

Dear Editor and Reviewers:

We appreciate your review of our manuscript and the valuable suggestions provided. Please find below point-by-point responses to the reviewer comments and a summary of the revisions made in the manuscript.

Reviewer #1: The simple review by Saito H. et al summarized current measures to prevent PEP. However, the review was not well structured and many important factors were missing.

1. Some content in the "Risk factors" section and "Patients selection" sections are repetition.

Our reply:

Our hypothesis in this study states that there is a higher risk of PEP in patients with asymptomatic CBDs. Therefore, we would like to retain the following statements in the section for risk factors. "Due to the absence of cholestasis, patients with asymptomatic CBDs have normal total bilirubin levels and non-dilated CBD, and can confound the assessment of patient-related risk factors for PEP[20]. Furthermore, floppy major duodenal papilla due to low bile duct pressure often results in difficult biliary cannulation in asymptomatic patients[20]. Therefore, the risk of PEP might be higher in patients with asymptomatic CBDs, who are susceptible to the synergistic effect of the independent risk factors for PEP, than in those with symptomatic CBDs."

2. The role of endoscopists in the development of PEP should not be included in patients selection.

Our reply:

We thank the reviewer for their suggestion. We have deleted the statement on the role of endoscopists in the development of PEP from the patient selection section of the revised manuscript.

3. The role ERCP techniques (EPT vs large balloon dilation, the duration of balloon dilation, et al.) were missing.

Our reply:

We thank the reviewer for their valuable suggestion. As pointed out by the reviewer, various ERCP techniques, including EPT vs. EPLBD, are associated with the development of PEP. However, as this is an opinion review, the contents of the review were strictly limited to addressing the unresolved issues associated with better prophylaxis of PEP.

4. Hydration lacks references to further discuss it.

Our reply:

We have added appropriate references that elaborated on the role hydration in the prevention of PEP. We have added the following sentences in the revised manuscript:

“Recent meta-analyses revealed that aggressive hydration with 35–45 mL/kg of lactated Ringer’s solution administrated over 8–10 hours was associated with a lower incidence rate of PEP, with odds ratios ranging from 0.29 to 0.47[59-61]. Furthermore, aggressive hydration was also found to reduce the incidence rate of moderate-to-severe PEP, with an odds ratio of 0.16<sup>[59]</sup> and no differences in fluid overload-related complications[60,61].”

5. The type of NASID may also plays a different role in preventing PEP

(indometacin vs indometacin ).

Our reply:

We thank the reviewer for their suggestion. As per the ASGE and ESGE guidelines, rectal diclofenac and indomethacin are considered to have similar efficiency for the prophylaxis of PEP. We have added the following statement in the revised manuscript:

“Rectal diclofenac and indomethacin are considered to exert similar beneficial effects for the prophylaxis of PEP, and a rectal NSAID dose of 100 mg is recommended in the ASGE and ESGE guidelines[3,4].”

6. The controversial role of somatostatin should be discussed.

Our reply:

Rectal NSAIDs and aggressive hydration are recommended by the ESGE and ASGE guidelines to prevent PEP. As shown in Table 3, the ESGE guidelines do not recommend the use of somatostatin owing to the controversial results obtained in studies examining its utility for the prevention of PEP. As mentioned earlier, the scope of this opinion review was limited to discuss the strongly recommended factors for the prevention of PEP as per the ESGE and ASGE guidelines. Therefore, we did not discuss the controversial role of somatostatin in this review.

7. The authors should draw a flowchart to clarify how to prevent PEP, from patient selection to post-ERCP measures.

Our reply:

There are no established criteria for patient selection to study prevention of PEP; therefore, it is extremely challenging to create a flowchart for the same that can

be utilized for PEP prevention. Although ASGE and ESGE guidelines recommend therapeutic ERCP in patients with CBDS regardless of the presence of symptoms or imaging evidence of stones, this opinion review questions the suitability of this approach.

8. Most importantly, many reviews have been published on this issue and nothing new found in this review.

Our reply:

As commented by the reviewer, numerous reviews have been published on this issue. However, this opinion review was focused on pointing out the unresolved questions regarding estimation of the synergistic effect of risk factors for PEP, selection of patients for ERCP, and selection of methods for PEP prophylaxis that should be addressed in future studies.

Reviewer #2: A mini review but well compiled. The following are the suggestions to improve the manuscript:

1. All guidelines on the subject to be out in a tabular form

Our reply:

We have added the recommendations for post-ERCP pancreatitis prophylaxis included in the ASGE and ESGE guidelines to the revised Table 3.

2. Summary of important systematic reviews and meta analysis to be provided

We have added the summary of important systematic reviews and meta-analyses to the sections discussing PEP prophylaxis during ERCP and the pharmacologic methods for PEP prophylaxis.

3. The following references be added to enhance the discussion :

批注 [Editor1]: Tip: **Redundancy & Repetition:** Repetition of the same word or a phrase that conveys the same meaning hampers the readability of a sentence.

a. Choudhary A, Bechtold ML, Arif M, Szary NM, Puli SR, Othman MO, Pais WP, Antillon MR, Roy PK. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. *Gastrointestinal Endoscopy* 2011; 73(2): 275-282→

b. Fan JH, Qian JB, Wang YM, Shi RH, Zhao CJ. Updated meta-analysis of pancreatic stent placement in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastroenterol.* 2015 Jun 28;21(24):7577-83.

c. Katalin Márta, Noémi Gede, Zsolt Szakács, Margit Solymár, Péter Jenő Hegyi, Bálint Tél, Bálint Erőss, Áron Vincze, Marianna Arvanitakis, Ivo Boškoski, Marco J. Bruno, Péter Hegyi, Combined use of indomethacin and hydration is the best conservative approach for post-ERCP pancreatitis prevention: A network meta-analysis, *Pancreatology*, Volume 21, Issue 7, 2021, Pages 1247-1255,

d. Xiang Ding, FuCheng Zhang, YaoJun Wang, Risk factors for post-ERCP pancreatitis: A systematic review and meta-analysis, *The Surgeon*, Volume 13, Issue 4, 2015, Pages 218-229,

Our reply:

We thank the reviewer for their helpful suggestion. We have added the following reference to enhance the discussion in the revised manuscript.

Ref.38: Choudhary A, Bechtold ML, Arif M, Szary NM, Puli SR, Othman MO, Pais WP, Antillon MR, Roy PK. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. *Gastrointestinal Endoscopy* 2011; 73(2): 275-282→

Ref.34: Fan JH, Qian JB, Wang YM, Shi RH, Zhao CJ. Updated meta-analysis of

pancreatic stent placement in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastroenterol.* 2015 Jun 28;21(24):7577-83.

Ref.64: Katalin Márta, Noémi Gede, Zsolt Szakács, Margit Solymár, Péter Jenő Hegyi, Bálint Tél, Bálint Erőss, Áron Vincze, Marianna Arvanitakis, Ivo Boškoski, Marco J. Bruno, Péter Hegyi, Combined use of indomethacin and hydration is the best conservative approach for post-ERCP pancreatitis prevention: A network meta-analysis, *Pancreatology*, Volume 21, Issue 7, 2021, Pages 1247-1255,

Ref.13: Xiang Ding, FuCheng Zhang, YaoJun Wang, Risk factors for post-ERCP pancreatitis: A systematic review and meta-analysis, *The Surgeon*, Volume 13, Issue 4, 2015, Pages 218-229,

Reviewer #3: It is an essential contemporary topic and is well addressed in this manuscript. The manuscript, I presume, will enrich current knowledge on this topic. However, I would suggest minor alterations to the manuscript title to make it more appealing.

Suggested title: Current approaches and questions yet to be resolved for the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Our reply:

We thank the reviewer for their recommendation. The title of the article has been revised.

Reviewer #4:

1 There are nearly ten publications of reviews about PEP following ERCP. Among them, the article titled as "Non-steroidal anti-inflammatory drugs, intravenous fluids, pancreatic stents, or their combinations for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and network meta-analysis" (PMID: 34214449 DOI: 10.1016/S2468-1253(21)00170-9), has systematically discussed the efficacy of combined treatment. So, it is not logical for the author to describe that "To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP is scarce."

Our reply:

We are grateful to the reviewer for the suggestion. We have revised "To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP is scarce." to "To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP should be discussed."

2 More importantly, the present manuscript does not discuss the synergistic effect of the independent risk factors on PEP. Please add the important

content. So, the manuscript did not exhibit its novelty.

Our reply:

As patients often harbor multiple risk factors for PEP, the potential synergistic effect of independent risk factors for PEP should be considered. We have added the result of a prospective multicenter study performed by Freeman ML.: "A prospective multicenter study revealed the escalation of PEP risk in patients with multiple risk factors for PEP. The odds ratios in female patients, in female patients with normal serum bilirubin levels, and female patients with normal serum bilirubin and difficult cannulation were 2.5, 4.8 and 16.2, respectively[5]." However, only a few studies examined the synergistic effect of independent risk factors for PEP. Therefore, this review suggested that further studies should be conducted to establish methods for estimation of the synergistic effect of independent risk factors for PEP.