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SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Evaluation of Pharmacologic Prevention of Pancreatitis After Endoscopic Retrograde Cholangiopancreatography: A Systematic Review

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This article has an accompanying continuing medical education activity on page e71. Learning Objective–Upon completion of this activity, successful learners will become familiar with characteristics of the post-ERCP pancreatitis pharmacoprevention literature and the role of non-steroidal anti-inflammatory drugs in this context.

BACKGROUND & AIMS: **There is controversy over the efficacy of pharmacologic agents for preventing pancreatitis after endoscopic retrograde cholangiopancreatography (PEP). We performed a systematic review of PEP pharmacoprevention to evaluate safety and efficacy.**

METHODS: **We performed a systematic search of the literature for randomized controlled trials (RCTs) and meta-analyses of PEP pharmacoprevention through February 2014. After identifying relevant studies, 2 reviewers each extracted information on study characteristics, clinical outcomes, and risk of bias. A research classification scale was developed to identify pharmacologic agents ready for clinical use, agents for which a confirmatory RCT should be considered a high priority, agents for which exploratory studies are still necessary, and agents for which additional research should be of low priority. Clinical and research recommendations for each agent were made by consensus after considering research classification results and other important factors such as magnitude of benefit, safety, availability, and cost.**

RESULTS: **After screening 851 citations and 263 potentially relevant articles, 2 reviewers identified 85 RCTs and 28 meta-analyses that were eligible. On the basis of these studies, rectal nonsteroidal anti-inflammatory drugs were found to be appropriate for clinical use, especially for high-risk cases. Sublingual nitroglycerin, bolus-administered somatostatin, and nafamostat were found to be promising agents for which confirmatory research is warranted. Additional research was found to be required to justify confirmatory RCTs for topical epinephrine, aggressive intravenous fluids, gabexate, ulinastatin, secretin, and antibiotics.**

CONCLUSIONS: **On the basis of a systematic review, NSAIDs are appropriate for use in prevention of PEP, especially for high-risk cases. Additional research is necessary to clarify the role of other pharmacologic agents. These findings could inform future research and guide clinical decision-making and policy.**

Keywords: Pancreas; Post-ERCP; Drug; Outcome.

[a]Authors share co-first authorship.

Abbreviations used in this paper: EBGSG, Evidence Based Gastroenterology Steering Group; ERCP, endoscopic retrograde cholangiopancreatography; NSAID, nonsteroidal anti-inflammatory drug; PEP, post-ERCP pancreatitis; RCT, randomized controlled trial; SO, sphincter of Oddi.

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See editorial on page 1240. Podcast interview: www.gastro.org/cghpodcast. Also available on iTunes.

Pharmacoprevention of post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) has been a major research priority for the last 3 decades. However, randomized controlled trials (RCTs) in this area have traditionally suffered from low methodological quality, inadequate sample sizes, and negative, conflicting, or inconclusive results. Furthermore, studies have failed to consistently use the consensus definition of PEP that requires (1) evidence of clinical pancreatitis, (2) serum amylase or lipase $\geq$3 times the upper limit of normal 24 hours after the procedure, and (3) hospitalization (or prolongation of existing hospitalization) of at least 2 days.[1] Therefore, until recently, no pharmacologic agent had been adopted into routine clinical use.

Within the last decade, research focusing on the prophylactic effect of rectally administered nonsteroidal anti-inflammatory drugs (NSAIDs) has provided renewed hope for PEP pharmacoprevention. Positive meta-analyses[2,3] of exploratory trials of rectal diclofenac and indomethacin led to a grade A recommendation for the use of these medications by the European Society for Gastrointestinal Endoscopy,[4] and a subsequent large-scale, methodologically rigorous RCT[5] has prompted increased acceptance of rectal NSAIDs in clinical practice.[6]

Despite the administration of rectal NSAIDs and the placement of prophylactic pancreatic stents,[7,8] PEP continues to affect 10%–15% of patients at increased risk. Because of the substantial morbidity, occasional mortality, and high costs associated with PEP,[9–11] additional research is necessary to further reduce the incidence of this complication. To this end, there are currently at least 9 ongoing, registered PEP pharmacoprevention RCTs.[12–20]

Adequately powered, methodologically rigorous clinical trials in this area require large sample sizes and substantial resources, incurring high economic and opportunity costs. Therefore, in this era of diminishing research funding, a responsible approach to the selection, design, and conduct of PEP pharmacoprevention trials is necessary to maximize limited resources and efficiently identify beneficial agents. Moreover, an informed appraisal of the existing literature is necessary to help guide clinical decision-making and policy.

To provide clinical guidance and a framework for future research in this important area, we performed a systematic review of the global literature on PEP pharmacoprevention. On the basis of existing RCT and meta-analytic data, we aimed to identify (1) pharmacologic agents that are ready for clinical use, (2) agents for which a confirmatory RCT should be considered a high priority, (3) agents for which exploratory studies are still necessary, and (4) agents for which additional research should be of low priority at this time. In addition, we aimed to construct a comprehensive catalogue of the existing literature on PEP pharmacoprevention for future reference by interested investigators.

Methods

Literature Search

This study was conducted in accordance with the PRISMA statement.[21] A systematic literature search was conducted by a biomedical research librarian by using 7 citation databases: PubMed/MEDLINE (National Library of Medicine), Embase, Biosis Previews, ISI Science Citation Index, Conference Proceedings Citation Index – Science, International Pharmaceutical Abstracts, and Scopus. These databases were searched for human studies of PEP pharmacoprevention from inception through February 2014. Search terms varied by resource and were composed of database-specific controlled vocabulary terms and keywords for the concepts of ERCP and relevant drug therapies. No limits were applied for dates, language, or publication type. The search strategy for each database is provided in Supplementary Appendix A.

Study Selection

Two investigators (N.K., M.A.) independently reviewed the titles and abstracts of all citations identified by the literature search. Potentially relevant studies were retrieved and reviewed in detail, and the following selection criteria were applied: (1) RCT or meta-analysis that primarily examines the prophylactic effect of a pharmacologic agent on the incidence of clinical pancreatitis (not pancreatic enzyme elevation alone) after ERCP, (2) study in humans, (3) study published in the English language, and (4) original data not duplicated in another manuscript. Identified studies focusing on pharmacoprevention of PEP that did not meet eligibility criteria, such as observational studies, studies solely in abstract form, or those examining pancreatic enzyme elevation as the primary end point, were excluded from the primary analysis but catalogued in Supplementary Appendix B for future reference.

Data Extraction

The following data were abstracted from eligible RCTs onto standardized data extraction forms by 2 investigators (N.K., MA) in duplicate and independent fashion: (1) first author, (2) year of publication, (3) pharmacologic agent(s) evaluated, (4) sample size, (5) definition of PEP, and (6) incidence of PEP in all arms. The following data were abstracted from meta-analyses: (1) first author, (2) year of publication, (3) pharmacologic agent evaluated, (4) measure of heterogeneity between included studies, and (5) summary estimate of

effect with 95% confidence interval. Discrepancies were resolved by consensus.

We considered suspected sphincter of Oddi dysfunction, a history of prior PEP, a history of recurrent pancreatitis, young age, female gender, difficult or failed cannulation, balloon dilation of an intact sphincter, pancreatic sphincterotomy, and pancreatic contrast injection as factors that independently increase the risk of PEP.[22] RCTs that predominantly enrolled such cases were considered high-risk studies. The remaining studies were considered low- or mixed-risk studies on the basis of the proportion of enrolled patients with high-risk factors.

Quality Assessment

The methodological quality of each randomized trial was assessed by 2 investigators (N.K., MA) by using criteria set forth by the Evidence Based Gastroenterology Steering Group (EBGSG).[23] These criteria were (1) concealed random allocation and stratification, (2) blinding of patients and caregivers about allocation to treatment/placebo group, (3) equal use of co-interventions for treatment and placebo groups, (4) complete follow-up of study patients, and (5) use of an intention-to-treat analysis. We considered a score of 5 to denote a high-quality study of optimal design for evaluating a pharmacoprophylactic agent. When necessary, the post hoc statistical power of each included RCT was calculated by using the sampsi command in the STATA 12 statistical package (StataCorp LP, College Station, TX). For meta-analyses, we considered a negative ($P > .1$) Cochrane Q test and an I^2 inconsistency index $<50\%$ as denoting absence of significant statistical heterogeneity between included studies.

Data Synthesis

To assess the status of the existing evidence for each pharmacologic agent, we developed a novel research classification system to inform future investigation. The classification system was initially developed by 2 authors (N.K. and B.J.E.) and revised iteratively by consensus among the authors through electronic and telephone communications. The overall goal of this classification scale is to encourage the conduct of large-scale methodologically rigorous (confirmatory) trials for agents with largely positive but not definitive results, to promote additional exploratory research for agents with encouraging but still hypothesis-generating results, and to minimize additional research efforts for medications that have already been proved effective or are very unlikely to be beneficial. In addition, we developed consensus clinical recommendations for each agent that are based on research classification results and the following factors: magnitude of benefit, robustness and consistency of supporting RCTs, safety profile, ease of administration, availability, and cost.

The conceptual framework for our research classification system was developed on the basis of a qualitative review of the existing PEP pharmacoprevention literature and by using principles adapted from the following clinical grading systems: the Agency for Healthcare Research and Quality's National Guideline Clearinghouse, the GRADE framework, and the Scottish Intercollegiate Guidelines Network.[24–26] The following research classes were defined by author consensus, as described above.

Research class 1. This class indicates an agent appropriate for clinical use. Additional research is unlikely to significantly change our confidence in the estimate of benefit: (1) at least 1 positive, adequately powered, high-quality (EBGSG score 5) RCT directly applicable to the target population and (2) at least 1 positive meta-analysis without statistical heterogeneity.

Research class 2. This class indicates high priority for a confirmatory research. The agent is probably effective, but confirmatory research is necessary to establish confidence in the estimate of effect: (1) 3 or more positive RCTs with moderate risk of bias (EBGSG score 3 or 4) and/or inadequate statistical power, (2) at least 1 positive meta-analysis without statistical heterogeneity, and (3) absence of a negative meta-analysis without statistical heterogeneity.

Research class 3. This class indicates lower priority for a confirmatory RCT. The agent may be effective, but additional exploratory research is necessary to justify large-scale clinical trials: (1) at least 1 positive RCT with moderate risk of bias (EBGSG score 3 or 4) and/or inadequate statistical power and (2) at least 1 positive meta-analysis (regardless of heterogeneity) or absence of a negative meta-analysis without statistical heterogeneity.

Research class 4. This class has lowest research priority. The agent is unlikely to be effective, or there are inadequate data to determine status: not meeting any of the criteria above.

Interpretation and analysis of the data were primarily conducted by 3 authors (N.K., B.J.E., M.A.) and subsequently reviewed and verified by the remaining authors through electronic and telephone communications.

Results

Literature Search and Selection Process

A flow diagram depicting the search and selection process is provided in Figure 1. Eight hundred fifty-one potentially relevant publications were identified through the initial literature search. Five hundred sixty-eight articles remained after removal of duplicates. Of these, 305 studies were excluded because they were not relevant to our clinical question, were not conducted in a randomized controlled fashion, or could not be retrieved. Two hundred sixty-three full-text articles were assessed for eligibility.

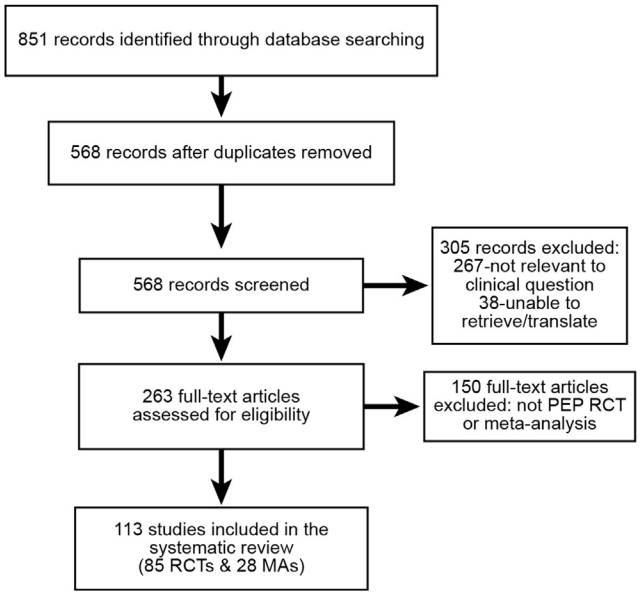

Figure 1. Flow diagram depicting the article search and selection process. MA, meta-analysis.

Eighty-five RCTs and 28 meta-analyses met our selection criteria and were included in the systematic review.

Characteristics of Included Studies

Supplementary Appendix C details the 85 RCTs included in this systematic review. A total of 28,857 patients were randomly assigned to treatment with 1 of 28 unique agents or placebo. Supplementary Appendix D details the 28 meta-analyses included in this systematic review. Eight agents were evaluated in ≥2 meta-analyses, leading to substantial redundancy of RCTs within the meta-analytic component of our review. A comprehensive catalogue of publications for each agent is available in Supplementary Appendix B.

Data Synthesis and Analysis

A summary of agents in research classes 1–3 is outlined in Table 1.

Agents Appropriate for Clinical Use

Rectally administered nonsteroidal anti-inflammatory drugs. Four studies evaluating the protective effects of single-dose rectal indomethacin[27,28] or diclofenac[29,30] were reported between 2003 and 2008 and demonstrated conflicting but generally encouraging results.[27–30] A meta-analysis of these RCTs, involving 912 patients, demonstrated a robust 64% reduction in PEP associated with rectal NSAIDs (relative risk, 0.36; 95% confidence interval, 0.22–0.60) and no increase in associated adverse events.[2]

Despite this meta-analysis, however, NSAIDs were seldom used in clinical practice because of the absence of conclusive RCT evidence.[31] Moreover, it remained unclear whether NSAIDs provide incremental benefit over temporary pancreatic stent placement in high-risk cases. Therefore, a large-scale, multicenter, methodologically rigorous RCT was conducted to definitively evaluate the efficacy of prophylactic rectal indomethacin for preventing PEP in high-risk cases.[5] In this study, rectal indomethacin was associated with 7.7% absolute risk reduction (number needed to treat = 13) and 46% relative risk reduction in PEP (P = .005). Additional RCTs of low-dose rectal diclofenac,[32] the combination of rectal diclofenac plus infusion somatostatin,[33] and the combination of indomethacin plus sublingual nitroglycerin[34] also demonstrated benefit.

On the basis of available data, rectal NSAIDs (100 mg diclofenac or indomethacin immediately before or after ERCP) can be recommended for patients undergoing high-risk ERCP. Controversy remains regarding the role of NSAIDs in low-risk cases. However, an adequately powered clinical trial in low-risk cases would require a very large sample size. In light of the very low cost of a single dose of NSAIDs, the highly favorable safety profile, and prior meta-analyses suggesting that it is equally effective in low-risk cases,[2,35] the time and resources necessary to conduct a definitive RCT may not be justified. The European Society of Gastrointestinal Endoscopy recommends rectal indomethacin or diclofenac for almost all patients undergoing ERCP as a grade A recommendation.[4]

An RCT of oral diclofenac,[36] an underpowered study of intramuscular diclofenac,[37] and a trial of intravascular valdecoxib[38] did not demonstrate prophylactic benefit. As such, there are no existing data to support administration of prophylactic NSAIDs via any nonrectal route. Additional studies evaluating the optimal dose[16] and timing[17,18] of rectal NSAID administration are ongoing.

In summary, rectally administered indomethacin and diclofenac are appropriate for clinical use at a dose of 100 mg immediately before or after ERCP in high-risk cases; strong consideration should be given to their use in low-risk cases.

Promising Agents for Which There Is High Priority for Additional Research

Nitroglycerin. Nitroglycerin is a smooth muscle relaxant that may lower sphincter of Oddi (SO) pressure and increase pancreatic parenchymal blood flow.[39] Seven placebo-controlled RCTs have examined the effect of nitroglycerin on PEP. Three of these studies demonstrated a significant reduction in PEP,[40–42] whereas the remaining 4 showed no benefit.[43–46] The 2 RCTs that used sublingual administration yielded positive results.[40,42] However, these results have been questioned

Table 1. Agents Categorized by Research Class

Research class	Agent	Evidence	Benefit	Safety profile	Cost	Availability	Ease of administration
1	Rectally administered NSAIDs	Very strong	Moderate	Very favorable	Very low	Widespread	Easy
2	Nitroglycerin	Moderate	Moderate	Favorable when administered sublingually	Very low	Widespread	Easy when administered sublingually
2	Bolus-administered somatostatin	Moderate	Moderate	Favorable	Medium	Widespread	Medium when delivered as bolus
2	Nafamostat	Strong	Moderate-high	Favorable	Medium	Limited, not available in U.S.	Difficult
3	Topical epinephrine	Weak	Moderate-high	Very favorable	Very low	Widespread	Very easy
3	Aggressive intravenous lactated Ringers	Weak	Moderate-high	Moderate; favorable in young, healthy adults	Low	Widespread	Easy when administered as bolus
3	Gabexate	Moderate	Unclear	Favorable	High	Limited; not available in U.S.	Difficult
3	Ulinastatin	Moderate	Moderate-high	Favorable	High	Limited, not available in the U.S.	Medium
3	Secretin	Weak	Moderate	Favorable	High	Widespread	Easy
3	Antibiotics	Weak	Moderate-high	Favorable	Low	Widespread	Easy

because neither study defined pancreatitis according to the consensus definition[1], which may have contributed to the higher than expected event rates in the placebo groups (18%[40] and 25%[42]). Transdermal administration of nitroglycerin has yielded conflicting results, with 3 RCTs showing no benefit[43–45] and 1 achieving a positive outcome.[41] One RCT evaluating the role of intravenous nitroglycerin in preventing PEP in moderate- to high-risk cases was terminated prematurely because of an interim analysis suggesting futility and a concerning frequency of adverse hemodynamic events.[46] Five meta-analyses have demonstrated approximately 30%–40% reduction in risk associated with the use of nitroglycerin in the prevention of PEP.[47–51] Because nitroglycerin is postulated to work by reducing SO pressure, it is unclear whether it would provide incremental benefit over pancreatic stent placement. Nevertheless, sublingual nitroglycerin may have a role in lower-risk cases, in resource-limited environments, or in place of pancreatic stent insertion. A recent small comparative effectiveness RCT demonstrated that the combination of sublingual nitroglycerin plus rectal indomethacin was more effective than indomethacin alone in a study sample that largely did not receive a pancreatic stent.[34] Another methodologically rigorous large-scale multicenter RCT is warranted to confirm the effectiveness of combined sublingual nitroglycerin and rectal indomethacin in the appropriate patient population (high-risk cases in environments where stenting is not widely available). In the interim, sublingual nitroglycerin may be reasonable to consider in patients with an NSAID allergy or as an adjunct to rectal NSAIDs in high-risk cases that do not receive a prophylactic pancreatic stent.

In summary, nitroglycerin is not appropriate for immediate clinical use. The use of sublingual nitrates may be considered in patients with NSAID allergy or as an adjunct to NSAIDs in high-risk patients who do not/cannot receive a prophylactic pancreatic stent. A large-scale methodologically rigorous RCT of sublingual nitroglycerin is necessary.

Bolus-administered somatostatin. Somatostatin is a potent inhibitor of pancreatic exocrine function and may therefore prevent or mitigate the pathophysiological processes that lead to pancreatic inflammation. Five of the 11 RCTs comparing somatostatin with placebo have yielded positive results. Benefit has been demonstrated more consistently with bolus administration (3 of 5 published studies positive) than with infusion (3 of 8 published studies positive). All 4 published meta-analyses have suggested benefit associated with somatostatin, especially when delivered as a bolus, with a number needed to treat of approximately 12.[52–55] In addition, an RCT of somatostatin in combination with diclofenac demonstrated benefit.[33] Because of these inconclusive but promising results, a confirmatory RCT of bolus somatostatin (the most practical and likely cost-effective approach) is necessary.

In summary, somatostatin is not appropriate for clinical use; a confirmatory RCT of bolus somatostatin is necessary.

Nafamostat. Nafamostat mesylate is a low-molecular-weight protease inhibitor that inhibits trypsin, a proteolytic enzyme considered to play an initial role in the pathogenesis of pancreatitis. Nafamostat has a half-life that is 20 times longer and a potency 10–100 times greater than gabexate mesylate, another protease inhibitor that has been the focus of much prior research and has been used in clinical practice in parts of the world.[4] Three RCTs have identified a significant reduction in PEP associated with nafamostat: Yoo et al,[56] n = 266 (2.8% vs 9.1% in the nafamostat group vs control group, $P = .03$), Choi et al,[57] n = 704 (3.3% vs 7.4% in the nafamostat vs control group, $P = 018$), and Park et al,[58] n = 608 (three arms: 13.0% in control group vs 4.0% in 20-mg nafamostat group vs 5.1% in 50-mg nafamostat group, $P < .0001$). A recent meta-analysis demonstrated approximately 60% benefit associated with nafamostat (relative risk, 0.41; 95% confidence interval, 0.28–0.59).[59] Major concerns related to the use of nafamostat are its high cost, need for a prolonged intravenous infusion (7–25 hours), and apparent absence of benefit in high-risk cases. In light of these potentially prohibitive disadvantages, statistical modeling analyses are necessary to determine whether a confirmatory RCT could show a magnitude of benefit large enough to justify use of nafamostat in clinical practice.

Research Class 3: Additional Exploratory Research Necessary to Justify a Confirmatory Randomized Controlled Trial

Additional details are available for each agent in the Supplementary Appendix E: topical epinephrine, aggressive intravenous administration of lactated Ringer's solution, gabexate, ulinastatin, secretin, and antibiotics.

Epinephrine sprayed directly on the papilla at the time of ERCP has been postulated to prevent PEP through direct relaxation of the SO and reduction of papillary edema by decreasing capillary permeability. Two RCTs have been published with conflicting results. The larger trial, which demonstrated a statistically significant benefit, was limited by the exclusion of therapeutic ERCPs and an atypical definition of PEP. On the basis of available data, topical epinephrine is not appropriate for clinical use. Additional exploratory research is necessary, but a large-scale methodologically rigorous RCT in an appropriate patient population may be warranted.

Aggressive intravenous fluid resuscitation with lactated Ringer's solution (which attenuates the acidosis that appears to promote zymogen activation and pancreatic inflammation) may be an effective intervention for PEP by favorably affecting physiologic (pH) and microanatomic (pancreatic parenchymal perfusion) parameters. Only 1 small hypothesis-generating RCT has demonstrated benefit, although intravenous fluid resuscitation has a well-established role in treating non-ERCP pancreatitis. On the basis of available RCT data pertaining to PEP, aggressive intravenous fluid is not appropriate for clinical use but may be reasonable to use in clinical practice on the basis of non-ERCP pancreatitis data, safety profile, and widespread availability. Additional exploratory research is necessary, but large-scale methodologically rigorous RCTs may be warranted on the basis of data pertaining to fluid resuscitation in non-ERCP pancreatitis.

Gabexate mesylate is a protease inhibitor with a short half-life that may prevent PEP by inhibiting the activation of trypsin, an important initial component in the inflammatory cascade that leads to pancreatitis. RCT data are conflicting, but 6 of 7 meta-analyses published after 2006 have failed to demonstrate prophylactic benefit. On this basis, gabexate is not appropriate for clinical use. Additional exploratory research is necessary but is of lower priority than research on nafamostat and several other class 3 agents (epinephrine, intravenous fluids, and antibiotics).

Ulinastatin is also a protease inhibitor, but it can be delivered as a bolus because of its stability and longer circulating half-life compared with gabexate. Two higher quality but underpowered multicenter RCTs comparing ulinastatin with placebo for preventing PEP yielded conflicting results. Underpowered comparative effectiveness studies have failed to demonstrate the superiority of ulinastatin over gabexate or a synergistic effect with risperidone. As such, ulinastatin is not appropriate for clinical use. Additional exploratory research is necessary but is of lower priority than research on nafamostat and several other class 3 agents (epinephrine, intravenous fluids, and antibiotics).

A dose of intravenous secretin administered immediately before ERCP (with a second dose administered selectively during ERCP) was found to reduce the risk of PEP by approximately 40% in a mixed population of patients in a large single-center RCT. However, the definition of PEP did not include measurement of serum lipase or amylase and was primarily based on post-procedural pain. Furthermore, the study predated routine prophylactic stent placement and did not use an intention-to-treat analysis. On this basis, the results remain hypothesis-generating, and secretin is not appropriate for clinical use. Additional exploratory research is necessary.

For antibiotics, a single, small RCT of low methodological quality demonstrated that 2 g ceftazidime administered intravenously 30 minutes before ERCP reduced the risk of PEP. Because an infectious etiology for PEP is biologically plausible, additional exploratory research is necessary. On the basis of available data, antibiotics are not appropriate for clinical use to prevent PEP.

Research Class 4: Lowest Research Priority at This Time—Agent Unlikely to Be Effective or There Are Inadequate Data to Determine Status

The agents listed in Supplementary Appendix F have been minimally studied and/or have demonstrated predominantly negative results. Agents with predominantly negative results in both RCTs and meta-analyses include allopurinol, antioxidants, corticosteroids, and octreotide. The remaining agents in this category have predominantly negative results in a small number of RCTs and have not been meta-analyzed. On the basis of existing data, these agents are unlikely to represent effective options for PEP pharmacoprevention.

Discussion

Despite the enormous economic and opportunity costs incurred, relatively little progress has been made toward the goal of pharmacologically eliminating PEP. Research in this area has been limited by a multitude of factors, including inadequate sample sizes, lack of methodological rigor, and absence of a systematic approach to study selection. In this era of diminishing resources, improving the quality of PEP pharmacoprevention research is mandatory. This systematic review serves to provide clinical guidance and a framework for future study selection in this area.

On the basis of available RCT data, rectal NSAIDs are appropriate for widespread clinical use at least in high-risk cases and perhaps in all patients undergoing ERCP as recommended by the European Society of Gastrointestinal Endoscopy.[4] There are ongoing trials evaluating the optimal dose and timing of rectal NSAIDs; additional studies primarily evaluating the effectiveness of rectal NSAIDs are unlikely to further impact clinical practice.

Sublingual nitroglycerin and bolus-administration somatostatin should be considered high priority for a confirmatory clinical trial. Nafamostat may have a role in clinical practice, but limiting factors such as cost, duration of administration, and availability mandate statistical modeling analyses to justify a confirmatory RCT. Gabexate, ulinastatin, topical epinephrine, secretin, antibiotics, and intravenous fluids have shown promise but should be considered of lower research priority at this time, although cogent arguments can be made in favor of large RCTs evaluating topical epinephrine and intravenous fluids.

Future confirmatory PEP pharmacoprevention RCTs should be double-blind, multicenter studies that define the primary end point by using standard consensus criteria.[1] Subject risk strata (low, average, high, very high) should be well-defined and specified a priori, because prophylactic benefit may not be observed across all risk groups, and the absolute risk reduction may only justify use of certain medications in high-risk cases (eg, higher cost, less safe medications). An adequately sized sample should be enrolled and analyzed. For reference, assuming a two-tailed alpha of 0.05 and a power of 80%, 2282 subjects (1141 per arm) are necessary to detect a 50% reduction in PEP in low-risk cases (reduction from 4% to 2%), and 948 subjects (474 per arm) are necessary to detect the same reduction in high-risk cases (reduction from 10% to 5%). Analyses should be conducted according to the intention-to-treat principle, and subject crossover and follow-up loss should be minimized and accounted for. For all future studies, because of the robust evidence-base and safety profile in favor of rectal NSAIDs, the ethics and scientific merit of a placebo-controlled approach (vs using rectal NSAIDs as the active control) should be thoughtfully considered and discussed with a regulatory committee.

Future comparative effectiveness research will be necessary to maximally reduce the incidence of PEP. There is currently an ongoing RCT comparing the effectiveness of 2 dosing regimens of rectal indomethacin,[16] and another study comparing indomethacin alone with the combination of indomethacin and prophylactic stent placement is in the final planning phases. Once the efficacy of additional pharmacologic agents is established, studies evaluating potentially complementary combination therapies will be necessary. Ultimately, a combination of multiple pharmacologic and mechanical prophylactic measures addressing different mechanisms of injury may be the most effective approach to PEP prevention.

The results of this systematic review must be interpreted in the context of several important limitations. First, the classification system we developed to define research priority is not validated and was developed with an a priori knowledge of the PEP pharmacoprevention literature. This necessary process was subject to inherent expert bias, which could have influenced the development of the classification system by "fitting" it to available data. Second, some agents allocated to classes 3 and 4 could actually hold more promise than previously demonstrated because negative studies may have been due to type 2 statistical error associated with small sample sizes. Ideally, future RCTs of agents with such limited supporting evidence would only be conducted if justified by very strong preclinical data, as is the case with heme-oxygen-1 up-regulating agent Panhematin,[13] or strong non-ERCP pancreatitis data, such as with intravenous fluid administration.

In addition, a relatively high proportion of potentially relevant articles were not retrievable or translatable, possibly missing reports that could (but are unlikely to) affect the classification of borderline agents. Finally, the exploratory research that we believe is necessary to justify a definitive RCT of a class 3 agent has not been defined. Ideally, this research should not take the form of low quality or underpowered RCTs. Surrogate biomarkers that predict PEP for exploratory research have not been discovered; without these, a small exploratory RCT may be justifiable in some cases. Identifying

intermediate biomarkers for exploratory research and investigating agents in robust preclinical models may represent the best approach to improving the evidence in support of these lower priority agents.

In summary, only rectal NSAIDs can be recommended for pharmacologic PEP prophylaxis in clinical practice. Interested investigators should consider the findings of this systematic review when selecting agents and dosing regimens for future RCTs of PEP pharmacoprevention. A systematic and evidence-based approach to study selection as well as a commitment to conducting high-quality clinical trials may improve our research success in this traditionally disappointing area.

Supplementary Data

Note: To access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2014.11.038.

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Conflicts of interest
The authors disclose no conflicts.