Peer Review File

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Reviewer A

The authors present a clear and well readable overview on imaging in IAP and IRAP. They discuss landmark studies and guidelines on this topic, as well as current knowledge gaps. Based on the available literature, they make clear and useful recommendations for clinical practice. Management of IRAP is a difficult problem and is the cause for much heated discussion among clinicians. This review will help clinicians distinguish between the diagnostic options and help recommend the best management option for individual patients (according to the knowledge in current literature).
However, partly due to the lively discussion on this topic, I do have a few suggestions as listed below:

Major issues:
Comment 1: "The phrase, "recurrent … the qualitative synthesis." (line 115-126): Currently, the study selection process is not entirely clear to me. Please clarify how many assessors performed the manual review of the articles resulting from the search, and how discrepancies between the assessors was resolved. Additionally, I do not understand the difference between the first round of review and the second round (in Figure 1 stated next to "screening" and "eligibility", and in the main text "Manual review of … after manual review." (line 117-124) and "The articles were … were further excluded." (line 124-125)). Were the two rounds performed by different assessors? Was the first round based only on title and abstract while the second round was based on full-text? Please clarify.
Reply 1: In the first round of review, two assessors (author P.C. and B.Y.) performed the systematic search to collect articles as outlined in the methods based on the title and abstract of the articles. In the second round of review, two assessors performed the manual review (author P.C. and B.Y.) of the articles. Discrepancies between assessors were arbitrated by a third assessor (M.R). Following the second round, these were the articles that were assessed and included for further assessment in the narrative review.
Changes in the text: Please see the attached Word document with track changes on the manuscript for the paragraph between lines 120-121, and
"During the first phase of review, one assessor searched the three databases to collect articles on recurrent idiopathic pancreatitis based on their titles and abstracts."
"After the first round of review, the articles were then assessed for eligibility by two assessors based on their full-text, and 5 additional articles were further excluded. Discrepancy between the two assessors was arbitrated by a third assessor."

Comment 2: "Occult etiologies of … 6) hereditary mutations."(line 150-156): Much discussion is still at hand on the certainty of pancreas divisum as an etiology of AP. The same goes for IPMN and sphincter of Oddi dysfunction as a cause for IRAP or IAP. I believe mention of the discussion on these potential etiologies would increase the integrality of this review.
Reply 2: We agree that pancreatic divisum, IPMN, and sphincter of Oddi as etiologies of AP are disputed. We have added another paragraph for the evidence behind

pancreatic divisum and IPMN as causes of AP in the "What etiologies should be considered?" section, lines 171-208. We have deferred a discussion on SOD as it is beyond the scope of this review and it requires further discussion on the role ERCP and Sphincter of Oddi manometry to fully address this question. Our review focused on the role of EUS and MRCP. We have provided a sentence in the paragraph on the prevalence of SOD in patients with IAP and provided a reference to a review article that specifically addressed SOD and pancreatitis.

Changes in the text: Please see the attached manuscript with track changes, lines 190-204.

"There is disagreement in the field on the certainty of PD, IPMN, and SOD as causes of IRAP. In a cross-sectional study of 46 patients with IAP/IRAP compared with 500 healthy controls, the prevalence and rate of PD was significantly higher for patients with IRAP, but not for patients with IAP. Furthermore, multiple logistic regression showed that the presence of PD increased the odds of pancreatitis by 23.4 times compared to healthy controls. (15) Additional studies have found associations between genetic mutations (SPINK, PRSS1, and CFTR mutations, and L26V and r12338 polymorphisms in cathepsin B gene) and IRAP in patients with PD compared to those without PD, indicating PD may be a risk factor for the development of IRAP in the presence of an underlying genetic predisposition.(16-18) The association between IPMN and pancreatitis has been less well studied. In the largest study on IPMN-associated pancreatitis, only 7% of 489 patients with IPMN developed pancreatitis, and the rate was significantly higher in those with MPD-IPMN, than those with branch-duct (BD)-IPMN, 14% vs. 5%.(19) SOD as an etiology of IAP is a controversial topic as it is unclear if SOD is a precursor or a complication from recurrent acute pancreatitis. Interestingly, however, the prevalence of SOD in patients with IAP has been reported to be between 30-65%. (20) Further research is required in this field."

Comment 3: "Despite the utility … negative repeat TUS." (line 184-186): It is not clear whether the authors are stating that EUS should be the next step after a negative repeat TUS in all patients or only in obese patients. Also, do the authors mean that the EUS should be the next step after a single negative repeat TUS (as is recommended in the guidelines) or after multiple repeat TUS's (as performed in the study by Guilmanova et al.)? If the authors refer to the former, how many repeat TUS's do they recommend to perform before EUS?

Reply 3: The ACG guidelines do not explicitly recommend a repeat TUS after resolution of the episode of acute pancreatitis. Only the IPA/APA guidelines recommend repeating a TUS, which is defined as a repeat TUS 8 – 12 weeks after the most recent episode of acute pancreatitis. We have clarified the paragraph noted, whereby our recommendations are clearer. Given the limited data on alternative approaches (serial TUS in all patients versus only in obese patients), an EUS should be the next step in all patients, regardless of BMI, after a negative repeat TUS. Figure 2 summarizes this recommendation in the branch point of "Risk and Benefit" discussion.

Changes in the text: We have made changes to the paragraph to make our recommendations clearer, lines 230-237.

"Despite the utility of repeating a TUS, the role of serial TUS for IRAP remains unclear as studies on the diagnostic yield of serial TUS are limited. Importantly, however, serial TUS may prove to be limited in obese patients given the decreased sensitivity of TUS for the detection of occult biliary disease in this patient population. Another area of uncertainty is whether

serial TUS is more cost-effective at diagnosing a cause of IAP/IRAP compared to EUS after an initial repeat TUS. Based on the available data, however, an EUS should be the next step after a negative repeat TUS in all patients. Further studies are needed to determine which approach has the highest diagnostic yield."

Comment 4: "It is unclear … management with cholecystectomy." (line 186-189): I believe the hypothesis of cost-effectiveness of empiric cholecystectomy is driven by the partial prevention of recurrences by adequately treating underlying occult biliary disease with cholecystectomy vs. the costs and complications of empiric cholecystectomy. The lack of recurrences in IAP patients treated with cholecystectomy does not entail these patients had underlying biliary disease as not all IAP patients have recurrences. Thus the statement that cholecystectomy is (cost-)effective at diagnosing a cause is, in my opinion, not appropriate in this context. Please consider rephrasing.

Reply 4: Yes, we agree that cholecystectomy and decreased recurrent rates of acute pancreatitis may not be related, therefore, cholecystectomy cannot be "diagnostic" in patients with IAP who have resolution of attacks. We have removed this statement from the manuscript completely.

Changes in the text: The sentence between line 233-234 on cost-effectiveness has been clarified to remove the statement on the cost-effectives of cholecystectomy on diagnosing etiology of AP.

"Another area of uncertainty is whether serial TUS is more cost-effective at diagnosing a cause of IAP/IRAP compared to EUS after an initial repeat TUS."

Comment 5: "An MRCP/S-MRCP should … nature of invasiveness." (line 277-280): After the authors state that EUS is superior to MRCP in detecting etiology, they then recommend performing MRCP before EUS, despite diagnostic inferiority, higher costs and limited availability. Particularly when MRCP is mostly used to identify anatomical abnormalities and SOD, which are highly disputed etiologies of IAP (as I mention above). Based on the available and presented literature, I do not think it is accurate to make this recommendation and I would suggest the authors approach this with more moderation.

Reply 5: Yes, after re-consideration, noting that MRCP is mostly used to identify the disputed anatomical abnormalities and SOB, we have changed our recommendations in the manuscript and Figure 2 and described it as an option for centers with the capabilities of MRCP/S-MRCP.

Changes in the text: Please see attached manuscript with track changes between lines 332-335, lines 340-343, and on Figure 2 in the box labeled "Standard Evaluation" for MRCP/S-MRCP.

"Some limitations of both S-MRCP and MRCP should be considered, however, and include limited availability at smaller health centers, higher costs, and unstable medical supply of secretin to perform the study. Given the limitations of MRCP, it should be performed only if it is readily available."

"An MRCP/S-MRCP should be performed only if readily available, and only after a repeat TUS is negative as the MRCP/S-MRCP may identify pancreaticobiliary neoplasms, anatomic abnormalities, and SOD. EUS should be considered superior to MRCP/S-MRCP due to its higher diagnostic yield."

Minor issues:

X Comment 6: "We present the following article in accordance with the narrative review reporting checklist." (line 104-105): I would suggest this line on the methods of your study is more appropriate in the Methods section itself.
Reply 6: We have moved the line to the methods sections.
Changes in the text: This statement is now found on line 109.
"We present the following article in accordance with the narrative review reporting checklist."

Comment 7: "Search were conducted … abstract were unavailable." (line 107-114): I would suggest clarifying that the authors searched for articles on idiopathic recurrent acute pancreatitis.
Reply 7: We have added clarification to the first paragraph of the Methods section.
Changes in the text: We have added clarification to the paragraph, on line 111.
"Searches were conducted in sequential order using the databases of PubMed/MEDLINE, Embase and then Cochrane Library on recurrent idiopathic pancreatitis as outlined in (**Table 1).**"

Comment 8: "The phrase, "recurrent … were further excluded."(line 115-125): In my opinion, the searches do not have to be repeated in the main text if they are included in table 1. Readability would be improved if the authors would only refer to table 1. The same goes for the exclusion process for articles from each individual database: these are already stated in figure 1. Instead of repeating the information of figure 1, I would suggest only mentioning the total number of search results and the total number of assessments for eligibility and the total number of included studies.
Reply 8: Yes, we agree that referring to Table 1 instead of repeating the searches in Paragraph 2 in the Methods section would make the manuscript more readable. We have simplified paragraph 2 per the suggestions.
Changes in the text: Please see the attached manuscript with track changes between lines 121-124.
"The search yielded 104 items from PubMed/MEDLINE, 175 items from Embase, and 21 from Cochrane Library. Manual assessment of the title and abstract of the articles led to the exclusion of 179 out of 300 articles, mostly for being duplicates."

Comment 9: "A total of … the qualitative synthesis." (line 125-126): 116 articles were included, yet only 74 references are listed in the reference list. Please clarify or adjust.
Figure 1: To me, it is not yet clear what constitutes an "irrelevant study", please clarify the requirements to classify as an irrelevant study within the context of this review.
Reply 9: Although the literature search yielded 116 eligible studies on recurrent idiopathic pancreatitis, some of the articles were not applicable to the purpose of our manuscript. For example, the role of genetic testing was out of the scope of this manuscript, and there were 28 articles on this topic, which were not included in the discussion. An additional 10 studies were on the management or role of ERCP on IAP, which were also not included given the scope of this manuscript. Clarification has been added to explain this discrepancy between the 116 eligible studies and those referenced.
Most irrelevant studies came from the search performed on the Cochrane Library as searching for "recurrent idiopathic pancreatitis" yielded articles not related to idiopathic pancreatitis. For example, there were articles on growth hormone in

pediatric patients, cognitive behavioral therapy in adolescents with depression, and on lumen-apposing metal stents in management of pancreatic necrosis. Given these articles were not on idiopathic pancreatitis, these were labelled as "irrelevant".
Changes in the text: A statement has been added from lines 149-154 to explain the number discrepancy between the 116 eligible studies, and those referenced in the manuscript. A line clarifying what constituted an "irrelevant study" has been added to lines 117-119.

"A total of 116 articles were reviewed in the qualitative synthesis to formulate a diagnostic approach to determine the etiology of idiopathic acute pancreatitis. Given this narrative review focused on the diagnostic approach, excluding genetic testing, and not the management, or on endoscopic retrograde cholangiopancreatography [ERCP], a further 38 articles were not included in the discussion of the manuscript."

"Irrelevant studies, defined as studies not pertaining to idiopathic pancreatitis after review of the article's title and abstract, were excluded."

Comment 10: Table 2: If I am correct, this table is based on Lankisch et al., as also referenced in the main text, however I believe it would be correct to also reference Lankisch et al. in the legend of this table or mention the table has been adjusted from Lankisch et al.
Reply 10: Table 2 is based on the PICUS protocol, which includes Table S1 "Drugs associated with acute pancreatitis" in the supplementary additional file 1. In contrast to Table S1 from the protocol, however, we characterized the medications by class of medication, i.e., antimicrobials, chemotherapy, etc. The table in the PICUS protocol is further based on the two articles, Nitsche et al. "Drug-induced pancreatitis" and on the Lankisch et al. paper. I have included a note underneath Table 2 indicating that it was adjusted from the PICUS protocol.
Changes in the text: A note has been added to Table 2 indicating we have adjusted it from the PICUS protocol.

" * Table 2 has been adjusted from Table S1 "Drugs associated with acute pancreatitis" from the PICUS protocol, found in the online supplementary additional file 1."

Comment 11: "Less common causes … and pancreaticobiliary neoplasms." (line 147-149): I would suggest including auto-immune acute pancreatitis in this list.
Reply 11: We agree, and have added this to the sentence.
Changes in the text: Please see attached manuscript with track changes on line 177.

"Less common causes of pancreatitis include autoimmune, drug-induced,…"

Comment 12: "Third, studies have … of 43.5 months." (line 227-232): To increase the integrality of this review, please consider adding the data as published by Ahmed Ali, Issa, Hagenaars et al. (Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroent Hepatol. 2016;14:738–746). For transparency purposes, I am not one of the authors of this article.
Reply 12: We have included this article in our review.
Changes in the text: Please see attached manuscript with track changes between lines 289 – 293.

"Additionally, a large multicenter study of 669 patients (15% idiopathic) found that 25% of patients with IAP progressed to IRAP, and 10% to chronic pancreatitis. The study further found that having IAP was an independent risk factor for progression to recurrent

pancreatitis (aOR 2.51, p =0.001) and chronic pancreatitis (OR 3.12, p = 0.005)."

Comment 13: "1) Without a … a repeat TUS."(line 236-238): I most definitely agree with this statement and would like to add that repeat TUS is also less invasive than EUS.
Figure 2: This is a very elegant, easily readable and comprehendible summary of your recommendations. Please add an extra line in your main text stating that this figure is an graphic summary of the suggested management approach of IAP (at line 290).
Reply 13: Thank you for your complements. We have added the statement to the manuscript stating this figure is our graphical summary.
Changes in the text: Please see attached manuscript with track changes between lines 358-359.
"A graphical summary of the suggested diagnostic approach is provided in **(Figure 2)."**