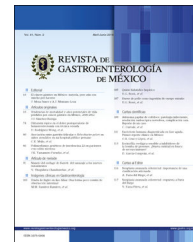




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LETTER TO THE EDITOR

Response to Pérez-Nieto et al., "Considerations about the balanced crystalloid solution recommendation in acute variceal bleeding"

Respuesta a Pérez-Nieto et al., "Consideraciones sobre la recomendación de soluciones balanceadas en hemorragia variceal aguda"

Dear Editors,

We sincerely appreciate the valuable comments sent by Pérez-Nieto et al. about our document, "Mexican consensus on the approach to and treatment of acute variceal bleeding".¹ The primary aim of our consensus document was to establish recommendations based on the best available evidence and the opinion of national experts in gastroenterology for the diagnosis, management, and treatment of acute variceal bleeding (AVB) in patients with portal hypertension (PHT), for the purpose of improving clinical decision-making, reducing the associated mortality, and standardizing care protocols at the different levels of medical care in Mexico.

The use of balanced crystalloid solutions in critically ill patients is known to be associated with lower rates of major adverse kidney events and mortality, compared with saline solution, although some studies have found no significant differences in general mortality.²⁻⁴ However, we know that new evidence is being generated daily. Statement 3 of our consensus says, "Intravascular volume replacement, with a restrictive resuscitation strategy with balanced crystalloid solutions is recommended, given that it has been associated with a decrease in adverse events and death"¹; this is based on a lack of specific studies for the population with cirrhosis.

Regarding the comment of Pérez-Nieto et al.⁵ on the open-label randomized clinical trial (RCT) conducted by McIntyre et al.⁶ in Ontario, Canada, involving 43,626 patients, in which two 12-week periods were completed using either Ringer's solution or normal saline, for their comparison, we wish to specify that said article could not be taken into account for our consensus, given that it was published in June 2025, and our bibliographic search covered articles from January 2010 to June 2024. It also remains to be seen whether that new clinical trial resolves the

controversies raised in previous publications. In addition, the statistical power of the study was reduced, given that 16 hospitals (~144,000 admissions) were to be included and only 7 centers completed the study due to COVID-19. This signifies that there could be a possible type II error in the face of small but clinically relevant effects at the population level. The study by McIntyre et al. does not change the preference for balanced crystalloids in resuscitating critically ill patients with no traumatic brain injury (TBI), which is supported by trials in intensive care units (ICUs) and meta-analyses, but rather indicates that, at the hospital level and with mixed use and moderate volumes, the absolute net effect is small and may be diluted. The study does not perform stratification by subgroups with cirrhosis or report laboratory findings, and so, does not change the pathophysiology-based practice (preventing hyperchloremia/acidosis). Utilizing evidence in ICU patients, it suggests an inclination for balanced solutions in critically ill cirrhotics without TBI. Finally, we believe that because said study sample is a broad mixture of patients (including those from obstetrics and psychiatry), it is not an "ICU resuscitation" trial but rather a hospital fluid policy, as stated by Pérez-Nieto et al.

The meta-analysis by Zampieri et al.⁷ mentioned by Pérez-Nieto et al. included 6 clinical trials, with a total of 34,685 patients. As a complement to that recent publication (2024), we found another, with some of the same authors, but published in 2022. Along with 7 other RCTs, it includes those same 6 clinical trials described in the 2024 publication, with concordant conclusions in the final recommendation. Here is the conclusion published in 2022: "Our Bayesian analysis suggests there is a high probability that the average treatment effect of using balanced crystalloids in a heterogeneous population of critically ill patients is to reduce mortality".⁸ Likewise, the conclusion in the publication by Zampieri et al. states, "overall, there is a high probability that use of balanced solutions compared with saline in the ICU is associated with reduced in-hospital mortality [...], with the evidence being of moderate certainty. However, in patients with traumatic brain injury, balanced solutions probably increase mortality". In their letter to the editor, Pérez-Nieto et al. suggest that this increase in mortality in patients with traumatic brain injury may be secondary to the risk of cerebral edema resulting from the administration of intravenous solutions with lower sodium concentrations. Although cerebral edema may be a distinctive feature of hepatic encephalopathy,

the behavior does not come close to being similar to that of traumatic brain injury, even in patients with cirrhosis or acute-on-chronic liver failure (ACLF), in whom the onset of edema is faster, with frequencies reported as low as 4%.⁹ Therefore, extrapolation would not be appropriate.

Regarding the choice of intravenous solution, the clinical practice guideline of the European Society of Intensive Care Medicine on fluid therapy in adult critically ill patients, which expressly takes into account the above-cited 2024 meta-analysis, recommends the following: "Because the balance of benefits and harms favored balanced crystalloids over isotonic saline in critically ill patients, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients".¹⁰

In our opinion, given that in the classic pyramid of evidence-based medicine (EBM), systematic reviews and meta-analyses (especially those of RCTs) are situated at the top and the RCTs are located just below them,¹¹ we cannot consider the new publication by McIntyre et al. as evidence of greater power, at present, for modifying the recommendation of our consensus.

We accept that having based our recommendation on a single publication reduces its certainty, and so we appreciate the complementary input provided by Pérez-Nieto et al. in their letter to the editor. It allowed us to further broaden our search, in the process of strengthening the recommendation, which aligns with our narrative review and guidelines previously published in this journal.¹²

Declaration of competing interest

The authors declare that there is no conflict of interest.

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