TGH Translational Gastroenterology and Hepatology
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Peer Review File

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Review Comments A

Comment 1:
This study is not a RCT. How can you allocate the patients?

Reply 1:
Thank you for this comment. Our study is a retrospective analysis of prospectively maintained data. Prior discussions with our pharmacists and anecdotal experience suggested that the use of Azithromycin might be more as or possibly effective than Erythromycin. Therefore, the decision to give Azithromycin vs Erythromycin was up to the discretion of the covering attending provider at the time of the endoscopy. All patients treated by G.S. were ordered Azithromycin. Additionally, a national shortage of Erythromycin encouraged other providers to choose Azithromycin due to being more available.

This response is described in the manuscript. Please see Page 5/ Lines 19-21

Comment 2: Is there any possibility of selection bias?

Reply 2:
Thank you for this comment. The possibility of selection bias is very low, given that all patients treated by one attending provider (G.S.) were given Azithromycin. Other providers were not instructed or advised to give one drug over the other. The patients' characteristics are very similar between the two groups (Azithromycin vs Erythromycin) including demographic, admission laboratory, and medical history/comorbidity data. There was no significant difference between the two groups in terms of key characters.

This is described in the manuscript. Please see Methods – Patient Selection paragraph.

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Review Comments B

Comment 1:
Intravenous erythromycin prior to performing emergency endoscopy for upper GI bleed to improve visualisation is evidence based and well accepted. The authors have attempted to compare Iv azithromycin with Iv erythromycin in this clinical scenario. The reason cited was that Azithromycin was readily available compared to erythromycin in the authors institution as well as national shortage of iv erythromycin in the USA. This issue may not be a global issue hence restricts this manuscript to US clinicians.

Reply 1:
We thank the reviewer for this comment. We agree the statement about national shortage is limited to the United States. Generalizing the findings to a global audience is not suggested. We have added a comment to emphasize this point.

Please see page 11/ line 23, and page 12/ line 1-2

Comment 2:
It appears to me that this was a retrospective study from the hospital chart review in patients admitted between 2014-2017. The authors need to be upfront with this and mention clearly in the study design. This study design is inherently flawed to test an interventional drug study. Nevertheless, we can accept it as an observational retrospective case control study to inform future randomised trials to confirm this finding.

Reply 2:
Thank you for this comment. We agree. We have added the following phrase to the Study Design and Patient Characteristics: "This is an observational, retrospective, case control study including patients admitted with upper GIB, along with patients hospitalized for other reasons and developed in-hospital upper GIB between January 2014 and August 2017. All patients were included in the final analysis if they met the following criteria..."

Please see page 5, lines 8-10

Comment 3:
The study aims and outcome are clear.

Reply 3:
Thank you.

Comment 4:
There is too much jargon in the statistics paragraph. It is important to know how the study was powered with this small numbers. There were nearly twice the number in the erythromycin group compared to the azithromycin group. It is acceptable if the authors make a 2:1 matched case/controls and analyse the data. The discussion seems reasonable and the authors have accepted the limitations of the retrospective nature of the study. I would suggest they are cautious about recommending any change to current practice until this is proven in a randomised double blinded trial. The title can be misleading as a randomised trial. Please correct this to a case control study

Reply 4:
Thank you for this comment. We have included all patients who met inclusion/exclusion criteria as provided in the Methods. We only excluded patients who did not fulfill the eligibility criteria. Therefore, the power of the study was subject to the available patients with upper GI bleeding who underwent endoscopy in the timeline provided for the study. We understand this is a limitation of retrospective study and we included this limitation in the Discussion.

Please see page 5, section STUDY DESIGN & PATIENT SELECTION
Please see page 11, paragraph of limitations.

We also shortened the Statistical Analysis paragraph as advised. We deleted the following statements: ", using a log-rank test," "if the statistical assumptions were not satisfied", "An analysis of the unadjusted models demonstrated that the proportional hazard assumption was not rejected for any of the variables."

Please see page 6, section of STATISTICAL ANALYSIS.

Review Comments C

Comment 1:
Intravenous erythromycin prior to endoscopy for upper gastrointestinal bleeding (GIB) promotes gastric emptying and improves treatment outcomes. In the present study, the authors proved that azithromycin, another macrolide, is superior to erythromycin,

which provides valuable information as azithromycin is easier to prepare. However, several questions regarding the present study need further clarification.

Reply 1:
Thank you.

Comment 2:

How to decide which people use azithromycin, decided by the operator? Please explain more in detail.

Reply 2:
The decision whether to use a motility agent or not was up to the discretion of the operating endoscopist attending based on the time of the most recent bleeding episode and the estimation of the GIB severity. The administration of the motility agent had to be started within 6 hours pre-procedure for the patient to be included in the study.

Please see page 5, line 19-23

Comment 3:

Was there any difference between the two groups concerning the reasons of GIB? The authors only provided cirrhosis or not, please provide more in detail, such as peptic uler, etc.

Reply 3:
There was no statistical difference between the cause of bleeding between the two groups.

Erythromycin group: esophageal varices n=16, esophagitis n=8, esophageal ulcer/erosions n=6 Mallory Weiss tear n=4, gastric varices n=5, gastric ulcer n=4, duodenal ulcer n=4, and others n=7 (including neuroendocrine tumor, post-banding ulcers, portal hypertensive gastropathy)

Azithromycin group: esophageal varices n=6, esophagitis n=2, esophageal ulcer/erosions n=2, Mallory Weiss tear n=2, gastric varices n=4, gastric ulcer n=3, duodenal ulcer n=3, and others n=7 (including neuroendocrine tumor, post-banding ulcers, portal hypertensive gastropathy)

We preferred not to include the source of bleeding in the results as we thought it deviated from the purpose of this paper and would not add pertinent data to the study aims. However, we will be happy to include it if advised by the Editors and Reviewers.

Comment 4:

It would be better the authors provided endoscopic images to support the adavantanges of azithromycin.

Reply 4:

Thank you for this comment. We have now added figures on patients with and without pre-endoscopy azithromycin. Please see Figures 2, 3. Thank you.