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HEPATOBILIARY DISORDERS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASES

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Editor comments

I think reviewer's comment is proper. I think thromboembolic complications in IBD may be associated with coagulation abnormalities. Please comment platelet count, factor V, VIII levels, fibrinogen and antithrombin III in IBD.

Thank you for the important comment. We have addressed this issue adding a specific part in the ***Portal vein thrombosis*** *paragraph.*

Reviewer comments

Reviewer #1
The review article entitled "Hepatobiliary disorder associated with inflammatory bowel disease" summarized hepatobiliary complications associated with IBD. The article is precise and well-written, and covering considerable situation to date. This review is helpful for readers. Please correct follows. 1. There are several abbreviations which do not spell out. "RUC" in page 4, "MRCP, magnetic resonance cholangiopancreatography" in page 6, "AP" in page 13. 2. If REL, IL2, CARD9 are gene names, please be italicized in page 5.

Thank you for the important review. We proceeded to make all the corrections indicated.

Reviewer #2
The topic of the manuscript is of major importance for colleagues working within the fields of IBD and hepatology. In general the paper is well disposed and well written although some minor corrections have to be made regarding the language throughout mostly in the sections dealing with drug induced liver disease in IBD. Besides it is a problem reviewing the manuscript that the pages do not seem to be numbered. Specific comments for consideration:

Key words: Viral hepatitis should be added.

Thank you for the important reviews.
We have added viral hepatitis in the key words.

Primary sclerosing cholangitis: Regarding aetiology of the disease it is stated that environmental factors may play a role. Could this be specified somewhat ?

*We have better clarified the role and types of environmental factors involved in the development of primary sclerosing cholangitis in the **aetiology** subparagraph.*

Overlap syndromes between PSC and AIH are mentioned which is highly relevant. I miss a short section regarding the relation between AIH in its own and IBD. Although the occurrence of both IBD and AIH is rather rare AIH is more prevalent in IBD than in the general population (e.g. Halling et al., World J Gastroenterology 2017).

We proceeded to add a specific paragraph regarding autoimmune hepatitis in IBD patients, based on the latest literature evidence.

Omit "other" from the head line "other non-immune-mediated disorders.

We have modified the text accordingly.

Portal vein thrombosis: The incidence of thromboembolic complications is 2.6/1000 persons/year. Is this the incidence of all cases of thrombosis or does the given incidence relate only to portal vein thrombosis ?

We proceeded to specify that the incidence of 2.6/1000 persons/year is related to all cases of venous thromboembolism in IBD patients. Portal vein thrombosis is specifically discussed soon after in the paragraph.

Thiopurines: The importance of the 6-MMP metabolite for the occurrence of hepatotoxicity is noted. However it would have been highly relevant to briefly describe the concept of shunting and

the possibility to treat shunters by reducing the dose of azathioprine and the addition of allopurinol.

We proceeded to add a specific part regarding the concept of shunting (or hypermethylation) in thiopurine treatment, and the opportunity to treat shunters with a combination of low dose thiopurine and allopurinol, in the ***Thiopurines*** *paragraph.*

Methotrexate: Two different incidence rates regarding transaminase elevation in patients treated with methotrexate are given 1.4 per 100 patient months and 0.9 per 100 patient months. As I see it these numbers are taken from the same reference. An explanation for this different incidence rates is needed.

We have modified the text to better clarify the difference between the two incidence values: 1.4 per 100 patient months refers to incidence of abnormal hepatic aminotransferase levels, defined as up to a 2-fold increase over the upper limit of the normal; 0.9 per 100 patient months refers to hepatotoxicity, defined as aminotransferase levels greater than a 2-fold over the upper limit of the normal.

Anti-interleukin 12/23: The risk of HBV reactivation is noted. This risk is not specific for anti-interleukin 12/23 treatment and the subject is touched upon in the sections regarding IBD and viral hepatitis B and C.

As you suggested, we have removed the part related to the risk of HBV reactivation from the ***Anti-interleukin 12/23*** *paragraph, since this issue is already addressed in the* ***IBD AND VIRAL HEPATITIS B AND C*** *chapter.*

Figure 1: In the box "First line tests" fibroscan could be added.

We proceeded to modify the Figure 1 accordingly.