



Reply

# Reply to Omansen, T.F.; Ramharter, M. Intensive Therapeutic Plasma Exchange for Severe Yellow Fever: What Is the Evidence? Comment on “Ho et al. Intensive Therapeutic Plasma Exchange—New Approach to Treat and Rescue Patients with Severe Form of Yellow Fever. *Trop. Med. Infect. Dis.* 2025, 10, 39”

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Academic Editor: John Frean

Received: 20 March 2025

Accepted: 30 May 2025

Published: 8 December 2025

**Citation:** Ho, Y.-L.; Nukui, Y.; Villaça, P.R.; Okazaki, E.; Tatsui, N.H.; Netto, L.C.; Joelsons, D.; da Rocha, T.R.F.; de Mello Malta, F.; Pinho, J.R.R.; et al. Reply to Omansen, T.F.; Ramharter, M. Intensive Therapeutic Plasma Exchange for Severe Yellow Fever: What Is the Evidence? Comment on “Ho et al. Intensive Therapeutic Plasma Exchange—New Approach to Treat and Rescue Patients with Severe Form of Yellow Fever. *Trop. Med. Infect. Dis.* 2025, 10, 39”. *Trop. Med. Infect. Dis.* 2025, 10, 343. <https://doi.org/10.3390/tropicalmed10120343>

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Dear Drs. Omansen and Ramharter, we appreciate your thoughtful comments regarding our experience of intensive therapeutic plasma exchange for severe yellow fever [1]. We agree that randomized clinical trials (RCTs) are the gold standard for generating scientific evidence to inform healthcare decision-making. However, it is important to note that RCTs are only feasible when there is an established treatment that modifies the natural course of a disease, allowing for a comparative analysis to demonstrate, at the very least, non-inferiority. To the best of our knowledge, at the time of our article’s publication, there were no reports of therapeutic measures that modify the lethality of severe yellow fever. Even in liver transplant cases, the survival rate was 42.8%, which is lower than that observed with our intervention [2].

Regarding the possibility of patient selection bias, all of our patients met the criteria for severe yellow fever as defined by the Brazilian Ministry of Health and also fulfilled the Clichy criteria [3,4], widely used for liver transplantation in cases of fulminant hepatitis—further reinforcing the severity of their condition. Our approach aims to halt clinical deterioration in patients with severe yellow fever and prevent fatal outcomes. We agree that this strategy represents an initial step toward reducing the mortality of severe yellow fever cases and should be tested in other centers, ideally through a randomized clinical trial, if it is feasible.

As for the improvements in supportive care in intensive care units, we certainly learned valuable lessons throughout the outbreak. However, these improvements were the most significant in the early weeks, when patients in Group 1 predominated. Supportive therapies in Groups 2 and 3 were similar.

Finally, regarding albumin-based dialysis systems, our experience with MARS was not favorable, and these patients ultimately had fatal outcomes. In our understanding, considering the multiple mechanisms involved in bleeding in yellow fever, although MARS has the potential to remove toxins and restore metabolic balance, it may not be able to restore

hemostasis [5,6]. As consequence, patients still require massive transfusions of plasma and cryoprecipitate to correct coagulation disorders. Nonetheless, we believe that MARS is worth testing in centers where the necessary equipment is available, in order to compare its results with those of intensive therapeutic plasma exchange.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References

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