



REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

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LETTER TO THE EDITOR

Emergency management of hepatic encephalopathy



Manejo de urgencia de encefalopatía hepática

Dear Editors,

After reading and analyzing the article “*Evaluation and management of emergencies in the patient with cirrhosis*”, we wish to share our thoughts and comments on the theme. Hepatic encephalopathy (HE) is one of the main complications of cirrhosis. It consists of brain dysfunction, as a consequence of liver failure, and produces alterations at the subclinical level that can lead to coma. Thus, it is considered a medical emergency and should be treated immediately.¹

Nonabsorbable disaccharides, such as lactulose and lactitol, are the first-line treatment. The article does not precisely state under which circumstances they should be used. Their administration depends on the grade of HE. In cases of grade I and potential grade II, oral administration is indicated, whereas in grades II, III, and IV, administration can be carried out through a nasogastric tube or by means of an enema, if the patient is unable to receive oral administration.²

Nonabsorbable antibiotics are of great use as an alternative to nonabsorbable disaccharides, and include neomycin, metronidazol, and rifaximin. Of those three, rifaximin is the most important, due to its current approval by the Food and Drug Administration. However, demonstrating its efficacy as adjuvant therapy is still greatly relevant. In addition, the study by Sharma et al. reinforces the information of the article. Those authors conducted a double-blind randomized trial, in which 120 patients with HE received only lactulose or lactulose plus rifaximin (1,200 mg/day). The patients that received the combined treatment had better HE resolution, as well as a statistically significant decrease in the number of days of hospital stay (5.8+3.4 vs 8.2+4.6 days, $p = 1/4 \ 0.001$), compared with the patients that received only lactulose.³

Intravenous L-ornithine L-aspartate (LOLA) can be added in patients that do not respond to conventional treatment. In a double-blind randomized trial, a higher improvement rate in grade of HE (92.5% vs 66%, $P < .001$), shorter recovery time (2.70 ± 0.46 vs 3.00 ± 0.87 days, $P = .03$), and a lower mortality rate (16.4% vs 41.8%, $P = .001$) were reported in patients that received the combination of LOLA, lactulose, and rifaximin, compared with patients that received placebo, lactulose, and rifaximin.⁴

Including the complementary administration of nonabsorbable disaccharides, according to HE classification, is suggested as a better approach. Likewise, the search for and/or carrying out of clinical trials that evaluate the efficacy of the different treatment combinations for HE is considered opportune, favoring rapid patient recovery and a reduced mortality rate.

Financial disclosure

No financial support was received in relation to this study/article.

Conflict of interest

The authors declare that there is no conflict of interest.

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☆ Please cite this article as: Rodríguez-Peralta KL, Santiago-Ferrer JA. Manejo de urgencia de encefalopatía hepática. *Rev Gastroenterol Méx.* 2023;88:191–192.

See related content in DOI: <https://doi.org/10.1016/j.rgmx.2023.03.005>

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Response to Rodríguez-Peralta concerning the article "Evaluation and management of emergencies in the patient with cirrhosis"



Respuesta a Rodríguez-Peralta del artículo «Evaluación y manejo de emergencias en el paciente con cirrosis»

Dear Editors,

We appreciate the interest shown by Rodríguez-Peralta and Santiago-Ferrer in commenting on our article "Evaluation and management of emergencies in the patient with cirrhosis". In that review article, our aim was to analyze the available literature on the special management required by patients with liver cirrhosis (LC) in an emergency context. Topics focusing on the initial approach to the patient with decompensated LC, with respect to the evaluation and management of emergencies, were selected in the methodology, all of which were supported by the existing information available in Spanish and English, within the time frame of 1980 and the first trimester of 2021.

Regarding their first comment on the management of hepatic encephalopathy (HE) with nonabsorbable disaccharides, such as lactulose and lactitol, we cited in our review that the initial dose of lactulose recommended by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), the primary international associations, is 25 ml (16.7 g) every 2 h, until achieving at least 2 soft bowel movements, which is the goal for the urgent correction of HE, and that its adequate administration in patients whose neurologic status prevents them from swallowing adequately, or who require airway protection, is carried out through the use of enteral tubes.¹ By specifying the fact that in those cases of severe HE, with the accompanying neurologic status, adequate administration must be guaranteed by the use of enteral tubes, along with our knowledge of the West Haven Criteria, we clearly understand that the recommendation in patients with grade III or IV HE, or patients with any oral route incapacity due to neurologic status, is lactulose administration through a nasogastric tube. No reference to administration via enema as a therapeutic option was made in our article, which was intentional on our part, given the scant amount of high-quality evidence on the subject and the fact that the

procedure is not very practical or effective in actual clinical practice. No related evidence has been published since the 1987 article by Uribe et al.²

With respect to the observations about nonabsorbable antibiotics, we agree that rifaximin is the only drug currently approved by the Food and Drug Administration (FDA) and that its role is mainly one of adjuvant therapy to a nonabsorbable disaccharide, which we echoed in our article when we described its chief function as "add-on therapy" to lactulose, supported in the 2014 AASLD and EASL guidelines (GRADE I, A1).³ Likewise, Rodríguez-Peralta and Santiago-Ferrer refer to the work by Sharma et al. (described in the article by Reinert et al.) that recommends the combination of lactulose and rifaximin because it achieves greater HE resolution, compared with lactulose alone.⁴ It should be pointed out that our article had already been submitted for publication, when the literature review by Reinert was published in December 2021, and that in their original 2013 reference, Sharma et al. concluded that the combination of lactulose plus rifaximin was more efficacious than lactulose alone, in the treatment of overt HE,⁵ an assertion that does not change the similar idea expressed in our review. We also cited a systematic review and meta-analysis (that included the study by Sharma et al.), commenting that initial treatment with the combination of rifaximin and lactulose significantly increased clinical efficacy, with a number needed to treat of 5, as well as a decrease in the mortality rate.⁶

We completely agree with adding intravenous (IV) L-ornithine L-aspartate (LOLA) in nonresponders to conventional therapy, which is why we stated in our article that it can be used intravenously, as an alternative or additional agent in such patients, supported by studies showing improvement on psychometric tests and in serum ammonia levels in patients with persistent HE, as well as mortality rate improvement described in a meta-analysis.¹⁻⁷ The article referred to by Rodríguez-Peralta and Santiago-Ferrer, in which LOLA improved the grade of HE, reduced the recovery time, and was associated with a lower mortality rate, is indeed interesting, but again, that study came out in 2022, after our review had already been published.

Lastly, it is important to reiterate that the aim of our work was to offer the reader a review of the basic aspects of initial resuscitation of critically ill patients with LC, with a special focus on the evaluation and management of emergencies, and not to concentrate exclusively of the management of HE, given that extensive and specific clinical guidelines on each complication of cirrhosis already exist.

Ethical considerations

The authors declare they have met all ethical responsibilities regarding data protection, right to privacy, informed consent.

☆ Please cite this article as: Velarde-Ruiz Velasco JA. Respuesta a Rodríguez-Peralta del artículo «Evaluación y manejo de emergencias en el paciente con cirrosis». *Rev Gastroenterol Méx.* 2023;88:192-193.