Introduction

Although endoscopic retrograde cholangiopancreatography (ERCP) is commonly performed for diagnosis and management of pancreato-biliary disease, the procedure itself may result in a host of potential adverse events (AEs) – the most common of
which is post-ERCP pancreatitis [1–3]. While the current literature estimates incidence of post-ERCP pancreatitis to be between 3% to 5%, a recent systematic review including over 2000 high-risk patients who underwent ERCP demonstrated an incidence of 14.7% with an associated 0.2% mortality rate [4–6].

Given this high incidence of post-ERCP pancreatitis in association with substantial morbidity, mortality, and healthcare costs of $200 million annually in the United States, it is not surprising that several preventive strategies, both pharmacologic and endoscopic, have been employed [7]. Currently, there are several studies evaluating a variety of pharmacologic prophylaxes for post-ERCP pancreatitis in high-risk patients that include administration of rectal non-steroidal anti-inflammatory drugs (NSAIDs) or aggressive hydration with lactated ringer’s solution (LR) [8–13]. In addition, several studies have demonstrated the efficacy of prophylactic pancreatic stent placement in reducing the rate of post-ERCP pancreatitis and more importantly in reducing the risk of severe post-ERCP pancreatitis [14–16].

However, due to paucity of data, it remains unclear whether pharmacologic, endoscopic, or a combination of both approaches is the preferred strategy to prevent post-ERCP pancreatitis. While previous direct pairwise meta-analyses have attempted to answer this question about prevention of post-ERCP pancreatitis, these types of studies are only able to provide partial information due to inherent design limitations. The primary aim of this study is to design a network meta-analysis, simultaneously analyzing direct and indirect evidence, to compare the effectiveness of pharmacologic and endoscopic treatment approaches to prevent post-ERCP pancreatitis.

Methods
Study design
This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline for reporting systematic reviews and meta-analyses and was conducted following a priori established protocol [17, 18]. We utilized a network meta-analysis and Bayesian framework to combine direct and indirect evidence comparing the relative efficacy of pharmacologic and endoscopic prophylaxis treatments for post-ERCP pancreatitis. This method was chosen to compare multiple interventions and synthesize evidence across a network of randomized controlled trials [19, 20]. In brief, this method allows for simultaneous analysis of direct evidence from comparator trials as well as indirect evidence from different treatments compared to a common comparator (i.e., placebo or no intervention) [21].

Selection criteria and study outcomes
Only randomized controlled trials for high-risk patients were included in this network meta-analysis. High-risk patients were defined in randomized controlled trials by procedure-related factors such as difficult cannulation, pancreatic duct injection, pancreatic sphincterotomy, and pre-cut sphincterotomy in addition to patient-associated factors including female sex, those with sphincter of Oddi dysfunction, and patients with recurrent pancreatitis or prior history of post-ERCP pancreatitis [22–24]. Only trials involving high-risk patients were included.

Included studies involved adult patients (age ≥ 18 years) who underwent ERCP involving use of rectal NSAIDs (i.e., indomethacin or diclofenac), aggressive hydration with LR solution (defined as ≥ 3 mL/kg/h during the procedure and post-procedure intravenous bolus or high-rate infusion), prophylactic pancreatic stent placement, or placebo. Studies evaluating these treatments alone or in combination as well as studies evaluating direct comparator studies to placebo were included. Observational studies and trials evaluating prevention or reduction of post-ERCP pancreatitis were excluded. Post-ERCP pancreatitis was defined by the consensus criteria as a clinical syndrome consistent with pancreatitis as typical epigastric abdominal pain with an amylase or lipase level at least three times [25].

Data sources and literature search strategy
Two authors (BN and TRM) independently conducted a comprehensive search of the literature to identify articles that examined multiple electronic databases. Systematic searches of PubMed, EMBASE, Web of Science, the Cochrane Library databases, and major annual gastroenterology conference proceedings were performed from inception through May 31, 2017. Published abstract proceedings were extracted from major gastrointestinal meetings from January 2010 to May 2017. Scientific meetings included Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), and the American College of Gastroenterology (ACG) annual meeting.

Search terms included: “post-endoscopic retrograde choledochopancreatography (ERP) pancreatitis,” “rectal non-steroidal anti-inflammatory drugs (NSAIDs),” “lactated ringer’s (LR),” “prophylactic pancreatic stent,” and “post-ERP pancreatitis prophylaxis.” All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. Titles and abstracts of all potentially relevant studies were screened for eligibility. Reference lists of studies of interest were then manually reviewed for additional articles with additional references acquired through cross-checking bibliographies of retrieved full-text papers. Any differences were resolved by mutual agreement and in consultation with the third reviewer (UN). In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Data abstraction and quality assessment
Study data were abstracted by two authors (BN and TRM) independently. Risk of bias of individual studies was evaluated and assessed in the context of the primary outcome (i.e., development of post-ERCP pancreatitis) using the Cochrane Risk of Bias assessment tool [26]. The GRADE approach to rate the quality of evidence of estimates derived from this network meta-analysis was also performed [27, 28]. Direct evidence from randomized controlled trials was initially identified as high quality; however, it could be downgraded based on risk of bias, indirectness, imprecision, heterogeneity, or publication bias. Rating
of indirect estimates began at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate but could be down-graded further for imprecision or intransitivity. If direct and indirect estimates were similar (i.e., coherent), then the higher of their rating was assigned to the network meta-analysis estimates.

Statistical analysis

Direct meta-analysis was performed using DerSimonian and Laird random effects model to estimate pooled odds ratio (OR) and 95% confidence interval (CI) [29]. Multivariate random-effects meta-regression was utilized to present results using the Stata mvmeta command extension [30]. Heterogeneity was assessed using I² statistic with values >50% indicating substantial heterogeneity [31]. With regard to publication bias, funnel plot asymmetry and Egger’s regression test were performed as well [32]. Direct comparisons were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark) [33].

Indirect comparisons using a fixed effects Bayesian network meta-analysis was performed using a Markov chain Monte Carlo method in WinBUGS statistical analysis program version 1.4.4 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK) and Network Plots were created in Stata SE-13 [31, 34]. The Bayesian meta-analysis approach offers greater flexibility for the use of more complex models and different outcome types, thereby enabling the simultaneous comparison of all treatment options [35]. Comparative effectiveness of any two treatments were modeled as a function of each treatment in relation to the reference treatment (i.e., placebo or no intervention) to assume consistency of treatment effects across all included randomized controlled trials. This thereby ensures the direct and indirect effect estimates are the same effects.

With regard to network consistency, direct and indirect estimates were evaluated using a node-splitting technique. Posterior distribution of all parameters was estimated using non-informative priors to limit inference to data derived from the trials. No assumptions about efficacy of rectal NSAIDs, aggressive resuscitation with LR, or prophylactic pancreatic stent placement from data external to the trials was included in this systematic review and network meta-analysis.

We used the Markov chain Monte Carlo method to obtain pooled effect sizes [35]. All chains were run with 50,000 simulated draws after a burn-in of 5,000 iterations. The median of the posterior distribution based upon 50,000 simulations was obtained using the 2.5th and 97.5th percentiles, after adjusted for multiple arms. Risk of post-ERCP pancreatitis was reported using the estimate of the beta coefficient and calculated the 95% credible interval.

Information on the relative effects was converted into a probability that a treatment was best, (i.e., first-best, second-best, etc) and into a ranking for each treatment, called the surface under the cumulative ranking curve (SUCRA) [36, 37]. A SUCRA value of 1.0 guarantees when a treatment is certainly the best and 0 when a treatment is certainly the worst. SUCRA values enable overall ranking of treatments for a particular outcome. SUCRA simplifies the information about the effect of each treatment into a single number, thereby assisting the decision-making process.

Sensitivity analysis

Sensitivity analyses were also performed to assess the robustness and generalizability of our findings. Sensitivity analysis was performed for high-quality studies as determined by GRADE assessment. Low-quality studies were excluded. Additional sensitivity analysis was performed for full-text manuscripts. Abstracts that did not result in full manuscript publication were excluded.

Results

Based on previously discussed literature search criteria, a total of 29 trials were included in this study – comprising 7,862 participants comparing four preventive strategies for post-ERCP pancreatitis. A PRISMA flow chart of search results is shown in Fig. 1. A network plot of network meta-analysis comparisons of included studies is highlighted in Fig. 2.

Characteristics of included studies

The primary outcome of post-ERCP pancreatitis was reported in all studies (Table 1). Thirteen studies, including 5,955 patients with rectal NSAID use for prevention of post-ERCP pancreatitis were included [8–10, 17, 38–46]. All but one study (abstract) were fully published manuscripts [45]. Eight studies involving 754 patients evaluated use of aggressive hydration with LR solution in the prophylaxis of post-ERCP pancreatitis [11–13, 47–51]. Four studies were fully published manuscripts, three studies were major gastroenterology meeting abstracts, and a final study was a RCT identified through ClinicalTrials.gov. One of the fully published manuscripts was a double-blinded, placebo-controlled trial that included both LR solution independently, as well as in combination with rectal NSAID use (n=96) [51]. Nine studies, including a total of 1057 participants, evaluated use of prophylactic pancreatic stent placement [14–16, 52–57].

Quality assessment

GRADE assessment was performed for all included studies. These review authors’ judgements about each risk of bias item for each included study is highlighted in Supplemental Fig. 1. A risk of bias summary graph is also available in Supplemental Fig. 2.

Direct treatment comparisons

For direct treatment comparisons, all pharmacologic and endoscopic modalities were compared to placebo or no intervention (Supplemental Table 1). Compared to placebo, use of rectal NSAID therapy significantly reduced odds of post-ERCP pancreatitis by 49% (OR = 0.51, 95% CI [0.33 to 0.77]) (Fig. 3). With regard to the effect of aggressive LR solution, this strategy was also effective in significantly reducing post-ERCP pancreatitis by 52% (OR = 0.48, 95% CI [0.24 to 0.97]) (Fig. 4). When these two modalities were combined and compared to placebo, use of rectal NSAID and aggressive LR solution demonstrated...
75% reduced odds of developing post-ERCP pancreatitis; however, this was not statistically significant (OR = 0.25, 95% CI [0.06 to 0.99]). Prophylactic pancreatic duct stent placement was effective in decreasing post-ERCP pancreatitis by 71% (OR = 0.29, 95% CI [0.17 to 0.48]) (▶ Fig. 5).

Sensitivity analyses

Results from sensitivity analyses are reported in the Supplemental Table 1. Overall, for the primary outcome, the results were largely similar to the main analysis.

Publication bias

There was no evidence of publication bias, based upon either qualitative on funnel-plot asymmetry or quantitative (i.e., Egger regression test, P > 0.05 for all comparisons) (Supplemental Fig. 3, Supplemental Fig. 4, Supplemental Fig. 5).

Network meta-analysis comparisons

With this network meta-analysis, we calculated the mixed effect estimate as a weighted average of both direct and indirect treatment effects. On direct network meta-analysis, all strategies (i.e., both pharmacologic and endoscopic treatments) were associated with a reduced risk of post-ERCP pancreatitis. In a direct network meta-analysis, compared with placebo, use of rectal NSAIDs (B = −0.69, 95% CI [−1.18 to −0.21]), pancreatic stent (B = −1.25, 95% CI [−1.81 to −0.69]), high-volume LR solution (B = −0.67, 95% CI [−1.20 to −0.13]), and combination of LR plus rectal NSAIDs (B = −1.58, 95% CI [−3.0 to −0.17]), were all associated with a reduced risk of post-ERCP pancreatitis. Summary results of our network meta-analysis are summarized in ▶ Table 2. Indirect comparisons were largely similar to those obtained in direct meta-analysis for treatment...
<table>
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<tr>
<th>Author</th>
<th>Year, place of study</th>
<th>Place of study</th>
<th>Type of manuscript</th>
<th>Study design</th>
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<th>Mean age of treatment group (years)</th>
<th>Female gender (%)</th>
<th>Primary ERCP indication of bile duct stone (%)</th>
<th>Trial-specific treatment details</th>
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<td>Sudan</td>
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<td>62</td>
<td>43</td>
<td>51.61 %</td>
<td>74.20 %</td>
<td>IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 20 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h</td>
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<td>Year, place of study</td>
<td>Type of manuscript</td>
<td>Study design</td>
<td>Sample size</td>
<td>Mean age of treatment group (years)</td>
<td>Female gender (%)</td>
<td>Primary ERCP indication of bile duct stone (%)</td>
<td>Trial-specific treatment details</td>
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<td>61.9</td>
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<td>–</td>
<td>IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 10 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h</td>
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<td>49.6</td>
<td>66 %</td>
<td>95.35 %</td>
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<td>2016 Portugal</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 20 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h</td>
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<td>84.62 %</td>
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<td>Initial bolus LR solution of 7.58 mL/kg pre-ERCP, IV LR solution of 5.0 mL/kg/h during ERCP, following by post-ERCP bolus of 20 mL/kg for 90 minutes</td>
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<td>171</td>
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<td>–</td>
<td>50 %</td>
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<td>Initial bolus LR solution of 10 mL/kg pre-ERCP, IV LR solution of 3.0 mL/kg/h during ERCP and continued 8 h post-ERCP, following by post-ERCP bolus of 10 mL/kg</td>
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<td>Mok et al.</td>
<td>2017 United States</td>
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<td>Single-center comparator with multiple therapies*</td>
<td>48</td>
<td>60.25</td>
<td>60.60 %</td>
<td>–</td>
<td>Treatment arms included standard normal saline solution vs normal saline plus indomethacin versus LR versus LR plus indomethacin</td>
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modalities compared to placebo. However, in indirect network meta-analysis, there was no statistically significant difference when treatment modalities were compared with each other. There were overlapping confidence intervals, although differences were observed in effect size.

**Ranking probability**

Ranking probability based on SUCRA indicated that prophylactic pancreatic duct stent placement had the highest probability (SUCRA = 0.81, 95% CI [0.83 to 0.80]) of being ranked the best prophylactic treatment (▶ Fig.6). As highlighted in the SUCRA probabilities figure, a combined strategy of LR solution plus rectal NSAIDs was the second most effective treatment to prevent post-ERCP pancreatitis (SUCRA = 0.76, 95% CI [0.79 to 0.72]), followed by aggressive infusion of LR solution alone (SU-
In this systematic review and network meta-analysis, compared to other treatment approaches, pancreatic duct stent placement appears to be the most effective strategy for the prevention of post-ERCP pancreatitis followed by prophylaxis using aggressive LR hydration and rectal NSAIDs, followed by high-volume LR infusions alone, and finally use of rectal NSAIDs. Pancreatic duct stents reduce post-ERCP pancreatitis by relieving pancreatic ductal hypertension that may develop as a result of transient procedure-induced stenosis [58]. The most recent European Society of Gastrointestinal Endoscopy (ESGE) guideline on prophylaxis of post-ERCP pancreatitis recommends placement of a 5 Fr prophylactic pancreatic stent in high-risk cases [59]. However, pancreatic stent placement is technically challenging. Pancreatic stent requires deep cannulation of the duct and placement of a guidewire. Attempting to place a pancreatic duct stent with subsequent failure actually increases risk of post-ERCP pancreatitis by inducing injury to the pancreatic orifice. Hence, it is these authors’ belief that pancreatic stent placement should only be attempted by providers with familiarity and expertise, in individuals deemed to be high risk.

### Discussion

In this systematic review and network meta-analysis, compared to other treatment approaches, pancreatic duct stent placement appears to be the most effective strategy for the prevention of post-ERCP pancreatitis followed by prophylaxis using aggressive LR hydration and rectal NSAIDs, followed by high-volume LR infusions alone, and finally use of rectal NSAIDs.

![Fig.3](image-url)  
**Fig.3** Direct treatment comparison of rectal NSAIDs to placebo for the prevention of post-ERCP pancreatitis.

![Fig.4](image-url)  
**Fig.4** Direct treatment comparison of aggressive LR solution to placebo for the prevention of post-ERCP pancreatitis.

CRA = 0.51, 95% CI [0.55 to 0.49]), and finally independent use of rectal NSAID use (SUCRA = 0.41, 95% CI [0.44 to 0.38]). A rankogram of interventions to prevent post-ERCP pancreatitis based upon cumulative SUCRA probabilities is highlighted in Supplemental Fig. 6.
a high-risk, and in cases in which cannulation is not intentional and stent placement would be recommended in case of inadvertent cannulation. In patients in whom pancreatic stent placement is not feasible, use of alternative measures to reduce post-procedure pancreatitis should be employed.

Based on our study, aggressive hydration with LR appears to be effective when combined with rectal NSAIDs rather than using rectal NSAIDs alone or LR alone. Use of rectal NSAIDs, potent inhibitors of phospholipase A2, has been increasingly adopted in clinical practice [59, 60]. Current ESGE guidelines recommend routine rectal administration of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication [59]. Aggressive hydration with LR, which attenuates the acidosis that appears to promote zymogen acti-
vation and pancreatic inflammation, may be an effective intervention for preventing post-ERCP pancreatitis. Given the different mechanisms to prevent pancreatitis, it is not surprising that both work synergistically. Moreover, as both rectal NSAID therapy and LR infusion are inexpensive with relative few AEs, combination strategy is now has become a preferred strategy for post-ERCP pancreatitis prevention.

Our study observations are different from a previous network meta-analysis which reported that use of rectal NSAIDs when indirectly compared with pancreatic stent placement alone were associated with lower odds for developing post-ERCP pancreatitis [61]. However, that analysis included both observational studies and randomized controlled trials, which may have contributed to the divergent results. Furthermore, this previous study examined the efficacy of rectal NSAIDs and prophylactic pancreatic duct stent placement among both average-risk and high-risk cohorts. Our study specifically included only high-quality randomized controlled trials in high-risk patients and demonstrates the superiority of pancreatic stent placement as the best prophylactic measure for post-ERCP pancreatitis. Importantly, these findings do not take into account the cost-effectiveness of various therapies (i.e., rectal NSAIDs are inexpensive, easy to use, efficacious, and low risk). Despite our findings, questions still remain about whether all high-risk patients should receive a pancreatic stent—especially individuals who require multiple cannulation attempts of the biliary orifice.

It is important to note that the current systematic review and network meta-analysis is not without limitations. There were no studies comparing treatment strategies other than placebo except for one study that compared aggressive LR hydration to use of rectal NSAIDs. No currently published studies have examined the role of pancreatic duct stent versus rectal NSAIDs; although it should be pointed out there is an actively recruiting clinical trial designed to directly compare these two treatment modalities [62]. This study, with an expected enrollment of over 1400 patients, is a comparative effectiveness multicenter, non-inferiority trial of rectal indomethacin alone versus the combination of rectal indomethacin and prophylactic pancreatic stent placement for prevention of post-ERCP pancreatitis.

While we included indirect comparison in a Bayesian network meta-analysis design, we cannot discount the possibility of conceptual heterogeneity whereby differences may exist in trial design, patient population, intervention (i.e., timing of rectal NSAID administration or operator variability in pancreatic duct stent placement), and outcome assessment which may limit true comparability between included studies [19,27]. Though we performed sensitivity analyses to minimize heterogeneity and generalize our findings, it is important to understand that not all risk factors for post-ERCP pancreatitis are created equal, and combinations or risk factors are not simply additive, but multiplicative [63–66]. Additional limitations include a lack of data on follow-up—though the primary endpoint of post-ERCP pancreatitis lends itself to definitive diagnosis as defined over a discrete period of time as detailed above [25].

Treatment-related AEs were not reported in our systematic review and network meta-analysis as well, which may limit clinical adoption of these strategies, especially pancreatic duct stent placement.

Despite these limitations, our study possesses several strengths. These include the comprehensive and simultaneous assessment of the relative efficacy of four competing or combination strategies to prevent post-ERCP pancreatitis in a high-risk cohort. Although SUCRA probabilities may not easily substitute for clinical judgement on a patient-by-patient basis, focusing on summary effect estimates and GRADE to rate overall quality of evidence allows for better approximations [27]. In addition, while conceptual heterogeneity was present in our study, strategies to limit the effect of conceptual heterogeneity included strict inclusion and exclusion criteria and use of multiple sensitivity analyses to assess the robustness of the results.

Furthermore, although there are several available strategies available to potentially reduce incidence post-ERCP pancreatitis, our results validate the current American Society of Gastrointestinal Endoscopy (ASGE) guidelines recommending pancreatic duct stenting in high-risk individuals—strong recommendation [22]. Future trials such as the one discussed above to assess rectal indomethacin alone versus combination therapy...
with rectal NSAID and prophylactic pancreatic stent placement may help development of future recommendations; however, these are unlikely to occur [62]. Comparison of these different strategies alone may be of limited benefit clinically because the combination of the different treatments has already readily been adopted in clinical practice and shown to be effective with few complications.

Conclusion

In conclusion, based upon this systematic review and network meta-analysis, prophylactic pancreatic stent placement appears to be the most effective preventive strategy for post-ERCP pancreatitis in high-risk patients. Despite these findings, it is these authors’ belief that combination therapy will likely predominate clinical practice. This is in part due to the increased risk of post-ERCP pancreatitis with failed cannulation of the pancreatic duct and the ease and cost of combination therapy with rectal NSAID use and aggressive LR infusion.

Competing interests

Dr. Shyam Varadarajulu is a consultant for Boston Scientific and Olympus. Dr. Udayakumar Navaneethan is a consultant for Janssen, AbbVie, Pfizer and Takeda.

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