

Dear Editorial team and reviewers

We have incorporated the suggestions made by the reviewers and the editorial team. We have restructured the entire manuscript into conventional sections as suggested to us. We are resubmitting the revised manuscript with changes (highlighted in blue).

Reviewer 1:

This article covers a wide remit of the genetic basis, natural history and clinical outcomes of PFIC 1,2,3 and finally the current and future treatment strategies. In the first section on ATP8B1 deficiency, the severe and mild phenotypes are described in turn. The subsection on 'clinical outcomes' is therefore an overlap and should be integrated into the subsections above. Similarly when describing BSEP and MDR3 there is overlap between clinical presentation and outcomes. Please structure these sections conventionally and distinctly - pathogenesis, presentation, natural history / prognosis etc. At present this information seems intermingled.

Response: We have restructured the entire manuscript into conventional sections for each of the subtypes of PFIC.

Please avoid abbreviations in section headings (ICP,LPACetc). This section is not well explained but is worthwhile to describe the more frequently encountered clinical scenarios of ICP, DILI in adults, the associations with genetic abnormalities of cholestasis genes, and future chronic liver disease.

Response: We have removed the abbreviations. The section on these disorders has been re-written with emphasis on the genotype, clinical presentations and prognosis.

The term used in Table 1 "expanded role in childhood/ adulthood" is not clear - description such as 'associations with other cholestatic presentations' would be preferable.

Response: Corrected

The article then comprehensively reviews different treatment strategies, including novel therapy targets. The outcomes of biliary diversion surgery in terms of survival and need for liver transplant should be described.

Response: Outcome in terms of need of liver transplantation after surgical biliary diversion added in table 3 and summarized in text under the heading “Surgical Interruption of Enterohepatic Circulation”

The NAPPED cohort study is a key reference.

Response: The NAPPED consortium study on PFIC2 had been already included at reference number 29. A very recently published data from the NAPPED consortium on PFIC1 included at reference number 20 and quoted at relevant places in text.

Table 2 should be a summary and detailed description of the MOA of each drug which was already included in the main text is unnecessary.

Response: We have kept the mechanism, dose and adverse effects in table 2 while removing the repetitive portions from the text to make it shorter and focused.

Table 4 could be supplemented by a diagram to show the therapeutic targets involved.

Response: Added (Figure 5)

Some of the included references are not central to the review, e.g. 34, 36, 39.

Response: Removed

Regarding treatments, established strategies and anti-pruritic agents do not need extensive description but a summary table with an overview in the text would suffice, to focus on the newer agents.

Response: The text on established therapy including antipruritic medications has been considerably shortened and only recent data has been kept.

The article should end with a conclusion.

Response: Added

There are some typographic / grammatical errors throughout.

Response: Checked and corrected

Reviewer 2:

A nice review of progressive familial cholestasis which is well written

Response: Thank you

Editorial Office Comments:

(1) The authors did not provide original pictures. Please provide the original figure files. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Figures 2, 3, 4 and 5 were prepared in PPT and the editable PPT files have been attached. Figure 1 was prepared in Corel and saved as image file. So for figure 1, we only have image file/ corel.

(2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Response: All references corrected in line with journal's style.

(3) Please obtain permission for the use of picture(s). If an author of a submission is reusing a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published and correctly indicate the reference source and copyrights. For example, " Figure 1 Histopathological examination by hematoxylin eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L,

Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc [And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable;

Response: All figures including the histopathology slides are our original figures.