April 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7539-review.doc).

Title: Hepatitis B Vaccination in Patients with Inflammatory Bowel Disease (IBD)

Author: Ruwaida Ben Musa, Anuhya Gampa, Sanjib Basu, Ali Keshavarzian, Garth Swanson, Michael Brown, Rana Abraham, Keith Bruninga, John Losurdo, Mark DeMeo, Sohrab Mobarhan, David Shapiro, Ece Mutlu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7539

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

We thank all three reviewers for their positive reviews and constructive comments. We have now revised the manuscript as suggested and hope that the reviewers will find it acceptable with the new changes. Below are our responses to the comments and critiques by the reviewers. The manuscript has been improved according to the suggestions of reviewers:

ANSWERS TO REVIEWER 1

Ascertainment of hepatitis B infection and immunity with subsequent treatment or vaccination has been recommended in several guidelines. However, the strength of evidence on which these recommendations are based is relatively weak. There is therefore critical need for observational studies that can highlight the magnitude of risk and/or the variability of practice in following guidelines. The authors have conducted an extensive and topical review of the practice pattern at their institution and highlighted the need for greater vigilance in screening within the IBD population. The article is in need of revision but likely without the need for extensive new analyses.

1. **Abstract length appears excessive and includes results of many sub-analyses; consider confining results to those regarding primary study aims**

We have now reduced the length of abstract and the results from the subanalyses have been removed from the abstract, as suggested by the reviewer. These changes are also now marked in the manuscript.

2. **The introduction would benefit from a brief summary of current screening and vaccination recommendations (sentence 1 from Discussion paragraph 3 could be moved here, for instance)**

The length of introduction has been reduced. A brief summary of current screening and vaccination recommendations have been added.

3. **Study design needs to carefully state how IBD cases were ascertained, was this through billing codes or ICD-9 codes, if so list the codes.**

Subjects were included in the study if a specific diagnosis of IBD was written into the clinic notes by a board certified gastroenterologist in our practice. In general it is our practice that a diagnosis of IBD is made on the basis of classic IBD symptoms such as diarrhea, blood in the stool, urgency, abdominal pain, extraintestinal manifestations of IBD etc, AND classic radiology or endoscopy findings. All cases in our practice additionally are required to have endoscopic or surgical histopathology data and two expert board certified gastrointestinal pathologists review all of the biopsies.

4. Define "an HBV serology." Is there a standard panel in the Rush practice (there appears to be considerable variability in what was actually ordered (see below).

While there is a standard acute hepatitis panel at our institution, we do not have a standard hepatitis B screening panel. Stemming from the latter problem, the reviewer is absolutely correct about the variability in what was actually ordered. We thank him for especially highlighting the need for a standard panel. This is most important especially for our trainees (such as internal medicine residents and gastroenterology fellows) who place orders when seeing patients with our board certified gastroenterologists. This is also now highlighted as a quality improvement project in our institution as a result of our data.

5. In study design, formally define how prior infection, carrier status and prior vaccination were defined, especially by serology results (suggest CDC criteria: Centers for Disease Control and Prevention, Hepatitis B information for health professionals: Interpretation of hepatitis B serologic test results. Available from the CDC website.)

We have defined these as recommended by the reviewer.

6. In Results, Hepatitis B virus screening, of 220 who had "serology" checked there are variable denominators for what was ordered. HBsAg, anti-HBs-Ab and anti-HBcAb would be minimum required to identify IBD-relevant HBV disease states of current infection, past infection and immunity. In Discussion highlight that the variation in orders may constitute evidence of variability in providers understanding of screening standards. Also, HBeAg would likely only be required/checked in a patient with a positive screen. Since this is a diagnostic/prognostic test, please consider removing this from results on screening practices.

We thank the reviewer for highlighting this variability and the discussion has now been changed according to the reviewer's recommendations. We did remove the HBeAg from the results as recommended.

7. In Results, HBV vaccination according to age group, there is vague reasoning in the last sentence as to why younger patients would be more likely to be vaccinated; after moving this speculation to Discussion, consider adding references on CDC requirements for HBV vaccination in the age range of 0-18 in the general population (http://www.cdc.gov/mmwr/pdf/wk/mm62e0128.pdf). HBV is also required of many healthcare workers, college students, and military recruits (http://www.vaccines.mil/documents/371hbvaccination.pdf).

We have made the recommended changes and have moved the comment about younger patients being vaccinated to the discussion section. We also added the current vaccine recommendations, as recommended by the reviewer.

8. Prevalence of HBV markers….should be combined with data on positive serology ("Hepatitis B virus screening") section of results.

We combined and moved the prevalence of HBV markers section into the screening section of results.

9. Table 3 should include racial/ethnic information of patient and or parents to determine if this was a risk factor (for instance, if all are from an endemic area like Africa or Asia, do we really need to screen all IBD patients?).

In the table 3, we added racial/ ethnic information about the patients. Six patients were African Americans and two patients were White, and they were all from the Chicagoland area, an urban but non-endemic area. Our evidence suggests that we probably need to screen all our IBD patients, as hepatitis B is found even not in an endemic area.

10. Although obvious, it would improve clarity and speed for readers to include the HBV disease states of the patients in Table 3 (acute infection, chronic carrier, naturally immune). Patient 8 is likely a false positive HBeAg (unclear why this would ever have been checked without positives on other serologic tests, highlighting the need for practice standardization in test ordering).

These have now been added into Table 3 for each patient. We have now highlighted the need for standardization of orders in the discussion as requested. We have removed patient 8 from the results and agree that this case is a false positive upon further review of the patient's chart.

11. In Results, Comparisons of HBV prevalence…., please list the numbers positive and the number at risk for each study instead of percentages and re-cite the references. In Discussion, authors will need to clearly state that the study was in no way adequately powered to test single-digit percentage point differences in disease prevalence. Therefore, the statement "In this study, the prevalence of chronic HBV

We have now listed the numbers positive and the number at risk for each study instead of percentages and have re-cited the references as requested by the reviewer. We have added to the discussion that the study is not adequately powered to test single-digit percentage point differences

in disease prevalence. Please note that we are unable to see the reviewer's additional comments in the journal's website and wonder if there is a limit for reviewer comments since the last sentence in the review appears cut off.

ANSWERS TO REVIEWER 2

I think this is good study about physicians managing IBD patients should be aware of the need for screening and vaccination to prevent HBV infection or other infective disease and the guidelines for HBV screening and vaccination. I commend you for a very thorough paper. I have a few concerns:

1. **The abstract results section and the introduction is quite verbose and can likely be cut down**

We have reduced the length of the abstract and the introduction sections.

2. **You mention in the introduction there is little to no research - which is it? little or no?**

This sentence has now been removed to reduce the length of the introduction.

3. **You comment that guidelines recommend testing for hbv status at time of IBD diagnosis. You quote four references of which only one is a guideline from Dr. Sands, but you do not quote the guidelines from ACG. Regardless though, none of these guidelines specifically recommended testing for hbv status at time of diagnosis. Also, there is no standard of care to confirm a patient's vaccination status if they state they have been vaccinated especially if they can prove when they were vaccinated. There is no standard of care to actually check titers. While it makes sense to check titers if administered while immunosuppresed it doesn't make sense prior to using a biologic.**

As pointed out by the reviewer, we failed to cite all the references for the guidelines, for which we apologize. We have now added all the necessary relevant references supporting our statement and the various recommendations from the guidelines.

Based on these added references, we respectfully point out to the reviewer that the European IBD guidelines and many IBD experts do explicitly recommend testing and vaccination in everyone with IBD at the time of diagnosis regardless of TNF inhibitor or biologic use and regardless of vaccination status [1]. While the evidence upon which these guidelines may be not strong (i.e. no high levels of evidence such as randomized trials exists), the recommendation to check and vaccinate everyone also makes total sense considering that we are even vaccinating infants and children against HBV, and considering that HBV vaccination is a highly cost effective intervention. As such, the European recommendations have also been communicated across the US to many gastroenterologists through many lectures given at professional meetings, although it is not yet in print in the US explicitly for IBD patients, as stated by the reviewer. In the US, the primary HBV

screening and vaccination recommendations are through guidelines of the AASLD and the CDC [2-7]. Neither of these organizations has provided specific guidelines for IBD and therefore do not specifically state that screening serologies should be done at the time of diagnosis of IBD. However both the AASLD and the CDC have guidelines for the general public as well as those patients who will be immunosuppressed. Both the AASLD and CDC guidelines state that anyone who wishes to be protected from HBV should be screened and vaccinated. This recommendation includes everyone and anyone with or without IBD; and with or without prior vaccination; and with and without immunosuppression. Given frequent contact with healthcare and need for medical interventions such as blood transfusions and surgeries etc, IBD patients should be educated about the risk of HBV and should be screened and vaccinated as recommended for anyone who wishes to be protected.

Furthermore, both the AASLD and the CDC guidelines state that any patient who will be on an immunosuppressant should ideally receive their vaccine before immunosuppression, which per CDC definitions includes not only biologics but also other drugs such as steroids and thiopurines at high doses. Both organization recommend screening tests of all patients who will be on long term immunosuppressants. Considering that almost all IBD patients will need steroids at some point in time (80% according to European guidelines), this could only be interpreted that patients will have to be screened before going on steroids and/or biologics of any kind and ideally vaccinated before receiving such drugs. Since there is no predictability as to when an IBD patient may need steroids or biologics, it makes total sense to check everyone with IBD for their vaccination status at the onset of their illness and vaccinate as necessary.

We also respectfully disagree with the reviewer about confirmation of vaccination status and screening for infection in patients who have proof of vaccine. Herein, we also refer the reviewer to the European IBD guidelines (now mentioned in the manuscript itself) and references by Morisco et. al. and Lopez-Serrano et. al. who recommend screening with titers on everyone even if they have proof of vaccination. Furthermore, clearly vaccination is not 100% effective. According to the CDC and AASLD, screening and vaccination should be offered to anyone who wishes to have protection from HBV and this includes those individuals who have been vaccinated (and who may want to know whether the vaccine has been effective). In fact, even US guidelines from the AASLD and CDC recommend checking titers on everyone who is going to be immunosuppressed (without eliminating those patients who have been vaccinated) and re-vaccination as necessary (and this recommendation is general and is regardless of whether the vaccine was administered while immunosuppressed or not).

4. You combine biologics and immunosuppresants. Only biologics require hep b status prior to initiation. Ideally in your results, and tables you should differentiate how many pts are on thiopurines vs biologics

As requested by the reviewer, we have now added the number of our patients on various immunosuppressive medications, into the end of the first paragraph of the results section.

However, we respectfully disagree with the reviewer that only patients who will be initiated on biologics require HBV screening as we have stated in response to question 3 of the reviewer.

We also respectfully disagree that the patients who are on thiopurines and biologics should be differentiated in the tables of all results, because the published evidence on HBV reactivation appears fairly similar on both of these drugs, as we detail in the following two paragraphs:

In fact, the current recommendation that biologics require HBV screening prior to initiation stems from case reports. This recommendation has also been widely publicized by the manufacturers of TNF inhibitors due to FDA labeling requirements of these drugs in the US. In the US, all TNF inhibitor manufacturers have also been mandated by the FDA to set up post marketing safety assessment registries. As such, it is no wonder that a more rapid compilation and communication of HBV reactivation cases have been reported on TNF inhibitors. However, when this data is closely examined, it is clear that the available data on HBV reactivation and TNF inhibitors is still limited to a small number of case reports and very small series. (We respectfully refer the reviewer to Morisco et. al. Digestive and Liver Disease 43S (2011) S40-48).

Comparable to the number of cases with HBV reactivation with TNF inhibitors, there are now at least seven cases of HBV reactivation that have been described on steroids and/or azathioprine in papers by Loras et al. in Gut 2010(59):1340-1346 and by Zeitz et al. in Hepatology 2009; 50:653-4, that we can readily locate in databases such as pubmed. (There could even be more cases described as our review was not broad in this instance). Therefore, the effect seems not only related to TNF inhibitors or biologics, but actually to immunosuppression in general (Loras et al. in Gut 2010(59):1340-1346). It also appears that the gastroenterology community at large has not taken a look at these additional cases not occurring on biologics as closely, as there has not been a driving force to do so at least in the US, at the same level for what was done for TNF inhibitors in the past decade.

Therefore, based on the above evidence, we believe that a reanalysis of the entire dataset broken down by those patients on thiopurines vs. TNF inhibitors is not necessary in this initial and first paper examining practice patterns in the US at a tertiary center. Future studies examining this issue could be undertaken at a later date, and may also allow for larger number of patients alone on each drug for statistical comparison purposes.

5. When giving an example of an anti-tnf ideally you should list all of them so as not to imply infliximab is superior.

We removed this sentence from the introduction to make it shorter, as recommended.

6. You do not tell us how many of your patients were seen by PCP's outside your EHR system as this would be very important in knowing how accurate some of the testing results are as patients may have been tested outside. You don't indicated if you read through all the notes to determine if a patient was tested outside your system

We have not collected the data on how many of our patients were seen by a PCP outside of our EHR system. However, in our medical record system, if a given patient has been screened elsewhere and has results and has provided these results to any of their providers in our system (including gastroenterologists, PCPs, nurses, physical therapists, other specialists, etc), all of these outside test results are scanned into the electronic record and a scanned copy is placed in the media section of

the electronic record. We reviewed all of these scanned test results in all the patients in this study. We have reviewed all of the gastroenterology notes to reveal gastroenterology practice patterns.

If the reviewer is also asking that we thoroughly review notes outside of our own system or those of PCPs elsewhere, practice patterns of PCPs in general are beyond the scope of our paper. Requesting records from outside physicians would not have addressed practice patterns of gastroenterologists, but general screening practices for the entire set of providers for IBD patients and is also beyond the scope of this paper, the focus of which is practice patterns in gastroenterology. Additionally, this requires dedicated resources because requesting outside records is an extremely time consuming process and is financially costly in the US considering manpower required, postage required and because some providers charge to send records. This perhaps can be explored in future studies of IBD patients, and practice patterns across gastroenterologists and other providers can be compared and contrasted.

In terms of the possibility of screening by PCPs outside our system, we have to consider that a gastroenterologist never thought about HBV or asked about it, if there is no record of results in the scanned media section; or any mention in any of the gastroenterology clinic notes that the patient was asked about hepatitis B and their outside care records were requested; or any screening orders for labs were given to a patient. We checked all of these for each patient. Given the nature of our cross-sectional observational study on practice patterns in a gastroenterology practice, there is no way but to consider that screening is not done if it is not documented by the gastroenterologist. We have made our best effort to look for screening results including outside results in our system.

While we acknowledge in our discussion this is a limitation of all studies like ours at centers that do not have common EHRs with outside PCPs, please also note that this is what actually typically happens in a gastroenterology practice in the US and our study is reflective of real life conditions in this regard.

7. **et al has a period after the al.**

This has been corrected.

8. **You don't describe your patients risk factors for hbv - i.e. ethnicity, ivdu history**

Race and ethnicity has now been added as requested. As in the aforementioned European guidelines, we consider having IBD and immunosuppression as risk factors for HBV. We did not collect iv drug use data, or data on travel to endemic countries, military or other potential healthcare exposures, etc. in our study. While some of these risk factors are probably recorded in the clinical chart of the patient, we doubt the accuracy and completeness of this information in the medical chart. In fact, it is unlikely that any of our gastroenterologists had the time to accurately record most of the recommended HBV risk factors, especially considering that our physicians have to see an IBD patient for a follow up visit with a maximum duration of 15-30 minutes, and considering that most patients in our tertiary referral center have a higher disease severity than the average IBD patient seen in the community. As such this is a limitation of this retrospective study and is a limitation of all retrospective studies. Future prospective studies could keep track of this information more accurately. The retrospective nature of this study, and the limitations related to the inherent nature of

the study design have been acknowledged in the discussion.

9. What is the average or median duration of IBD disease?

The mean IBD disease duration is given in Table 1.

10-In the results instead of mo for months you should probably just write months

This has now been corrected as requested by the reviewer.

ANSWERS TO REVIEWER 3

1. The conclusions of the paper must only be limited to the practice of the Rush University Medical Center Gastroenterology section and not extend to the US). Additional studies have to be performed in order to extend these data to the US.

This has now been changed as requested by the reviewer.

2. The abstract is too long and must be reduced in length.

The abstract length has been reduced as requested.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely,

Ece A. Mutlu, MD, MS, MBA
Director, IBD Program
Director, Clinical Research
Associate Professor of Medicine
Section of Gastroenterology and Nutrition

References:

1 Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *Journal of Crohn's & colitis* 2014; **8**(6): 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]

2 Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology (Baltimore, Md)* 2009; **50**(3): 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]

3 Lok AS MB. Chronic hepatitis B: update 2009. *Hepatology (Baltimore, Md)* 2009; **50**(3): 1-36

4 General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2011; **60**(2): 1-64 [PMID: 21293327]

5 Recommended adult immunization schedule--United States, 2011. *MMWR Morbidity and mortality weekly report* 2011; **60**(4): 1-4 [PMID: 21381442]

6 Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2008; **57**(RR-8): 1-20 [PMID: 18802412]

7 Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM, Jr., Janssen RS, Ward JW. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2006; **55**(RR-16): 1-33; quiz CE31-34 [PMID: 17159833]