khoshbaten	2007	(Excluded)	0.00
Li	2019	(Excluded)	0.00
Mansour	2016	(Excluded)	0.00
Masjedizadeh	2017	(Excluded)	0.00
Millitania	2017	(Excluded)	0.00
Montano	2007	(Excluded)	0.00
Nawaz	2020	(Excluded)	0.00
Otsuka	2012	(Excluded)	0.00
Shafique	2016	(Excluded)	0.00
Sotoudehmanesh	2007	(Excluded)	0.00
Overall (I-squared =	: 39.0%, p = 0.194)	> 1.68 (0.50, 5.68)	100.00
NOTE: Weights are	from random effects analysis		

OR of Post-Sphincterotomy Bleeding in Linselected Patients with prophylactic NSAIDs

Supplementary Figure 2A. Odds ratios of postsphincterotomy bleeding in unselected patients with prophylactic NSAIDs. *NSAID*, nonsteroidal anti-in-flammatory drug.



Supplementary Figure 2B. Odds ratios of moderately severe/severe post-ERCP pancreatitis in unselected patients with prophylactic NSAIDs. *NSAID*, nonsteroidal anti-inflammatory drug.



OR of Post ERCP Pancreatitis with Prophylactic Rectal NSAIDs in Unselected Patients (Published Full Text Only)

Supplementary Figure 3A. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (published full text only). *NSAID*, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 3B. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (diclofenac only). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 3C. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (indomethacin only). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 3D. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (dose given \geq 30 minutes before procedure). *NSAID*, Nonsteroidal anti-inflammatory drug.



OR of Post ERCP Pancreatitis with Prophylactic Rectal NSAIDs in Unselected Patients (0-30 Minutes Prior)

Supplementary Figure 3E. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (dose given <30 minutes before procedure). *NSAID*, Nonsteroidal anti-inflammatory drug.



OR of Post ERCP Pancreatitis with Prophylactic Rectal NSAIDs in Unselected Patients (100mg dose)

Supplementary Figure 3F. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in unselected patients (dose 100 mg). NSAID, Nonsteroidal anti-inflammatory drug.

		Selection bias: Random sequence generation	Selection bias: Allocation concealment	Reporting bias: Selective reporting	Other bias	Performance bias: Blinding participants/pers onnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data
Alcivar-Leon	2017	0	0	0	0	0	0	0
Arain	2013	\bigcirc	\bigcirc	\bigcirc	\bigcirc		\circ	\circ
Dobronte	2014	0	0	0			0	0
Hosseini	2016	<u> </u>		0		•	0	•
Katoh	2020	<u> </u>	<u> </u>	<u> </u>		•	•	
Khoshbaten	2007	<u> </u>	•	<u> </u>	<u> </u>		0	•
Levenick	2016	0	•	0	<u> </u>	•	0	0
Li	2019	•	•	<u> </u>			0	•
Mansour	2016		•	<u> </u>			<u> </u>	
Masjedizadeh	2017	<u> </u>	<u> </u>	<u> </u>		•	<u> </u>	<u> </u>
Millitania	2017	<u> </u>	<u> </u>	<u> </u>	<u> </u>	<u> </u>	0	<u> </u>
Montano	2007	<u> </u>	<u> </u>	<u> </u>	0	<u> </u>	0	•
Nawaz	2020			<u> </u>			0	•
Otsuka	2012	<u> </u>	0	0	0	•	0	0
Patai	2015	<u> </u>	•	0	•		•	0
Shafique	2016	0	•	<u> </u>	•	<u> </u>	0	0
Sotoudehmanesh	2007			<u> </u>				
Ucar	2016	<u> </u>	<u> </u>	<u> </u>			0	

Supplementary Figure 4. Quality parameters of studies comparing rectal NSAIDs with placebo for PEP prevention in unselected patients. *NSAID*, Nonsteroidal anti-inflammatory drug; *PEP*, post-ERCP pancreatitis.



Supplementary Figure 5A. Funnel plot of renal failure in high-risk patients with prophylactic NSAIDs. *NSAID*, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 5C. Funnel plot of moderately severe/severe post-ERCP pancreatitis in high-risk patients with prophylactic NSAIDs. *NSAID*, Nonsteroidal anti-inflammatory drug.

	OR of Renal Failure in High Risk P	atients with Prophylactic NSAIDs	
Author	Year	OR (95% CI)	% Weight
Elmunzer	2012	- 0.21 (0.01, 4.33)	29.79
Mok (NS)	2017	1.00 (0.06, 16.46)	35.10
Mok (LR)	2017	1.00 (0.06, 16.46)	35.10
Murray	2003	(Excluded)	0.00
Andrade-Davila	2015	(Excluded)	0.00
Lua	2015	(Excluded)	0.00
Patil	2016	(Excluded)	0.00
Zaman	2019	(Excluded)	0.00
Li	2019	(Excluded)	0.00
Katoh	2020	(Excluded)	0.00
Overall (I-square	ed = 0.0%, p = 0.696)	0.63 (0.12, 3.29)	100.00
NOTE: Weights a	are from random effects analysis	_	

Supplementary Figure 5B. Odds ratios of renal failure in high-risk patients with prophylactic NSAIDs. NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 5D. Funnel plot of postsphincterotomy bleeding in high-risk patients with prophylactic NSAIDs. *NSAID*, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 6A. Funnel plot post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients. *NSAID*, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 6B. Odds ratios of postsphincterotomy bleeding in high-risk patients with prophylactic NSAIDs. NSAID, Nonsteroidal anti-inflammatory drug.

OR of Mode	rately Severe/Severe Pos	t ERCP Pa	ancreatitis in High R	isk Patients with Prophylactic	NSAIDs
					%
Author	Year			OR (95% CI)	Weight
Murray	2003			0.18 (0.01, 3.81)	4.84
Elmunzer	2012			0.46 (0.23, 0.91)	48.59
Andrade-Davila	2015	•	<u> </u>	0.29 (0.03, 2.82)	8.27
Lua	2015			8.01 (0.41, 158.06)	5.04
Patil	2016			0.05 (0.00, 0.83)	5.49
Mok (NS)	2017		•	- 2.72 (0.11, 68.71)	4.34
Mok (LR)	2017	 	•	- 2.60 (0.10, 65.76)	4.34
Zaman	2019 -		<u> </u>	0.49 (0.09, 2.80)	13.37
Katoh	2020 —		•	1.04 (0.06, 16.89)	5.72
Overall (I-square	d = 10.7%, p = 0.346)	\Rightarrow		0.53 (0.27, 1.05)	100.00
NOTE: Weights a	re from random effects analy	ysis			
		.2 .5	1 2 5		

Supplementary Figure 6C. Odds ratios of moderately severe/severe post-ERCP pancreatitis in high-risk patients with prophylactic NSAIDs. NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 7A. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (dose 100 mg). NSAID, Nonsteroidal anti-inflammatory drug.



OR of Post ERCP Pancreatitis in High Risk Patients with Prophylactic NSAIDs (full publication)

Supplementary Figure 7B. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (published full text only). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 7C. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (dose before ERCP). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 7D. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (dose after ERCP). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 7E. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (indomethacin only). NSAID, Nonsteroidal anti-inflammatory drug.



Supplementary Figure 7F. Odds ratios of post-ERCP pancreatitis with prophylactic rectal NSAIDs in high-risk patients (diclofenac only). NSAID, Nonsteroidal anti-inflammatory drug.

		Selection bias: Random sequence generation	Selection bias: Allocation concealment	Reporting bias: Selective reporting	Other bias	Performance bias: Blinding participants/pe rsonnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data
Andrade-Davila	2015	0		0				
Elmunzer	2012	ŏ	ă	ŏ			ă	
Katoh	2020	ŏ	Ŏ	ŏ	ŏ	ĕ	Ŏ	Ŏ
Koshbaten	2008	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ
Li	2019	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ	Ŏ
Lua	2015	0	Õ	0	0	•	0	0
Mok	2017			0				0
Murray	2003	0		0				0
Patil	2016		0	0		\bigcirc	0	0
Zaman	2019	0	0	0	0	0	0	0

Supplementary Figure 8. Quality parameters comparing rectal NSAIDs with placebo for PEP prevention in high-risk patients. NSAID, Nonsteroidal antiinflammatory drug; PEP, post-ERCP pancreatitis.

	GV	N	co			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Artifon 2007	7	150	6	150	28.9%	1.17 [0.40 , 3.39]	
Gruchy 2007	6	241	3	135	17.5%	1.12 [0.28 , 4.41]	
Katsinelos 2008	5	167	5	165	22.0%	0.99 [0.29 , 3.35]	
Kobayashi 2013	0	163	1	159	3.2%	0.33 [0.01 , 7.92]	
Lee 2009 (1)	0	150	0	150		Not estimable	
Masci 2015	2	160	3	160	10.4%	0.67 [0.11 , 3.94]	
Nambu 2011	3	86	6	86	17.9%	0.50 [0.13 , 1.94]	
Total (95% CI)		1117		1005	100.0%	0.87 [0.49 , 1.54]	
Total events:	23		24				Ť
Heterogeneity: Tau ² =	0.00; Chi ²		0.01 0.1 1 10 100				
Test for overall effect:	Z = 0.48 (F	P = 0.63)					Favors GW Favors CC
Test for subgroup diffe	erences: No	ot applica	ble				

Footnotes

(1) GW: guidewire-assisted cannulation, CC: contrast-assisted cannulation

Supplementary Figure 9. Relative risk of post-sphincterotomy bleeding with wire-guided cannulation.

Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.

	GV	N	С			Risk Ratio	Ris	k Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ran	dom, 95% CI
Artifon 2007	1	150	3	150	40.5%	0.33 [0.04 , 3.17]		
Gruchy 2007	0	241	0	135		Not estimable		
Katsinelos 2008	0	167	0	165		Not estimable		
Kawakami 2012	4	199	0	201	31.3%	9.09 [0.49 , 167.73]		↓ →
Kobayashi 2013	0	163	1	159	28.2%	0.33 [0.01 , 7.92]		
Lee 2009 (1)	0	150	0	150		Not estimable		
Masci 2015	0	160	0	160		Not estimable		
Nambu 2011	0	86	0	86		Not estimable		
Total (95% CI)		1316		1206	100.0%	0.93 [0.11 , 8.23]		
Total events:	5		4					T
Heterogeneity: Tau ² =	1.73; Chi ²	= 3.74, d	f = 2 (P = 0	0.15); l ² =	46%		0.01 0.1	1 10 10
Test for overall effect:	Z = 0.06 (F	P = 0.95)					Favors GW	Favors CC
Test for subgroup diffe	erences: No	ot applica	ble					

Footnotes

(1) GW: guidewire-assisted cannulation, CC: contrast-assisted cannulation

Supplementary Figure 10. Relative risk of perforation with wire-guided cannulation.

Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.

Apostolopoulos 2005	0	67	0	63		Not estimable	
Artifon 2007	0	150	0	150		Not estimable	
Bailey 2008	3	215	4	215	22.0%	0.75 [0.17 , 3.31]	
Katsinelos 2008	1	167	2	165	8.5%	0.49 [0.05 , 5.40]	
Kawakami 2012	0	199	2	201	5.3%	0.20 [0.01 , 4.18]	←
Kobayashi 2013	6	163	2	159	19.3%	2.93 [0.60 , 14.28]	
Lee 2009	1	150	2	150	8.5%	0.50 [0.05 , 5.46]	
Lella 2004	0	200	1	200	4.8%	0.33 [0.01 , 8.13]	
Mangiavillano 2007	0	100	1	100	4.8%	0.33 [0.01 , 8.09]	
Masci 2015	3	160	4	160	22.1%	0.75 [0.17 , 3.30]	
Nambu 2011	0	86	1	86	4.8%	0.33 [0.01 , 8.07]	
Zhang 2007	0	342	0	171		Not estimable	
Subtotal (95% CI)		1999		1820	100.0%	0.76 [0.38 , 1.52]	-
Total events:	14		19				T
Heterogeneity: Tau ² = 0.00;	Chi ² = 4.	53, df = 8	(P = 0.81); I ² = 09	%		
Test for overall effect: Z = 0.79 (P = 0.43)							

Supplementary Figure 11. Relative risk of moderately severe post-ERCP pancreatitis.

Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.

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1.3.3 Severe post-ERCP pancreatitis

1.3.3 Severe post-ERCP pancreatitis									
Apostolopoulos 2005	0	67	0	63		Not estimable			
Artifon 2007	0	150	0	150		Not estimable			
Bailey 2008	0	215	0	215		Not estimable			
Katsinelos 2008	0	167	3	165	10.5%	0.14 [0.01 , 2.71]	← ■		
Kawakami 2012	4	199	1	201	19.3%	4.04 [0.46 , 35.83]			
Kobayashi 2013	1	163	0	159	9.0%	2.93 [0.12 , 71.32]			
Lee 2009	1	150	1	150	12.0%	1.00 [0.06 , 15.84]			
Lella 2004	0	200	1	200	9.0%	0.33 [0.01 , 8.13]	.		
Mangiavillano 2007	0	100	1	100	9.0%	0.33 [0.01 , 8.09]	•		
Masci 2015	1	160	1	160	12.0%	1.00 [0.06 , 15.85]			
Nambu 2011	0	86	1	86	9.0%	0.33 [0.01 , 8.07]	_		
Zhang 2007	0	342	2	171	10.0%	0.10 [0.00 , 2.08]	← • – – –		
Subtotal (95% CI)		1999		1820	100.0%	0.69 [0.27 , 1.81]	-		
Total events:	7		11						
Heterogeneity: Tau ² = 0.00; Ch	2 = 6.7	71, df = 8 (P = 0.57); I ² = 09	%				
Test for overall effect: $Z = 0.75$ (P = 0.45)									

Supplementary Figure 12. Relative risk of severe post-ERCP pancreatitis with wire-guided cannulation.

Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.

	GV	N	CC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
7.1.1 Studies permitte	ed PD stent	t					
Bailey 2008 (1)	16	215	13	215	11.0%	1.23 [0.61 , 2.50]	
Gruchy 2007	4	241	6	135	5.6%	0.37 [0.11 , 1.30]	
Katsinelos 2008	9	167	13	165	9.5%	0.68 [0.30 , 1.56]	
Kawakami 2012	8	199	6	201	7.2%	1.35 [0.48 , 3.81]	_ _
Kobayashi 2013	10	163	10	159	9.1%	0.98 [0.42 , 2.28]	
Masci 2015	8	160	19	160	9.8%	0.42 [0.19 , 0.93]	
Subtotal (95% CI)		1145		1035	52.1%	0.78 [0.52 , 1.18]	
Total events:	55		67				٦
Heterogeneity: Tau ² = 0	0.07; Chi ² =	6.66, df =	= 5 (P = 0.2	25); l² = 2	5%		
Test for overall effect: 2	Z = 1.18 (P :	= 0.24)					
7.1.2 Studies did not	permit PD s	stent					
Apostolopoulos 2005	1	67	6	63	2.4%	0.16 [0.02 , 1.27]	
Artifon 2007	5	150	18	150	7.9%	0.28 [0.11 , 0.73]	
Lee 2009	3	150	17	150	5.9%	0.18 [0.05 , 0.59]	
Nambu 2011	2	86	5	86	3.8%	0.40 [0.08 , 2.01]	
Subtotal (95% CI)		453		449	19.9%	0.24 [0.13 , 0.47]	▲
Total events:	11		46				•
Heterogeneity: Tau ² = 0	0.00; Chi ² =	0.89, df =	= 3 (P = 0.8	83); I² = 0	%		
Test for overall effect: 2	Z = 4.25 (P	< 0.0001)					
							1

Supplementary Figure 13. Relative risk of post-ERCP pancreatitis with wire-guided cannulation (stratified by whether study permitted PD stent or did not permit PD stent).

Used with permission from Tse F, Liu J, Yuan Y, Moavyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.



Supplementary Figure 14A. Relative risk of post-ERCP pancreatitis with wire-guided cannulation (wire follows tome).



RR of Post ERCP Pancreatitis Guidewire-assisted versus Contrast-assisted Cannulation (Guidewire Leads)

Supplementary Figure 14B. Relative risk of post-ERCP pancreatitis with wire-guided cannulation (wire leads tome).



Supplementary Figure 15. Quality parameters for wire-guided compared with contrast-guided cannulation.

Used with permission from Tse F, Liu J, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD009662.



Supplementary Figure 16A. Funnel plot of post-ERCP pancreatitis with prophylactic pancreatic duct stent.



Supplementary Figure 16B. Funnel plot of bleeding with prophylactic pancreatic duct stent.



Supplementary Figure 16C. Funnel plot of infection with prophylactic pancreatic duct stent.



Supplementary Figure 16D. Funnel plot of perforation with prophylactic pancreatic duct stent.



Supplementary Figure 16E. Funnel plot of moderately severe/severe post-ERCP pancreatitis with prophylactic pancreatic duct stent.



Supplementary Figure 16F. Funnel plot of severe post-ERCP pancreatitis with prophylactic pancreatic duct stent.



Supplementary Figure 17A. Odds ratios of bleeding with prophylactic pancreatic duct stent.



Supplementary Figure 17B. Odds ratios of infection with prophylactic pancreatic duct stent.



Supplementary Figure 17C. Odds ratios of perforation with prophylactic pancreatic duct stent.



Supplementary Figure 17D. Proportion successful pancreas stent placement.



Supplementary Figure 18A. Odds ratios of post-ERCP pancreatitis with pancreatic in high-risk patients (non-SOD). SOD, Phincter of Oddi dysfunction.



Supplementary Figure 18B. Odds ratios of post-ERCP pancreatitis with pancreatic stents in high-risk patients (PD access as additional step). PD, Pancreatic duct; PEP, post-ERCP pancreatitis.



Supplementary Figure 18C. Odds ratios of post-ERCP pancreatitis with pancreatic stents in high-risk patients (if PD already accessed). PD, Pancreatic duct; PEP, post-ERCP pancreatitis.



Supplementary Figure 18D. Odds ratios of post-ERCP pancreatitis with pancreatic stents in high-risk patients (exclude nonselected studies). PD, Pancreatic duct; PEP, post-ERCP pancreatitis.

		Selection bias: Random sequence generation	Selection bias: Allocation concealment	Reporting bias: Selective reporting	Other bias	Performance bias: Blinding participants/pe rsonnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data
Harewood	2005		0				•	•
Sofuni	2011		0		•	0	0	
Phillip	2019	•	0		•	0	0	
Khan	2020	• •	•			0	<u> </u>	
Pan	2011	<u> </u>	•		•	0	0	
Wang	2020	\circ	\circ					
Cha	2012		•	0	•	•	<u> </u>	
Lee	2012		0		•	0	0	
Kawaguchi	2012						<u> </u>	
Ito	2010		0		•	0	0	
Tarnasky	1998	<u> </u>				0	<u> </u>	
Yin	2016	0	0		•	0	0	
Sofuni	2007	· •	0	•	•	0	<u> </u>	
Tsuchiya	2007		0			0	<u> </u>	
Smithline	1993	0	•			0	<u> </u>	
Qian	2014	0	0			0	0	
Fazel	2003	0					0	

Supplementary Figure 19. Quality parameters of studies of pancreatic stents for PEP prevention in high-risk patients. PEP, Post-ERCP pancreatitis.



Supplementary Figure 20A. Funnel plot of post-ERCP pancreatitis with aggressive hydration.



Supplementary Figure 20B. Funnel plot volume overload aggressive hydration.



Supplementary Figure 20C. Funnel plot of moderately severe/severe post-ERCP pancreatitis with aggressive hydration.



OR of Volume Overload with Aggressive vs Standard Hydration

Supplementary Figure 21A. Odds ratios volume overload with aggressive hydration.

			%
Author	Year	OR (95% CI)	Weight
Buxbaum	2014	0.11 (0.00, 2.37)	3.48
Chuankrekkul	2015	7.76 (0.38, 157.14)	3.65
Rosa	2016	0.18 (0.01, 3.84)	3.50
Choi	2017	0.20 (0.02, 1.70)	6.89
Park (NS)	2017	0.96 (0.06, 15.55)	4.24
Park (LR)	2017	1.97 (0.18, 21.99)	5.56
Alcivar-Leon	2017	0.14 (0.02, 1.15)	7.21
Weiland	2021	0.70 (0.40, 1.24)	52.55
Chang	2021	0.74 (0.16, 3.41)	12.92
Hajalikhani	2018	(Excluded)	0.00
Overall (I-squar	ed = 9.0%, p = 0.360)	0.60 (0.34, 1.08)	100.00
NOTE: Weights	are from random effects analysis		

Supplementary Figure 21B. Moderately severe/severe post-ERCP pancreatitis with aggressive hydration.



Supplementary Figure 22A. Odds ratios of post-ERCP pancreatitis with aggressive hydration (published full-text only).



Supplementary Figure 22B. Odds ratios of post-ERCP pancreatitis with aggressive hydration (native papilla only).



Supplementary Figure 22C. Odds ratios of post-ERCP pancreatitis with aggressive hydration (8-hour hydration protocol only).



Supplementary Figure 22D. Odds ratios of post-ERCP pancreatitis with aggressive hydration (exclude NSAID combination trials). *NSAID*, Nonsteroidal anti-inflammatory drug.

Author	Year	Sequence	Allocation	Blinding	Blinding	Selective	Incomple	Other Sou	Overall
Buxbaum	2014	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Chuankrerkkul	2015	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low
Nejad	2015	Low	Low	Low	Unclear	Low	Low	Low	Low
NCT 02-05-0048	2016	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	High
Chang	2016	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Rosa	2016	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	Unclear
Park	2017	Low	Low	Low	Low	Low	Low	Low	Low
Choi	2017	Low	Low	Low	Low	Low	Low	Low	Low
Alcivar Leon	2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ghaderi	2019	Low	Low	Low	Low	Unclear	Low	Low	Low
Weiland	2021	Low	Unclear	Unclear	Low	Low	Low	Low	Low

Supplementary Figure 23. Quality parameters of studies of aggressive hydration for PEP, post-ERCP pancreatitis prevention. PEP, Post-ERCP pancreatitis.

SUPPLEMENTARY TABLE 1. Diagnostic criteria, dose, and timing of studies on prophylactic NSAIDs in unselected patients

Author	Year	Туре	Dose	Timing	Diagnostic criteria	
Alcivar-Leon	2017	Diclofenac	500 mg	Immediately before ERCP	Consensus	
Arain	2013	Diclofenac	100 mg	60 min before ERCP	Consensus	
Dobronte	2014	Indomethacin	100 mg	10-15 min before to ERCP	Consensus	
Hosseini	2016	Indomethacin	100 mg	2 hours before ERCP	Revised Atlanta Classification (RAC)	
Katoh	2020	Diclofenac	50 mg (25mg if weight <50kg)	30 min before ERCP	Consensus	
Khoshbaten	2007	Diclofenac	100 mg	Immediately before ERCP	Amylase 4X ULN/Pain	
Levenick	2016	Indomethacin	50 mg	In procedure room	Consensus/RAC	
Li	2019	Indomethacin	100 mg	15-20 min before ERCP	Consensus	
Mansour	2016	Naproxen	500 mg	Immediately before ERCP	Consensus	
Masjedizadeh	2017	Indomethacin	50 mg	Immediately before and 12 hours after ERCP	Consensus	
Millitania	2017	Ketoprofen		Immediately before ERCP	Imrie/Modified Glasgow	
Montano	2007	Indomethacin	100 mg	2 hours before ERCP	Ranson's	
Nawaz	2020	Diclofenac		15 minutes before ERCP	Consensus	
Otsuka	2012	Diclofenac	50 mg (25mg if weight <50kg)	30 minutes before ERCP	Consensus	
Patai	2015	Indomethacin	100 mg	1 hour before ERCP	Consensus	
Shafique	2016	Diclofenac	100 mg	Immediately before to ERCP	Amylase 4X ULN, pain	
Sotoudehmanesh	2007	Indomethacin	100 mg	Immediately before ERCP	Consensus	
Ucar	2016	Diclofenac	50 mg	30-90 min before ERCP	Consensus	

NSAID, Nonsteroidal anti-inflammatory drug; ULN, Upper limit of normal.

SUPPI EMENTARY	TABLE 2.	Inclusion/exclusion	criteria and r	population	features of s	studies on i	nronh	vlactic NSAIDs	in high-risk	natients
		interastori, exclasion	enterna anta p	opulation	icatales of s	readics on	propri	y la cule 110/ 110 5	in ingit tisk	patients

Author	Year	Туре	Inclusion criteria	SOD	PD stent
Murray	2003	Paper	SOD	24%	12.5%
Elmunzer	2012	Paper	SOD, difficult cannulation (8 attempts) pancreatic sphincterotomy, precut, ampullectomy, balloon dilation without ES	82%	82%
Andrade-Davila	2015	Paper	SOD, difficult cannulation (8 attempts) pancreatic sphincterotomy, precut, ampullectomy, balloon dilation without ES, PD cytology, recurrent pancreatitis, repeated injections <50+female		2%
Lua	2015	Paper			3%
Patil	2016	Paper			6%
Mok (NS)	2017	Paper	- SOD, difficult cannulation (8 attempts) pancreatic sphincterotomy, precut, ampullectomy, pancreatic cytology -		28%
Mok (LR)	2017	Paper			26%
Zaman	2019	Abstract	High risk	NR	NR
Li	2019	Paper	High-risk subgroup		
Katoh	2020	Paper	High-risk subgroup	NR	NR

SUPPLEMENTARY TABLE 3. Agent, dose, and timing of studies on prophylactic NSAIDs in high-risk patients							
Author	Туре	Dose	Timing	Diagnostic criteria			
Murray	Diclofenac	100 mg	Immediately after ERCP	Pain, amylase 4X ULN			
Elmunzer	Indomethacin	100 mg	Immediately after ERCP	Consensus			
Andrade-Davila	Indomethacin	100 mg	Immediately after ERCP	Consensus			
Lua	Diclofenac	100 mg	Immediately after ERCP	Consensus			
Patil	Diclofenac	100 mg	Immediately before during ERCP	Consensus			
Mok (NS)	Indomethacin + NS	100 mg	Immediately before	Consensus			
Mok (LR)	Indomethacin $+$ LR	100 mg	Immediately before	Consensus			
Zaman	Indomethacin	100 mg	Immediately after ERCP	Consensus			
Li	Indomethacin	100 mg	15-20 min before ERCP	Consensus			
Katoh	Diclofenac	50 mg (25 mg if < 50 kg)	30 min before ERCP	Consensus			

SUPPLEMENT	ARY TABLE	4. Inclusion and diagnostic criteria of studies on pancreas stents to	prevent PEP		
Author	Year	Inclusion criteria	% SOD	PEP_definition	Severity
Smithline	1993	Sphincter of Oddi dysfunction (SOD), precut sphincterotomy	76%	Consensus	Consensus
Tarnasky	1998	SOD	100%	Consensus	Consensus
Fazel	2003	SOD, Difficult cannulation (30min)	68%	Consensus	Consensus
Harewood	2005	Ampullectomy		3X amylase and abd	lominal pain
Sofuni	2007	Unselected (>50% pancreatography)	1%	Consensus	Consensus
Tsuchiya	2007	Unselected (pancreatography, and pancreatic juice aspiration)	1%	Consensus	Consensus
lto	2010	Difficult cannulation	3%	Consensus	Consensus
Pan	2011	High risk		Consensus	Consensus
Sofuni	2011	Age<60 & female, history of pancreatitis, SOD, pancreatography, pancreatic or precut or sphincterotomy, balloon dilation, difficult cannulation, pancreatic duct tissue sampling		Consensus	Consensus
Cha	2012	Precut sphincterotomy	48%	Consensus	Consensus
Kawaguchi	2012	Precut sphincterotomy, pancreatic duct biopsy, SOD, difficult cannulation, prior PEP		Consensus	Consensus
Lee	2012	Difficult cannulation	2%	Consensus	Consensus
Dong	2014	SOD, female & <50, repeated pancreatitis, periampullary diverticula and immunosuppression		Consensus	Consensus
Yin	2016	2 risk factors (pancreatitis, female, young, difficult cannulation, normal bilirubin)		3X amylase and abd	lominal pain
Phillip	2019	Inadvertent pancreatic duct cannulation		Revised Atlanta classification (RAC)	RAC
Khan	2020	High risk			
Wang	2020	Pre-cut sphincterotomy or papillary dilation, inadvertent injection or wire passage to PD		RAC	RAC

PEP, Post-ERCP pancreatitis; PD, pancreatic duct.

SUPPLEMENTARY TABLE 5. Timing of pancreatic stent placement and subsequent assessment, stent diameter, and length								
Author	Year	Timing of pancreatic duct stent placement	Width (F)	Length (cm)	Assessment (days)			
Smithline	1993	Additional step after biliary sphincterotomy	5-7	2-2.5	14			
Tarnasky	1998	Already accessed PD with wire: after biliary sphincterotomy and pancreatic manometry	5-7	2-2.5	27			
Fazel	2003	Additional step	5	2	7			
Harewood	2005	Additional step after ampullectomy	5	3-5	1			
Sofuni	2007	Additional step	5	3q	4			
Tsuchiya	2007	Not defined	5	3-4	14			
lto	2010	Already accessed: Stent placed over existing pancreatic duct wire if randomized	5	4				
Pan	2011	Not defined	5		7			
Sofuni	2011	Placed as final additional step of ERCP	5	3	4			
Cha	2012	Already accessed: PD stent placed before precut, if randomized to no stent ,removed	5, 7	2 -2.5	10			
Kawaguchi	2012	Additional step	5	3	7			
Lee	2012	Already accessed: Used double guidewire technique if randomized to stent	3	4-8	7			
Qian	2014	Not defined			4			
Yin	2016	Additional step	5	5-9				
Phillip	2019	Already accessed: Randomization after inadvertent PD wire access	5		5			
Khan	2020	Not defined						
Wang	2020	No defined						

SUPPLEMENTARY TABLE 6. Inclusion/exclusion criteria for studies of aggressive versus moderate hydration to prevent post-ERCP pancreatitis

Author	Abstract/ Year manuscript	Inclusion criteria	Exclusion criteria
Buxbaum	2014 Manuscript	Native papilla, inpatients	Acute/chronic pancreatitis, NYHA Class >II CHF, CKD (Crcl<40ml/min), liver dysfunction, respiratory insufficiency <90% RA, age>70, hyper or hyponatremia
Shaygan- Nejad	2015 Manuscript	Native papilla	μη
Chuankrerkku	l 2015 Abstract	Native papilla	
Rosa	2016 Abstract	Native papilla, consecutive patients	Acute/chronic pancreatitis, NYHA Class \geq 3 CHF, CKD \geq 3
Brown	2016 Abstract	Outpatients SOD, prior PEP, ampullectomy, precut or pancreatic sphincterotomy	Acute/chronic pancreatitis ,CHF, CAD, ascites, GI bleeding, CKD
Choi	2017 Manuscript	Native papilla	Acute/chronic pancreatitis, NYHA Class >II CHF, CKD(Crcl<40ml/min), liver dysfunction recent MI, COPD on home oxygen, age>75
Alcivar-Leon	2017 Abstract	Native papilla	
Park	2018 Manuscript	Native papilla, SOD, precut	Acute or chronic pancreatitis, NYHA>2 CHF, COPD, ESRD, age>80, sepsis, hyper or hyponatermia
Hajalikhani	2018 Manuscript	Elective ERCP	Ш
Ghaderi	2019 Manuscript	Native papilla	Age>70, Acute/chronic pancreatitis, NYHA Class >II CHF, CKD (Crcl<40ml/ min), hyper/hyponatremia
Weiland	2021 Manuscript	Moderate to high risk (Native papilla)	Chronic pancreatitis/pancreas mass active peptic ulcer disease, cardiac, pulmonary or liver insufficiency, age>85, 5, hypo or hypernatremia
Chang	2021 Manuscript	Native papilla	"" CAD, age<65, surgically altered anatomy

"" Same as Buxbaum et al.

Author	Year	Aggressive	Moderate	Diagnostic and severity criteria
Buxbaum	2014	20ml/kg bolus, 3ml/kg/hour lactated ringer's during procedure and after 8 hours, then reduced to 1.5ml/kg/hour	No bolus, 1.5ml/kg/hour lactated ringer's during procedure and 8 hours afterward	Consensus
Shaygan- nejad	2015	*	*	Consensus
Chuankrerkku	ıl 2015	*	*	Consensus
Rosa	2016	*	*	Consensus
Brown	2016	Bolus of 7.5cc/kg lactated ringer's over 1 hour prior, infusion at 5cc/kg/hour during procedure and 20cc/ kg post procedure bolus over 90 minutes	1.5ml/kg/hour lactated ringer's during procedure and 90 minutes afterward	Consensus
Choi	2017	10ml/kg bolus lactated Ringer's before and after procedure, 3ml/kg/hour during and after 8 hours	1.5ml/kg/hour lactated ringer's x 8 hours	Consensus, Severity Revised Atlanta Classification (RAC)
Alcivar-Leon	2017	*	1.5ml/kg/hour normal saline solution x 8 hours	Consensus
Park	2018	20cc/kg bolus, and 3cc/kg/hr during and for 8 hours after with either lactated Ringer's or normal saline solution	1.5ml/kg/hour lactated ringer's x 8 hours	Consensus, Severity RAC
Hajalikhani	2018	*	*	Consensus
Ghaderi	2019	*	*	Consensus
Weiland	2021	20ml/kg bolus of lactated Ringer's within 60 min ERCP followed by 3ml/Kg/Hour x 8 hours	Maximum 1.5ml/kg/hr or 3L/day of normal saline solution.	Consensus*
Chang	2021	150mL/hr LR starting 2hr before and continued x 24 hours	Maintenance (Holliday-Segar method) x 26 hours	Consensus

SUPPLEMENTARY TABLE 7. Fluid protocol and outcome definitions for studies of aggressive versus moderate hydration to prevent post-ERCP pancreatitis

*Per protocol of Buxbaum et al.