



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Reply: Does adjunctive hemoadsorption with CytoSorb® affect survival of COVID-19 patients on ECMO? A critical statement

Alessandro Putzu, MD*, Raoul Schorer, MD

Division of Anesthesiology, Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland

We would like to thank Köhler and colleagues for their comment on our manuscript [1] and on the CYCOV trial [2]. Supady and colleagues performed a single center, open-label, randomized, controlled trial on hemoadsorption in severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (ECMO) [2]. In the intervention group, a CytoSorb® adsorber was incorporated into the ECMO system and replaced every 24 h for a total treatment duration of 72 h. The protocol adherence was good: no delay between initiation of ECMO and start of cytokine adsorption was reported (median 0 h [interquartile range 0.00 to 0.75]) and the duration of cytokine adsorption was as planned (72 h [68.66 to 72.34]), as was cartridge use (3 cartridges [3–4]) [2].

Age, sex, body mass index, SOFA score, ECMO mortality prediction scores, and comorbidities were similar between groups [2]. The plasmatic inflammatory profile appeared to be less balanced, but not consistently in favor of one or the other group.

The last blood-gas values pre-ECMO showed a numerically lower pH in the control group (CytoSorb® 7.34 [7.17 to 7.39] vs control 7.28 [7.16 to 7.41]), while PaO₂/FiO₂ ratio was higher in the control group (CytoSorb® 62.7 mmHg [48.5 to 72.7] vs. control 84.2 [59.9 to 95.6]).

Köhler et al. suggested that the control group had received a more protective ventilation before ECMO initiation since higher peak pressures and higher tidal volumes were administered to CytoSorb® patients. While similar FiO₂ (100%) and PEEP (15 mbar) values were reported in both group, tidal volumes were different (5.30 ml kg⁻¹ [3.90 to 6.25] vs 3.85 [2.95 to 4.83]), while peak pressure (34 mbar [29.5 to 36] vs 32 [31 to 35]) and dynamic driving pressure (18 mbar [15 to 20] vs. 20 [14 to 20]) were closer. These were ventilation parameters reported at baseline, before ECMO treatment. On one hand, the use of ultra-protective mechanical ventilation (e.g. 4 ml kg⁻¹) in severe ARDS (without ECMO) could be an attractive treatment although it currently is an experimental therapy and is not supported by randomized trials. On the other hand, it is unlikely that those ventilation parameter differences induced the large mortality gap reported in the CYCOV trial (CytoSorb® 14 of 17 [82.3%] vs. control 4 of 17 [23.5%], $p < 0.01$, corresponding to a relative risk increase in mortality of 250% [95% confidence interval, 144% to 848%]). The use of large tidal volume ventilation

(>8 ml kg⁻¹) in comparison to protective ventilation in patients with moderate and severe ARDS was associated with a relative risk increase in mortality of 19% (95% confidence interval, 2% to 37%) [3]. Similarly, the ARMA randomized study found a relative risk increase of about 20% [4].

The impact of baseline imbalance was assessed by Supady and colleagues [2]. Multiple regression analyses including hemoadsorption and various baseline characteristics (age, inflammatory and coagulation parameters, SOFA score, noradrenaline support, PaO₂, and PaO₂/FiO₂ ratio) were performed and did not show any statistically significant factor associated to mortality other than CytoSorb® treatment [2].

The risk of false positive findings (increase in mortality) caused by uncontrolled confounders and random statistical variation could not be excluded. Finally, differences not following normal distributions are not at all surprising given the small study population and could limit the interpretation of the results.

We agree with Köhler and colleagues that the large difference in mortality is of concern to any clinician who wishes to use CytoSorb®. However, we do not agree that baseline imbalance and “timing, dosing, and application of supportive treatment” should “caution interpretation of study data and prevent meaningful conclusions”. No high-quality, large randomized trial found any survival benefit from extracorporeal blood purification therapies in critically ill patients without renal failure. Accordingly, a small negative randomized trial on hemoadsorption is not an unexpected finding. A possible detrimental, neutral, or beneficial effect of CytoSorb® hemoadsorption in critically ill patients cannot be excluded and deserves further investigation.

Disclosures

None. The authors declare that they have no competing interests. The study and the authors did not receive any financial support.

Declaration of Competing Interest

None.

References

- [1] Putzu A, Schorer R. Hemoadsorption in critically ill patients with or without COVID-19: a word of caution. *J Crit Care.* 2021;65:140–1. <https://doi.org/10.1016/j.jcrrc.2021.06.007>.

* Corresponding author at: Division of Anesthesiology, Geneva University Hospitals, 4 Rue Gabrielle Perret-Gentil, 1206 Geneva, Switzerland.
URLs: Alessandro.Putzu@hcuge.ch (A. Putzu), Raoul.Schorer@hcuge.ch (R. Schorer).

- [2] Supady A, Weber E, Rieder M, Lothar A, Niklaus T, Zahn T, et al. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single Centre, open-label, randomised, controlled trial. *Lancet Respir Med.* 2021;0. [https://doi.org/10.1016/S2213-2600\(21\)00177-6](https://doi.org/10.1016/S2213-2600(21)00177-6).
- [3] Sud S, Friedrich JO, Adhikari NKJ, Fan E, Ferguson ND, Guyatt G, et al. Comparative effectiveness of protective ventilation strategies for moderate and severe acute respiratory distress syndrome a network meta-analysis. *Am J Respir Crit Care Med.* 2021;203:1366–77. <https://doi.org/10.1164/rccm.202008-3039OC>.
- [4] Yndrome S, Etwork N. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301–8. <https://doi.org/10.1056/nejm200005043421801>.