Date: 8 Oct 2022

Re: Manuscript ID: 79894: Diagnosis, severity stratification and management of acute pancreatitis – current evidence and controversies

Dear Editor-in-Chief and Reviewers,

We thank you and the reviewers for the insightful criticism and comments. We also thank you for allowing us to resubmit after major revisions to the manuscript. This is a revised submission of our manuscript titled. We have enhanced the manuscript accordingly and enclosed below is the point-to-point response with the changes made in the manuscript underlined.

Yours sincerely,

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Reviewer 1

Comment 1: This editorial is well-written, overall. It provides a nice overview of the AP. However, I would suggest spending some more words on chronic forms, since recurrent AP can overlap and/or cause chronic pancreatitis. In general, some points should be completed. - Indeed, the authors themselves mention aspects/markers that may be more justifies in chronic forms , such as IgG4 screening (see: "In patients with no obvious etiology, a clinician must perform extended investigations before resorting to a diagnosis of idiopathic pancreatitis. These extended investigations include a repeat abdominal ultrasound scan, magnetic resonance cholangiopancreatography (MRCP) scan [2], endoscopic ultrasound (EUS) scan, autoimmune markers like serum IgG4 [7], viral markers like COVID-19 and genetic tests [10].). In this regard (IgG4 and, more in general, autoimmune pancreatitis), this recent review can be helpful to complete this discussion (World J Gastroenterol. 2021 Jul 7;27(25):3825-3836. doi: 10.3748/wjg.v27.i25.3825).

Reply 1: Thanks for this suggestion. We have added the following in the text to enhance the understanding of autoimmune pancreatitis. We have added a new citation 23 as suggested and all citations are adjusted accordingly.

"In patients with autoimmune pancreatitis, the immune-mediated pathology affecs multiple organs like salivary and lacrimal glands, kidneys, retroperitoneum, lungs, and bile ducts. In addition, autoimmune pancreatitis is implicated in pancreas

carcinogenesis [23]. Thus, diagnosis and management of this pathology is unique and requires detailed assessment as well as long-term follow up."

Comment 2: "In contrary, genetic testing involves assays for gene mutations such as mutations in the PRSS1 or CTFR gene." This sentence should be supported by references (e.g. Gastrointest Endosc Clin N Am. 2022 Jan;32(1):27-43. doi: 10.1016/j.giec.2021.08.006).

Reply 2: We have added this as citation no. 22. All other citations are adjusted accordingly.

Comment 3: The authors should also discuss the specific management of AP in the setting of chronic/recurrent pancreatitis, if any.

Reply 3: We have added an entire section on recurrent acute pancreatitis and provided a short descriptor of chronic pancreatitis. As the focus is not on recurrent nor on chronic, but on acute pancreatitis, we opine that this short additional paragraph serves a necessary and sufficient purpose for our audience. We have added in the relevant citations as well.

MANAGEMENT OF RECURRENT ACUTE PANCREATITIS

In some patients, AP recurs or relapses, especially when the initial aetiology is not treated or removed. In patients with AGP, this means that cholecystectomy is essential.

In patients with hypercalcemia or hyperlipidemia, appropriate management of underlying aetiology is essential. In patients with drug-induced pancreatitis, the culprit drug should be avoided and substituted with an alternative medication [9]. However, sometimes the underlying etiology may be multifactorial or idiopathic. The International State-of-the-Science conference defined recurrent AP as two or more well-documented separate attacks of AP with complete resolution for more than 3 months between attacks [135]. Recurrent AP is a complex pathology with possible anatomic, environmental, and genetic causal interplay. Thus, the diagnostic work-up should include EUS, autoimmune serological tests, and genetic studies. In rare situations, ERCP during the acute episode of abdominal pain may be necessary to identify and treat the causative aetiology [136]. Biliary and pancreatic ductal manometry and biliary sphincterotomy can potentially reduce recurrent AP rates in patients with anomalous pancreato-biliary junction, choledochocele, ampullary neoplasms, biliary parasitosis, and sphincter of Oddi dysfunction [137]. Empiric trial of steroids without compelling evidence of autoimmune pancreatitis is not advised [135]. Similarly, empiric cholecystectomy is not advised in patients with no evidence of gallbladder disease on EUS and other imaging modalities and with normal liver function tests [135]. About one-quarter of patients with recurrent AP may progress to chronic pancreatitis, and a diagnosis of chronic pancreatitis does not preclude a future diagnosis of AP or recurrent AP [138]. It is essential that patients with recurrent AP are managed by physicians with special interest in pancreatology and its management should be guided by local

multidisciplinary teams to not only reduce progression to chronicity, but also to maintain good quality of life in patients.

Comment 4: Moreover, the manuscript completely disregards the pediatric population: even if much more rarely, children can be affected by AP, both as an isolated episode and in the context of chronic recurrent forms (e.g. Front Pediatr. 2022 Aug 25;10:931336. doi: 10.3389/fped.2022.931336) and some concomitant episodes have also been observed during COVID-19 (Paediatr Child Health (Oxford). 2021 Dec;31(12):423-427. doi: 10.1016/j.paed.2021.09.001)

Reply 4: You are right. This editorial is meant for adult acute pancreatitis, and thus we have deliberated and disregarded pediatric considerations. Though some overlap of scope exists, in essence, we consider pediatric acute pancreatitis as distinct from an adult for aetiology, management, and follow-up; thus, we have not discussed pediatric population references and descriptors. Hope this is acceptable. To endorse this, we have edited the title of our manuscript to align with an adult population. The title now reads as

"**Diagnosis, severity stratification and management of adult acute pancreatitis – current evidence and controversies"**

In addition, we have also edited the last statement of the introductory paragraph as - This editorial will discuss the controversial and emerging themes regarding AP in adults with a critical appraisal of evidence and reference to existing guidelines.

Reviewer 2

Comment 1: This article comprehensively reviews the development, diagnosis, treatment, confusion, and problems to be solved of pancreatitis. It is a good review and is recommended for publication.

Reply 1: Thank you for the comments and encouragement.

Other edits:

Dear Editor, we have also edited some minor grammar and sentence formats in abstract and core tip sections. Numbering of citations in Table 1 have also been amended due to modification of citations in the main text.