

**To**  
**Editorial Board of**  
**World Journal of Hepatology**

Vienna, May 11<sup>th</sup>, 2021

**RE: Revisions Manuscript NO: 64216**

**Clinical algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis**

Dear Editorial Board of WJH,

We would like to thank the editors and the reviewers for the prompt and detailed review of our manuscript, and for providing excellent suggestions as well as an encouraging decision. We are grateful for the opportunity to submit a revised version of our manuscript. We have implemented all suggestions and revised the article.

The most important changes can be summarized as following:

- We included a more in-depth discussion on alternative treatment options for the management of variceal bleeding
- We critically revised our graphs and have edited them to increase clarity and the clinical message for the readers.
- We changed the title of the manuscript from “Algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis” to “Clinical algorithms for the prevention of variceal bleeding and rebleeding in patients with liver cirrhosis”.
- Finally, we meticulously assessed grammar style and spelling of the whole manuscript.

Below you will find a point-by-point response to the editor’s and reviewers’ comments as well as a revised version of our review [in blue](#).

Please do not hesitate to contact us if any further questions arise. We are looking forward to your evaluation of our revised review article.

Kind regards,

Dr. Nikolaus PFISTERER and Dr. Lukas W. UNGER, PhD  
on behalf of all authors.

## POINT-BY-POINT RESPONSE

### Reviewer #1:

**Specific Comments to Authors: In this review, the authors systemically discussed the screening, diagnosing, and treating methods for esophageal variceal bleeding. Some recent articles related to this topic were also cited and discussed. The algorithms for prevention and treatment of esophageal variceal bleeding were practical and reasonable, based on a large number of scientific evidence and data. And it is great to see that the authors discussed and considered the findings of some real-world study, which is important because of the availability of medical resources and the imbalance of development status (eg. early TIPS) between different countries and hospitals. It is crucial for the doctors to choose the best available method to help the patients suffering from portal hypertension and variceal bleeding. However, it would be better if the authors discuss some alternative methods for treating variceal bleeding, such as BROTO in patients with IGV.**

We thank the reviewer for her/his excellent suggestion. In the revised manuscript, we have expanded the discussion section regarding alternative treatments (e.g.: BROTO or surgical shunts) for acute variceal bleeding. Specifically, we have updated paragraphs in the renamed subsections “*Therapy-refractory variceal bleeding*” and “*Secondary prophylaxis of EV bleeding*”:

*“... Furthermore, in case of additional cardiofundal variceal bleeding and/or ongoing variceal bleeding after TIPS implantation, balloon occluded retrograde transvenous variceal obliteration (BROTO) should be considered.<sup>[1–4]</sup> A recently published meta-analysis showed improved outcome in terms of rebleeding, mortality and hepatic encephalopathy in patients who also underwent BROTO as compared to patients who only underwent TIPS implantation.<sup>[2]</sup>....”*

*“...In patients with gastric varices and contraindications for TIPS implantation such as spontaneous episodes of hepatic encephalopathy, BROTO can be considered as treatment option in selected patients, as it may even decrease portosystemic shunting through the collaterals that are scheduled for occlusion.<sup>[3]</sup> Furthermore, surgical shunts, devascularization, splenectomy or (partial) splenic embolization may be considered if first-line treatments fail.<sup>[3]</sup>...”*

Science editor:

- 1) Summary of the Peer-Review Report: The authors systemically discussed the screening, diagnosing and treating methods for esophageal variceal bleeding. However, it would be better if the authors discuss some alternative methods for treating variceal bleeding, such as BRT0 in patients with IGV.**

We thank the reviewer for this assessment of and are pleased by the opinion on the comprehensive value and interesting content of our manuscript. We have now included a brief “perspective” section further enhances the review and have added this to our review article. Specifically, the following changes have been implemented in the revised manuscript:

### **PERSPECTIVE**

*“While standard of care for variceal bleeding, as well as primary and secondary prophylaxis are well established, future research is very likely to refine and improve the clinical algorithms for TIPS implantation. Accumulating evidence is available that TIPS has several advantages and has proven to be beneficial in several setting, including end-stage liver disease patients awaiting transplantation<sup>[144]</sup> as well as the mentioned indications when conventional measures fail to avoid rebleeding. In addition, future research will have to better define the role of carvedilol in certain indications to favor carvedilol or classical NSBB in certain conditions. Overall, the field has been innovative in the past and international societies as well as individual centers of excellence keep pushing for refined treatment algorithms. Thus, the main limiting factor for applying some of the most recent findings is local availability, especially in smaller centers with limited funding and personnel...”*

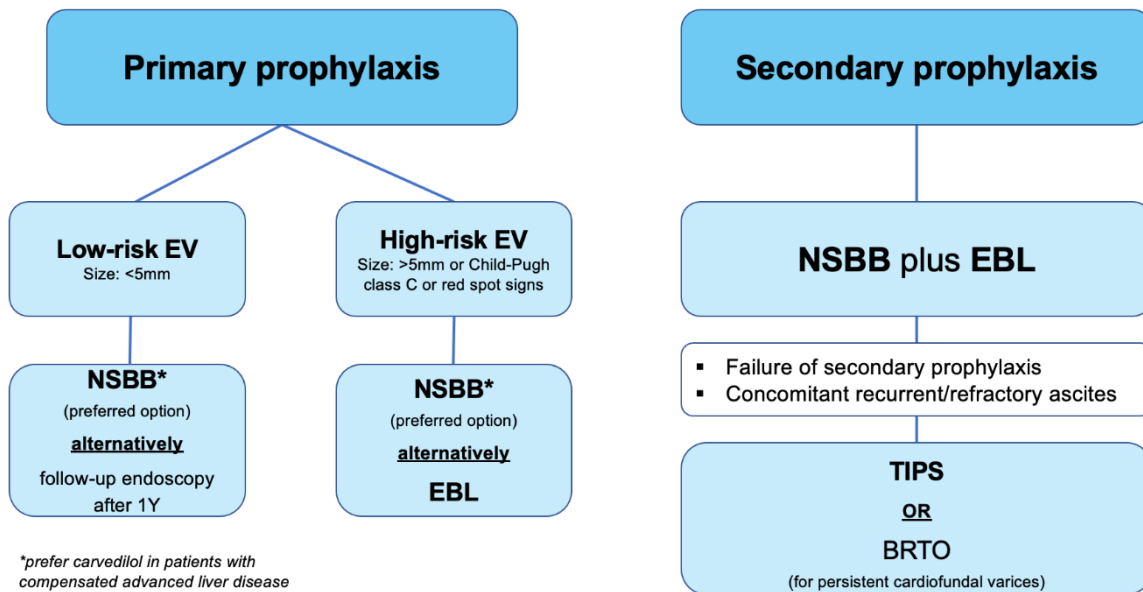
Additionally, as requested by the editor, we have now included BRT0 as additional treatment option in selected cases. Additionally, we have included new up-to-date references for the readers: Specifically, we have updated paragraphs in the renamed subsections “*Therapy-refractory variceal bleeding*” and “*Secondary prophylaxis of EV bleeding*”:

*“... Furthermore, in case of additional cardiofundal variceal bleeding and/or ongoing variceal bleeding after TIPS implantation, balloon occluded retrograde transvenous variceal obliteration (BRT0) should be considered.<sup>[1–4]</sup> A recently published meta-analysis showed improved outcome in terms of rebleeding, mortality and hepatic encephalopathy in patients who also underwent BRT0 as compared to patients who only underwent TIPS implantation.<sup>[2]</sup>...”*

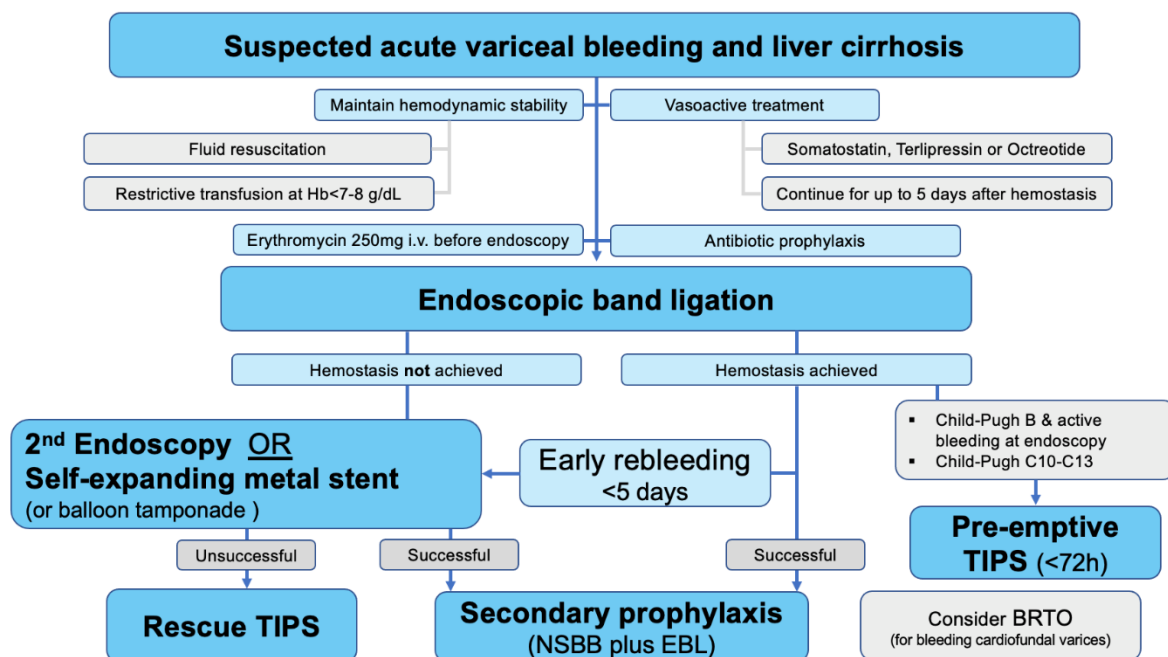
*“...In patients with gastric varices and contraindications for TIPS implantation such as spontaneous episodes of hepatic encephalopathy, BRT0 can be considered as treatment option in selected patients, as it may even decrease portosystemic shunting through the collaterals that are scheduled for occlusion.<sup>[3]</sup> Furthermore, surgical shunts, devascularization, splenectomy or (partial) splenic embolization may be considered if first-line treatments fail.<sup>[3]</sup>...”*

Regarding the tables and figures, we have revised figures 1 and 2 according to the reviewer’s comments and have now included an improved version, as shown below:

**Figure-1.: Clinical algorithms recommended for cirrhotic patients in primary prophylaxis and secondary prophylaxis (adapted from the Austrian Billroth-III guidelines).<sup>[4]</sup>** EV (esophageal varices), NSBB (non-selective betablocker), EBL (endoscopic band ligation), TIPS (transjugular intrahepatic portosystemic shunt), BRTO (Balloon occluded retrograde transvenous variceal obliteration), Y (year)



**Figure-2.: Clinical algorithm for treatment of patients with acute variceal bleeding (adapted from the Austrian Billroth-III guidelines).<sup>[4]</sup>** TIPS (transjugular portosystemic shunt), i.v. (intravenous), h (hours), NSBB (non selective betablocker), EBL (endoscopic band ligation), BRTO (Balloon occluded retrograde transvenous variceal obliteration)



- 2) References: A total of 131 references are cited, including 17 references published in the last 3 years; (5) Self-cited references: There are 15 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations.**

We do thank the editor for this reminder. We have now removed 4 published citations from our study group in order to keep the requested self-referencing rate below 10%.

- 3) Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)**

We do thank the editor for this reminder. We have now included the respective proof of funding for the grants supporting this work.

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

We have now included the updated and improved figures in the correct .ppt format and additionally included the figures and figure legends in the manuscript.

- 5) 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.**

We apologize for this mistake and have updated the reference list accordingly in the revised manuscript's version.

Again, we want to thank the reviewer and editor for their valuable suggestions.

#### References used in this response letter

- 1 Saad WEA, Darcy MD. Transjugular Intrahepatic portosystemic shunt (TIPS) versus balloon-occluded retrograde transvenous obliteration (BRTO) for the management of gastric varices. *Seminars in Interventional Radiology* 2011; **28**: 339–349. [DOI: 10.1055/s-0031-1284461]
- 2 Paleti S, Nutalapati V, Fathallah J, Jeepalyam S, Rustagi T. Balloon-occluded retrograde transvenous obliteration (BRTO) versus transjugular intrahepatic portosystemic shunt (TIPS) for treatment of gastric varices because of portal hypertension: A systematic review and meta-analysis. *Journal of Clinical Gastroenterology*. 2020; **54**: 655–660.
- 3 Lee SJ, Kim SU, Kim MD, Kim YH, Kim GM, Park S II, Won JY, Lee DY, Lee KH. Comparison of treatment outcomes between balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt for gastric variceal bleeding hemostasis. *Journal of Gastroenterology and Hepatology (Australia)* 2017; **32**: 1487–1494. [PMID: 28085232 DOI: 10.1111/jgh.13729]
- 4 Reiberger T, Püspök A, Schoder M, Baumann-Durchschein F, Bucsics T, Datz C, Dolak W, Ferlitsch A, Finkenstedt A, Graziadei I, Hametner S, Karnel F, Krones E, Maieron A, Mandorfer M, Peck-Radosavljevic M, Rainer F, Schwabl P, Stadlbauer V, Stauber R, Tilg H, Trauner M, Zoller H, Schöfl R, Fickert P. Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III). *Wiener klinische Wochenschrift* 2017; **129**: 135–158. [PMID: 29063233 DOI: 10.1007/s00508-017-1262-3]