



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.

## Cytokine adsorption and ECMO in patients with COVID-19

Cytokine adsorption during extracorporeal membrane oxygenation (ECMO) has been a subject of interest over the past decade. As a cytokine storm was proposed among pathogenetic mechanisms of severe COVID-19, interest in control of cytokines increased dramatically during the pandemic. Therefore, the trial by Alexander Supady and colleagues<sup>1</sup> is timely and offers interesting insights, but their findings must be carefully discussed before conclusions can be applied to clinical practice.

The manuscript reports the results of a small, single-centre, unblinded trial with small block sized randomisation that might have failed in balancing the two groups at baseline. Patients receiving cytokine adsorption were more frequently

in shock and required substantially more norepinephrine support (0.15 µg/kg per min [0.04–0.22] vs 0.03 µg/kg per min [0.00–0.36]) and over 3 L of fluids during the first 72 h, had a more severe acute respiratory distress syndrome (ratio of the partial pressure of oxygen in arterial blood to the fractional concentration of oxygen in inspired air was 62.7 [48.5–72.7] vs 84.2 [59.9–95.6] mmHg) and had higher concentrations of inflammation (ie, higher concentrations of C-reactive protein, ferritin, and D-dimers). In our clinical experience, adsorption filters have a shorter lifespan in patients with COVID-19; however, the trial reports an extremely high rate of adsorber thrombosis. Unfortunately, no anticoagulation protocol, nor activated prothrombin time value was reported in the study.

Furthermore, the authors investigated ten secondary outcomes despite only enrolling 17 patients, meaning the chance of false-positive findings is high. Therefore, the observed mortality difference could be attributed to chance rather than to a treatment effect. Finally, the trial enrolled patients treated in two different intensive care units between March and December, 2020—a period of time in which clinical management of COVID-19 was not standardised.<sup>2</sup>

In our opinion, cytokine adsorption efficacy should not be assessed in terms of interleukin-6 concentration alone. Its effects are wide and can be more properly assessed in terms of shock control (eg, reduction of inotropic requirements and shock laboratory parameters).<sup>3</sup> Moreover, patients on ECMO rarely benefit from or are rarely harmed by a

single treatment: outcome is the result of comprehensive intensive management, by which the strategy of therapy is supported by mechanical circulatory support and associated devices. The reported causes of death reflect the importance and outcome of intensive care in general (including more than 6 L of fluids per patient) rather than device-related thromboembolic complications.

To date, inflammation control and immunomodulation in patients who are critically ill and mechanically supported are not yet based on strong clinical evidence. For instance, the adsorption of antibiotics and clinically relevant drugs by the filter is currently still under investigation. However, a single, small trial should not steward worldwide clinical practice. More data arising from large, multicentre trials on cytokine adsorption are unquestionably needed and should not be delayed by these negative results; however, the growing body of non-randomised evidence cannot simply be overlooked.

We declare no competing interests.

Pasquale Nardelli, Marina Pieri,  
Evgeny Fominskiy,  
\*Anna Mara Scandroglio  
scandroglio.mara@hsr.it

Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy

- 1 Supady A, Weber E, Rieder M et al. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomized, controlled trial. *Lancet Respir Med* 2021; **9**: 755–62.
- 2 WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO solidarity trial results. *N Engl J Med* 2021; **384**: 497–511.
- 3 Scandroglio AM, Pieri M, Nardelli P, et al. Impact of CytoSorb on kinetics of vancomycin and bivalirudin in critically ill patients. *Artif Organs* 2021; published online March 9. <https://doi.org/10.1111/aor.13952>.



Pasquale Nardelli

