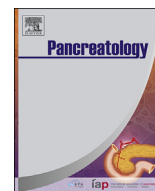




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Combined use of indomethacin and hydration is the best conservative approach for post-ERCP pancreatitis prevention: A network meta-analysis

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ABSTRACT

Objectives: Post-ERCP pancreatitis (PEP) is a life-threatening complication. Given the lack of a causative treatment for pancreatitis, it is of vital importance to minimize this risk of PEP. Multi-target preventive therapy may be the best choice for PEP prevention as disease development is multifactorial.

Aim: We aimed to assess the efficacy of a combination of indomethacin and hydration – type and amount – for PEP prevention via a network meta-analysis.

Methods: Through a systematic search in three databases, we searched all randomized controlled trials involving hydration and indomethacin and ranked the PEP preventive efficacy with a Bayesian network meta-analysis using the PRISMA for Network Meta-Analyses (PRISMA-NMA) guideline. The RoB2 tool was used for risk of bias assessment, surface under the cumulative ranking curve (SUCRA) for ranking and PROSPERO for the study protocol [reg. no. CRD42018112698]. We used risk ratios (RR) for dichotomous data with 95% credible intervals (95% CrI).

Results: The quantitative analysis included 7559 patients from 24 randomized controlled trials. Based on the SUCRA values, a combination of lactated Ringer's and indomethacin is more effective than single therapy with a 94% certainty. The percent relative risk ratios estimate preventive efficacy 70–99% higher for combinations than single therapies. Aggressive hydration with indomethacin (SUCRA 100%) is also significantly more effective than all other interventions (percent relative effect 94.3–98.1%).

Conclusions: A one-hit-on-each-target therapeutic approach is recommended in PEP prevention with an easily accessible combination of indomethacin and aggressive hydration for all average and high-risk patients without contraindication.

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1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is predominantly a therapeutic procedure for biliary or pancreatic duct-associated diseases. According to the American Gastroenterological Association (AGA), more than 650 000 ERCP procedures are carried out each year in the US [1]. The most common and feared

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Abbreviations

AGA	American Gastroenterological Association
AP	acute pancreatitis
ASGE	American Society for Gastrointestinal Endoscopy
AV	aggressive volume (3 mL/kg/h during ERCP, 20 mL/kg bolus after ERCP and 3 mL/kg/h for 8 h after ERCP)
CrI	credible intervals
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
IND	indomethacin
LR	lactated Ringer's
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drugs
NT	no treatment (i.e. placebo)
NV	normal volume (1.5 mL/kg/h during ERCP plus 8 h)
PEP	post-ERCP pancreatitis
RCT	randomized controlled trial
RoB	risk of bias
RR	risk ratio
SUCRA	surface under the cumulative ranking curve

complication is post-ERCP pancreatitis (PEP) occurring in 2–9% of cases [2–6], and <10% of those can be severe or even life-threatening [4–6] with an annual estimated cost that exceeds \$200 million in the U.S [2,3].

Both the European and American Societies of Gastrointestinal Endoscopy (ESGE, ASGE) recommend preventive therapies to lower the risk of PEP development with various levels of evidence [7–9]. Importantly, microcirculatory insufficiency and inflammation were defined as key elements in the pathophysiology of pancreatitis [10–13]. Subsequently, attempts were made to lower the risk of PEP by means of pre-procedural administration of an anti-inflammatory drug and by pro-actively correcting possible hypovolemia. In recent decades, researchers paid closer attention to fluid replacement in basic research and clinical trials as well. The recently published network meta-analyses comparing different preventive techniques, however, did not distinguish between the type and volume of fluid supplementation [14–16].

In this study we performed a network meta-analysis of randomized controlled trials (RCTs) involving PEP prevention with hydration and the most widely used NSAID suppository, *in casu* indomethacin (IND), to evaluate the efficacy of each strategy separately and combined in order to aid clinicians in their decision making which preventive strategy to use.

2. Methods

2.1. Protocol and registration

The study was registered in the PROSPERO database [reg. no. CRD42018112698], and the PRISMA-NMA guideline was followed from study preparation to manuscript finalization [17].

2.2. PICO and eligibility

The PICOS format (patient, intervention, comparison, outcome and study design) was applied to define our research (Table 1). Inclusion criteria were a) involvement at least two interventions of our interest with at least 10 patients above 18 years of age in RCT, b) without limitation of risk for PEP, and b) additional pharmaceutical

Table 1
PICOS criteria.

P	patient undergoing ERCP
I & C	IND – indomethacin; LR – lactated Ringer's; NS – normal saline; AV – aggressive volume; NV – normal volume; NT – no treatment as placebo; LR + IND; NS + IND; AV + IND; NV + IND.
O	Post – ERCP pancreatitis
S	RCT

Table 2

Chemical composition of NS and LR. Higher cc. of chloride may cause hyperchloremic acidosis in NS solution. Otherwise, lactate lowers the risk of acidosis, thus guaranteeing substrates for the biocarbonate base in pH balanced LR. NS – normal saline; LR – lactated Ringer's.

Ingredients	Saline	Lactated Ringer's
Sodium (mEq/liter)	154	131
Chloride (mEq/liter)	154	110
Potassium (mEq/liter)	0	4–5
Calcium (mEq/liter)	0	3
Lactate (mEq/liter)	0	28
Osmolarity (mOsmol/liter)	308	273
pH	5.6	6.5

treatments were exclusion criteria.

2.3. Search

A systematic literature search was conducted to identify all RCTs on PEP prevention in three databases: MEDLINE (via PubMed), Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). The keywords in the literature search were 'post-ERCP pancreatitis and prevention' from inception to May 2020 without any restrictions (searching MeSH via PubMed; post-ercp[All Fields] AND ("pancreatitis"[MeSH Terms] OR "pancreatitis"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields])).

2.4. Selection and data extraction

Full-text articles and conference abstracts were included in the synthesis. Duplicates were excluded in reference manager software (Endnote), with titles and abstracts then selected by two independent authors (KM and ZS). In the case of disagreement, a third author made the final decision (PH). Data was collected in an Excel file for synthesis in two groups with six interventions each (KM, ZS and PH in the case of disagreement). In *Group I* IND monotherapy was compared to crystalloids and their combinations; LR, NS, LR + IND, NS + IND and NT. In *Group II* we examined the relevance of fluid amount, the comparators for IND were therefore; AV, NV, AV + IND, NV + IND and NT (see network plots in Figs. 1 and 3, additional details in Sup Table 1). IND and NT were two treatments that were possible to include in both *Group I* and *II* analyses.

2.5. Risk of bias assessment

The risk of bias in randomized trials (RoB) of all included articles was assessed using the revised RoB 2 tool [18] (KM, ZS and PH in the case of a disagreement) (Sup Table 2).

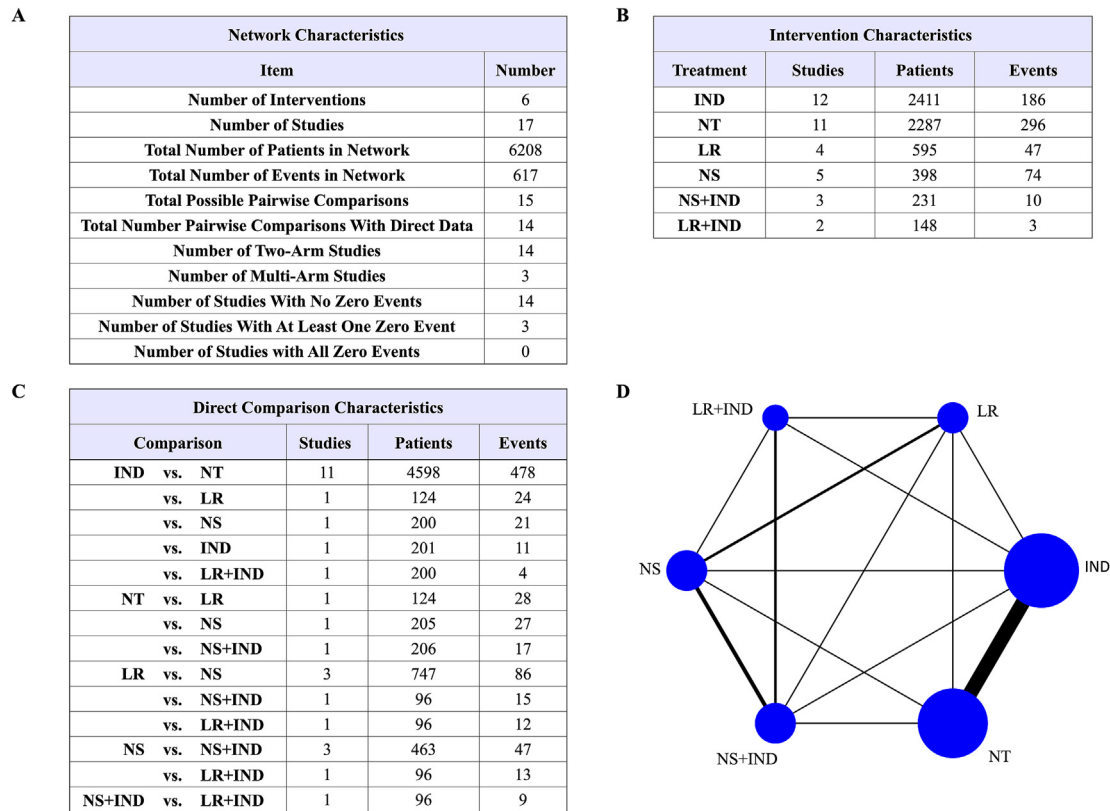


Fig. 1. Characteristics of network for fluid quality measurements. **A** Data for 17 articles comparing different interventions to prevent post-ERCP pancreatitis (efficacy outcome). Two-arm studies compared two interventions, while multi-arm studies compared four treatments (in two studies) and three treatments (in one study). **B** Intervention groupwise data characteristics. **C** Comparison features between arms. **D** Network plot of randomized controlled trials. Nodes are the different interventions weighted according to the number of studies with the respective interventions. Edges represent the direct comparisons weighted according to the number of studies testing the comparators. LR – lactated Ringer's; NS – normal saline; IND – indomethacin, NT – no treatment.

2.6. Statistics

A Bayesian method was used to perform pairwise meta-analyses and NMAs with the random effect model. The NMA takes advantage of two statistical innovations; 1) the evaluation of indirect comparisons; therefore, we can estimate the effect of 'A' vs. 'B' indirectly if both 'A' and 'B' is compared to 'C'; 2) the NMA combine direct and indirect comparisons and provide estimates of the relative effect of every alternative versus every other alternative [19]. We tested consistency with node splitting, when the associations are analysed between the direct and indirect comparisons [20]. We used risk ratios (RR) for dichotomous data with 95% credible intervals (95% CrI) and percent relative effect. We optimized the model and generated posterior samples using Monte Carlo methods running in four chains. We set at least 20 000 adaptation iterations to obtain convergence and 10 000 simulation iterations. We also ranked interventions with posterior probability by calculating the surface under cumulative ranking (SUCRA) curve values. The higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0 the SUCRA value, the more likely that a therapy is in the bottom rank, or one of the bottom ranks [21]. All calculations were performed with R (V. 3.5.2) package gemtc (V. 0.8–2) along with the Markov Chain Monte Carlo engine JAGS (V. 3.4.0) and STATA 17.0 (StataCorp LLC) [22].

3. Results

The database search yielded 1011 records that underwent a

rigorous selection process (see Methods) (Sup Fig. 1). Data from 24 RCTs including 7559 patients were analysed in this study; 17 RCTs comparing different fluid types (Group I) [23–39] and 23 RCTs reporting on different fluid quantities that were used (Group II) [23–37,40–46] (Figs. 1 and 3).

Originally, we planned to investigate the efficacy of indomethacin, lactated Ringer's and combination of these. Our search strategy gave an opportunity to add further interventions; therefore, we included normal saline and fluid volume as well. We did not have enough data to investigate one outcome of our interest, the severity of PEP.

3.1. Group I

Out of the 15 possible comparisons, articles contained data for 14 direct pairwise comparisons with the exception of the LR + IND vs NT group, meaning that these two interventions have never been examined in parallel in a randomized study design.

617 subjects out of 6208 ERCPs developed PEP (10.15%). The majority of the patients were involved in the IND vs NT group with almost 4600 cases from 11 studies (Fig. 1C) [24–30,32,34,35,37].

A forest plot of summarized data shows the level of difference between the treatments (Sup Fig. 2). $RR > 1$ and $CrI > 1$ demonstrate that LR + IND and NS + IND significantly reduced the frequency of PEP compared to all treatments. This analysis reveals that a combination of fluid and anti-inflammatory therapy is significantly more effective in PEP prevention than either single treatment.

Moreover, the ranks based on the SUCRA values indicate a greater importance of hydration in prevention and also suggest that

the quality of the solution makes difference in efficacy in combination (94% vs 85%) and single use (52% vs 46%) (Fig. 2A). It is worth mentioning that the administered fluid amounts were very similar (Fig. 2A). The percent relative effect was calculated from risk ratio estimates, proving that the efficacy in PEP prevention is 70–99% higher for combinations compared to single therapies. Risk ratio estimates are showed in Fig. 2C, calculation was made with a formula;

$$\text{percent relative effect}(\%) = (1 - \text{risk ratio estimate}) * 100$$

e.g. the percent relative effect of LR + IND compared to LR equals; $1 - 0.21 * 100$, therefore 79%.

Of note, a limitation should be acknowledged that comparability tests between direct, indirect and estimated comparisons show significant differences, meaning that a future RCT might lead to different results than is estimated by the network. This uncertainty is based on a zero event in one study [28] (NT vs NS + IND; direct OR 5.9e+7 (53, 5.7e+17), indirect OR 7.6 (2.8, 24), network OR 12 (4.6, 33) $p = 0.005$).

3.2. Group II - quantity

Although more RCTs were identified that compared various amounts of fluid replacement, fewer comparisons were examined: we were able to carry out eight out of the possible 15 pairwise comparisons (Fig. 3). Nevertheless, the network study design with indirect calculations is suited to estimate the difference between the arms without direct treatment comparisons, meaning that it is possible to estimate outcomes of treatments that have never been directly compared to each other. An inconsistency test shows comparability between the estimated, indirect and direct comparisons, showing that a RCT is likely conclude the same as is estimated

by the network. The inconsistency test showed that all estimates are probably true predictions (AV vs AV + IND: direct OR 8.8e-29 (4.2e-64, 0.0012), indirect OR 3.3e-12 (9.2e-33, 0.11), network OR 2.6e-14 (2.2e-49, 0.0088) $p = 0.3225$; NT vs AV + IND: direct OR 1.2e+8 (58, 1.2e+44), indirect OR 3.5e+12 (21, 1e+32), network OR 9.7e+13 (2.8e+2, 1.3e+49) $p = 0.828$).

A forest plot of summarized data presents the level of difference between the treatments as non-significantly or significantly worse or better or equal (Sup Fig. 3). $RR > 1$ and $CI > 1$ demonstrate that AV + IND significantly reduced the frequency of PEP compared to other treatments. NV + IND is significantly worse in preventing PEP compared to AV + IND and is equal to all other treatments. The efficacy of AV + IND is well represented by the SUCRA value-based ranking (Fig 4AB). The percent relative effect was calculated from risk ratio estimates, which show a superior efficacy (94.3–98.1%) in PEP prevention for the combination of AV and IND. Risk ratio estimates are showed in Fig. 4C, calculation was made with a formula;

$$\text{percent relative effect}(\%) = (1 - \text{risk ratio estimate}) * 100$$

e.g. the percent relative effect of AV + IND compared to NV + IND equals; $1 - 0.057 * 100$, therefore 94.3%.

4. Discussion

According to the latest guidelines, there is currently no causative treatment for pancreatitis; only supportive therapy and complication-preventive interventions are recommended [7,8,47]. Hence, those measures should be instituted that have the potency to prevent the development of the disease, based on either generally applicable or aetiology-based preventive principles. PEP is a complication of a therapeutic intervention; aetiology-based prevention is therefore not feasible because the therapy itself injure

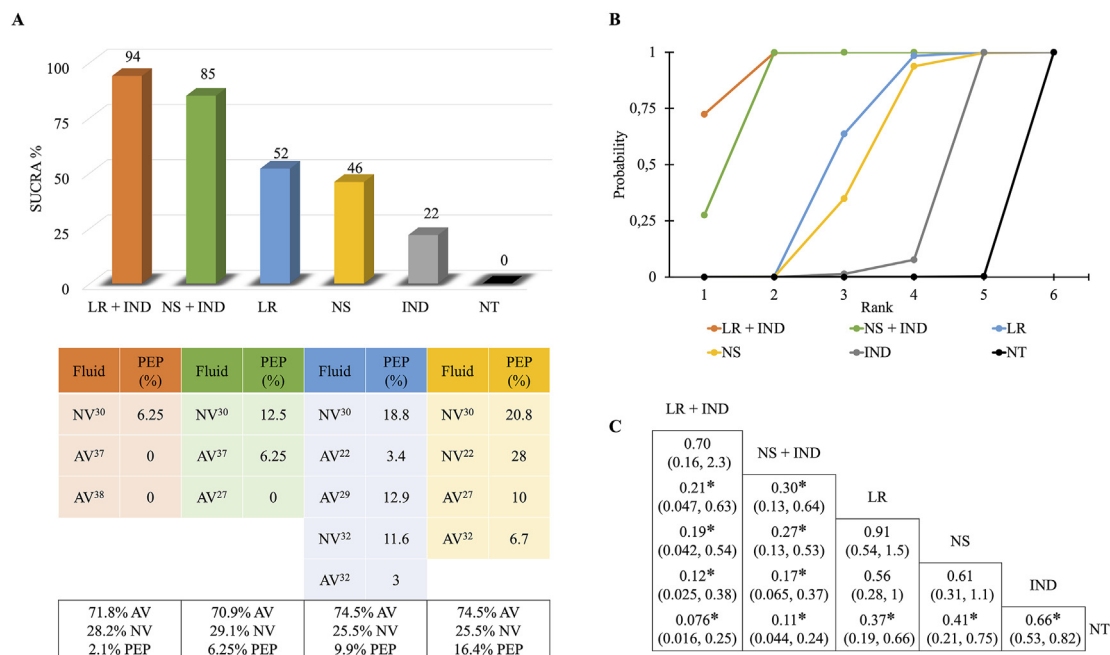


Fig. 2. Interventions with the possibility of being ranked from best to worst efficacy in PEP prevention. **A** Probability chart showing likelihood in percentage of treatments being ranked from best to worst based on the SUCRA values. The table at the bottom lists the amount of fluid that was administered in the cited study and the outcome rate for comparability considerations. **B** The analysis shows the probability of all interventions to match the top rank with a numerical representation of the SUCRA. The closer to 1 the SUCRA value is, the higher the likelihood that a therapy is in the top rank; the closer to 0 it is, the more likely that a therapy is in the bottom rank. **C** League table with RR estimates for each pair of interventions accompanied by 95% CrI according to the efficacy of PEP prevention (*significant difference where $RR < 1$ and $CrI < 1$). LR – lactated Ringer's; NS – normal saline; IND – indomethacin; NT – no treatment; AV – aggressive volume; NV – normal volume; PEP – post-ERCP pancreatitis, RR – risk ratio, CrI – credible interval, SUCRA – surface under the cumulative ranking curve.

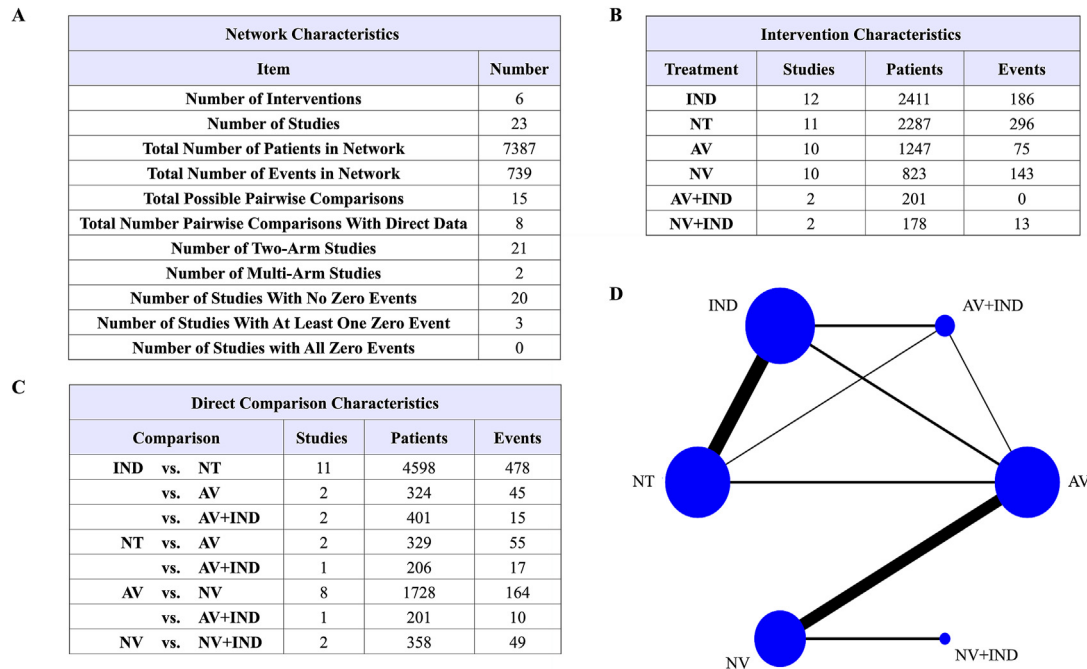


Fig. 3. Characteristics of network for fluid quantity measurements. **A** Data from 23 included articles. Two-arm studies compared two interventions, while multi-arm studies compared four treatments (in one study) and three treatments (in another). **B** Intervention groupwise data characteristics. **C** Comparison features between arms. **D** Network plot of randomized controlled trials comparing different interventions to prevent post-ERCP AP (efficacy outcome). Nodes are weighted according to the number of studies with the respective interventions. Edges are weighted according to the number of studies testing the comparators. AV – aggressive volume; NV – normal volume; IND – indomethacin, NT – no treatment.

the pancreas in a certain level as an insult by the equipment and cellular damage caused by the contrast media (pressure and chemical reaction), these two mechanism can not be avoided, however the damage can be decreased to a minimum level.

In ERCP the mechanical insult causes obstruction of the main pancreatic duct (mostly due to oedema and mechanical injury due to guidewire manipulation), triggering the inflammatory processes. If the obstruction and its consequences are efficiently prevented the pancreas might be saved from PEP. Stent insertion and epinephrine injection might be a solution to ameliorate the obstruction. Stent insertion maintains outflow of the pancreatic juice while epinephrine injection decreases the oedema through vasoconstriction and relaxing the oddi sphincter, however none of them have effect on the launched cellular damage (see Graphical abstract).

The mechanical prevention has been well investigated and there is quite strong agreement concerning the benefit of pancreatic duct stent insertion across guidelines [7–9]. Pancreatic stenting has proved to be efficient in PEP prevention; however, the success rate is dependent on the operator's skills to achieve swift pancreatic duct cannulation and the ductal anatomy of the pancreas. Those factors might be a reason for the wide PEP incidence range among studies in the literature and in this network meta-analysis (Figs. 2A and 4A). After multiple attempts, the risk of AP is significantly elevated; therefore, we only recommend this technique in selected cases, especially with inadvertent guidewire insertions into the pancreatic duct. We also need to mention that there is no agreement on the types of pancreatic stents, e.g. pigtail, diameter, flaps no flaps, etc. to be used for PEP prevention. In the current manuscript therefore, we decided to focus on the evaluation of non-invasive and relatively easy to apply techniques for PEP prevention (i.e., IND and fluid therapy) which are universally applicable independent from operator expertise. The focus of this paper is to

compare the fluid variants (type and quantity) as an addition to the recently published network meta-analyses [14–16,48]. None of these studies differentiated between lactated Ringer's or normal saline, and aggressive or normal volume [14–16].

The newly established ESGE 2020 guideline's algorithm for PEP prophylaxis prioritizes NSAID and suggests considering hydration only when NSAID is contraindicated [9]. Interestingly a recent network meta-analysis revealed that rectally administered indomethacin or diclofenac is not only efficient in high-risk patients to prevent PEP but the efficacy equals placement of a pancreatic stent [49].

4.1. One of the most important factors in PEP development is the microcirculatory insufficiency

In the earliest stage of PEP development, there is a microcirculatory impairment due to an increased parenchymal pressure that is propagated by the high pressure within the obstructed pancreatic duct by bouts of contrast injection and later on due to (temporary) outflow obstruction caused by papillary oedema. The impaired fluid distribution is reparable with fluid substitution as it maintains perfusion of the small vessels, thus lowering the risk of hypoxia, reactive oxygen species generation and mitochondrial injury. The most commonly used fluid infusions for volume expansion are normal saline and lactated Ringer's infusions. It is therefore important to understand their main differences, potential benefits, and disadvantages. Normal saline is a hypertonic acidotic fluid containing higher sodium and chloride than lactated Ringer's, which carries the risk of hyperchloremic acidosis (Table 2).

On the other hand, LR also contains sodium lactate, which is metabolized by the liver, producing bicarbonate as a base to reduce acidity (Table 2) [50]. Rumbus et al. examined the correlation between acidosis and pancreatitis in an experimental model and on

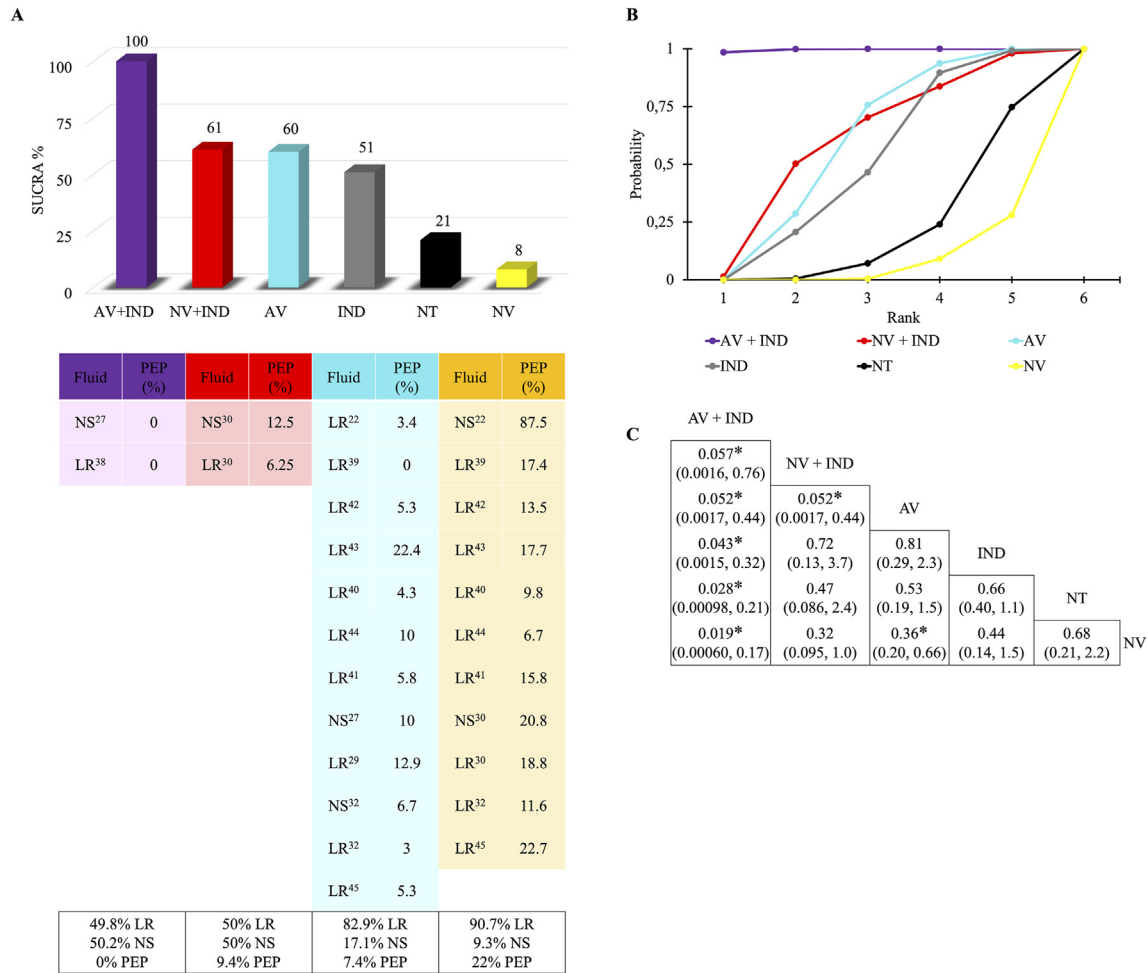


Fig. 4. Interventions with the possibility of being ranked from the best to the worst efficacy in PEP prevention. **A** Probability chart showing the likelihood in percentage of treatments ranked from best to worst based on the surface under the cumulative ranking curve (SUCRA). The table below lists the type of fluid administered in the cited study and the rate of outcome for comparability considerations. **B** The analysis shows the probability of all interventions to match the top rank with a numerical representation of the SUCRA. The closer to 1 the SUCRA value is, the higher the likelihood that a therapy is in the top rank; the closer to 0 it is, the more likely that a therapy is in the bottom rank. **C** Risk ratio estimates for each pair of interventions accompanied by 95% CI according to the efficacy of PEP prevention (*significant difference where $RR < 1$ and $CrI < 1$). AV – aggressive volume; NV – normal volume; IND – indomethacin; NT – no treatment; LR – lactated Ringer's; NS – normal saline; PEP – post-ERCP pancreatitis.

patient-based data, and found that acidosis significantly aggravated the severity of acute pancreatitis (AP) while severe AP further decreased the blood pH, causing a vicious circle [51]. Kellum et al. also called attention to the importance of acidity in inflammation development when they observed that the level of pro-inflammatory cytokines was increased in septic rats with hyperchloremic acidosis [52]. In an abdominal sepsis animal model, resuscitation with NS was associated with hyperchloremic acidosis, a more altered microcirculation leading to greater haemodynamic instability and more severe organ dysfunction. In this study, the survival time was significantly longer in the LR group compared to the NS group (17 h [14 to 20] vs 26 h [23 to 29], $p < 0.01$) [53].

4.2. Besides the composition of the fluid replacement, timing and fluid quantity are also intensively investigated

While an adequate volume of fluid replacement is essential to restoring perfusion and oxygenation, fluid overload on the other hand might cause complications, such as cardiac failure, pulmonary oedema, tissue damage and impaired bowel function [54]. However, carefully monitored aggressive intravenous fluid replacement therapy was found more effective in avoiding the negative

outcomes of AP in meta-analyses of RCTs [55–58]. The latest guidelines for AP treatment suggest fluid therapy as the first step after AP diagnosis because its beneficial effect is maximal in the first 24 h of disease development [47,59,60]. 'The sooner, the better' might therefore be a rational approach in PEP prevention as long as there are no contraindication.

Recent RCTs also suggest the efficacy of early aggressive fluid therapy in PEP prevention. In an RCT, Alcivar-Leon et al. investigated the preventive efficacy of AV LR compared to NV NS and showed a statistically significant and clinical favourable effect of the former in PEP prevention (3.4% and 87%, respectively, RR 0.41; 95% CI 0.20–0.86; $p = 0.016$) [23]. Park et al. also found significant differences in comparing AV LR to AV NS and NV LR groups (3.0%, 95% CI 0.1–5.9 vs 6.7%, 95% CI 2.5–10.9 vs 11.6%, 95% CI 6.1–17.2, $p = 0.03$) [33]. The quantitative importance of fluid substitution is shown with lower RR in PEP rate for the AV LR group (0.26) rather than for the NV LR group (95% CrI 0.08–0.76; $p = 0.008$). With reference to the importance of a balanced solution, this study resulted in no superiority of AV NS treatments to NV LR (RR 0.57, 95% CI 0.26–1.27; $p = 0.17$) [33].

When Masjedizadeh et al. compared AV LR and IND treatments to control cases, it was concluded that LR is the most effective

Table 3

Summary of PEP prophylaxis based on available guidelines and our newly established recommendations in bold.

Implementation to practice	Patient's risk of PEP	
	High risk	All risks
Stent	Strongly considered ³ Recommended ⁴	NA
Indomethacin	Recommended ³	Recommended ^{3,4}
Hydration		Suggested
Hydration and indomethacin		Suggested

intervention in PEP prevention ($p = 0.036$) [30].

4.3. Despite preventive efforts, if inflammation develops, the severity of the processes might be mitigated due to the interruption of the inflammatory cascade with anti-inflammatory drugs [61]

Nonsteroid anti-inflammatory drugs (NSAIDs) are widely prescribed to treat inflammatory diseases like arthritis (rheumatoid arthritis, osteoarthritis and gout), bursitis and tendinitis. Their efficacy is due to the inhibition of cyclo-oxygenase, which is responsible for prostaglandin and thromboxane formation from arachidonic acid-triggering inflammation [62].

Diclofenac and indomethacin are the two mostly investigated and used NSAIDs in the prevention of PEP and are compared in 11 meta-analyses to date. These MAs conclude that both have significant efficacy [63–72], in average-risk and high-risk patients as well [63,66,67,69,71], and that non-rectal administration like oral, intramuscular or intravenous are not efficient [63,66–68,70,71]. In addition, four more NSAIDs (valdecoxib, celecoxib, naproxen, ketoprofen) are examined in meta-analyses [66,68,70,73–75] of which only naproxen showed to be effective in PEP prevention [66]. In the current manuscript we focus on indomethacin because it provided the possibility to include hydration to this network meta-analysis.

In addition to the documented pharmacological effect of NSAIDs, efficacy for PEP prevention varies widely between studies. Choksi et al. found a positive correlation between the prevention of PEP and indomethacin usage, Moon et al. and Andrade-Dávila et al. found significantly fewer episodes in the indomethacin group compared with the placebo group ($p = 0.005$ and $p = 0.01$, respectively), and in a study by Elmunzer et al. indomethacin significantly reduced the occurrence and severity of PEP ($p = 0.005$ and $p = 0.03$) [24,27,36,37]. Studies by Döbrönte et al. Montano et al. and Levenick et al. however, did not find indomethacin effective for PEP prevention [25,26,29,32]. Sotoudehmanesh et al. reported that IND was ineffective in PEP prevention; however, a significant effect was shown in severity reduction [35].

Studies in which IND was used for PEP prevention, all with rectal application to lower the risk of side-effects, reported no higher risk of bleeding [24,27,29,31,34,35]. The absorption peak concentration of 30 min to 1 h and elimination half-life of 6–8 h allow rectally administered IND to be effective when added before or after ERCP [76].

4.4. The question arises whether the efficacy is further increased if volume expansion and NSAIDs are combined

There is much less uncertainty about the efficacy of IND when used in combination with fluid treatments. Selimah et al. examined combined fluid and drug treatment and found a positive effect for AV LR solution with IND compared to IND alone [39]. Hosseini et al. compared (1) IND, (2) NS and (3) an IND and NS combination to (4) a placebo and found that PEP could be significantly prevented if the combination was used [28]. In a different design, where (1) NS, (2)

NS + IND, (3) LR and (4) LR + IND were compared by Mok et al. it was also concluded that LR + IND was significantly more effective in PEP prevention than any other condition [31].

Considering the different pathological pathways and consequences of increased ductal pressure, impaired microcirculation and inflammation, a multi-faceted ‘one-hit-for-each-target’ seems a rational approach attempting to prevent PEP. Its potential benefit is dependent on the different modes of action of each individual intervention with microcirculatory reperfusion restoring adequate blood supply and oxygenation and anti-inflammation therapy decreasing the severity of AP.

4.5. Limitations

Several limitations of this network meta-analysis must be acknowledged. Some patients, equally distributed among the arms within the studies, had undergone stent insertions. We were unable to examine the role of these stents due to the limited access to data. Also, subjects in our pool had different a priori risks for developing PEP (Sup Table 1).

Future subgroup analyses of patient individualized data from RCTs could lead to more precise estimations with proper risk stratification of patients. It is also known that older age (over 60) brings significantly worse outcomes of pancreatitis [77,78]; however, we do not know if preventive efficacy is age-related. In the studies analysed here, the mean age varied between 45 and 62.

5. Conclusion

Our network meta-analysis shows that indomethacin and hydration has an additive effect over each treatment alone in PEP prevention. A combination of these therapies should be applied (Table 3). For liquid replacement there is no absolute contraindication. For indomethacin contraindications comprise allergy and kidney failure.

5.1. Implementation to research

Although the result of this analysis are already quite convincing with regard to which (combination of) therapy(ies) should be used to prevent PEP, there are some limitations to this network meta-analysis that were already addressed above. In order to address these limitations and to develop evidence-based level I recommendations, an adequately powered multicentre RCT should be designed and executed.

5.2. Implementation to practice

This network meta-analysis suggests that a combination therapy of i.v. fluid replacement and NSAID, i.e. lactated Ringer's and rectal indomethacin, is superior in preventing PEP compared to either other combination or single therapy.

Author contributions

KM: conceptualization, data curation, funding acquisition, investigation, methodology, project administration, supervision, visualisation, writing – original draft, NG: data curation, formal analysis, visualisation, writing – original draft, ZS: validation, methodology, writing – review & editing, MS: project administration, writing – review & editing, PJH: data curation, writing – review & editing, BT: validation, writing – review & editing, BE: supervision, writing – review & editing, AV: investigation, writing – review & editing, MA: writing – review & editing, IB: conceptualization, writing – review & editing, MJB: conceptualization, writing – review & editing, PH: conceptualization, investigation, supervision, resources, funding acquisition, writing – review & editing.

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Data transparency statement

The data that support the findings of this study are openly available in the supplementary material and tables of the article.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2021.07.005>.

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