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LETTER

The cytokine adsorber Cytosorb® does not reduce ammonia concentrations in critically ill patients with liver failure

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Dear Editor,

Hemadsorption techniques are used in critical care for numerous indications, although the evidence is often limited. One example is the elimination of ammonia with the cytokine adsorber Cytosorb® (adsorption based on hydrophobic interactions of substances with a molecular weight of 5–55 kDa). Most recently, in vitro and in vivo data postulated that Cytosorb® (combined with continuous kidney replacement therapy (CKRT)) could eliminate ammonia [1, 2]. Due to the physicochemical properties of ammonia, which is a 5 Da hydrophilic molecule, relevant adsorption by Cytosorb® is not to be expected [3]. If non-invasive therapeutic approaches fail (see supplementary material T1), ammonia can be eliminated by CKRT [4]. We present the results of the Cyto-SOLVE study which investigated the adsorption capacity of Cytosorb® for different substances (NCT04913298). In a subgroup-analysis, we investigated whether the use of Cytosorb® led to a relevant ammonia adsorption in intensive care unit (ICU)-patients with liver failure.

20 ICU-patients (14 male, median age: 53 years, median Simplified Acute Physiology Score II (SAPS-II) on therapy day: 78) with CKRT and hyperbilirubinemia (total bilirubin in serum > 10 mg/dL) were included (see supplementary material T2). Cytosorb® was installed primarily for bilirubin elimination and was integrated post-dialyzer into the CKRT circuit (supplementary Figure S1). Ammonia concentrations were measured at baseline, after six and twelve hours in different blood samples taken from arterial cannula or the CKRT circuit: arterial concentration (= blood in-flow line concentration pre-dialyzer), blood out-flow line concentration post-dialyzer (= pre-Cytosorb®), and blood out-flow line concentration post-Cytosorb®, respectively. The ammonia clearances of the dialyzer and Cytosorb® were calculated using the following formula:

$$\text{Clearance}\left(\frac{\text{ml}}{\text{min}}\right) = (\text{bloodflow}) \times \frac{\text{concentration(pre} - \text{post)}}{\text{concentration(pre)}},$$

T test with associated samples and Pearson correlation coefficient was used for statistical evaluation (see supplementary files T3, T4, and Table S1).

The median ammonia serum concentration at baseline was 77 µmol/L (Tables S2 and S3). There was a significant ($p < 0.001$) ammonia elimination by the dialyzer (pre- vs. post-dialyzer) at all time points with a median ammonia-clearance of 52, 42, and 42 mL/min, respectively. There was a significant correlation between ammonia-clearance and blood flow as well as effluent rate during therapy ($p < 0.001$, Tables S4 and T5). The median ammonia-clearances of Cytosorb® were at the same time points 4, -6, and -7 mL/min, with no significant elimination or correlation at any time (see T6). There was a significant ($p < 0.001$) decrease in ammonia-concentration during therapy (77 → 61 µmol/L). Figure 1 illustrates the

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The members of the Cyto-SOLVE study group are listed in the acknowledgements.

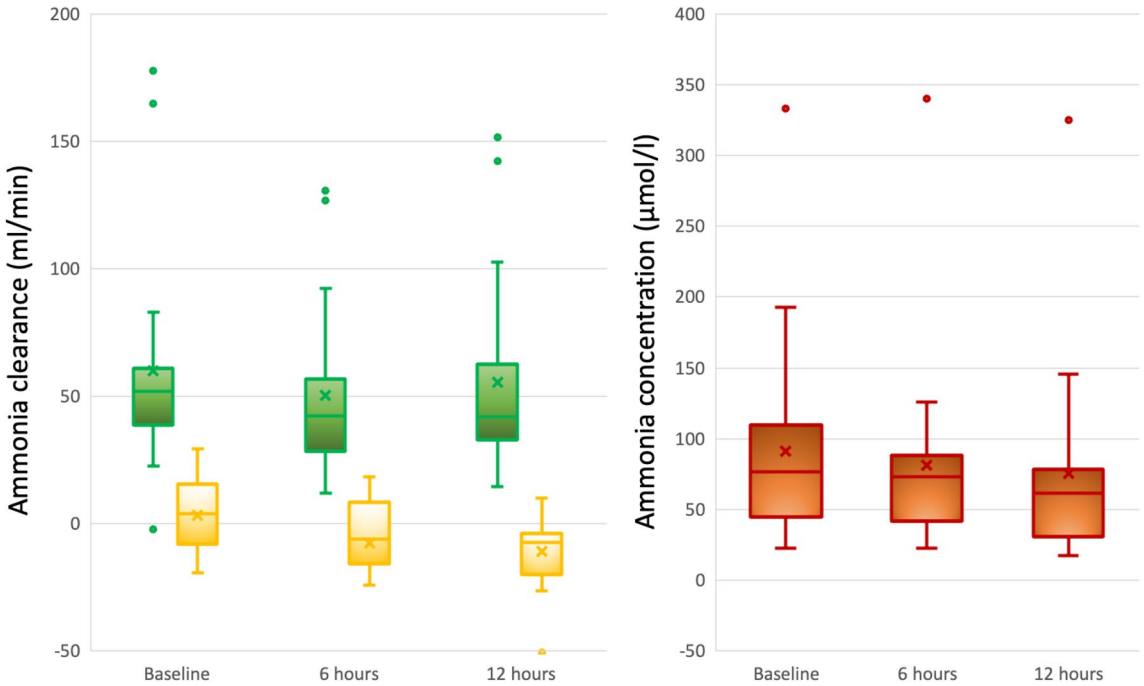

Fig. 1 Ammonia-clearance (mL/min) and -concentration (µmol/L) during therapy. Note: Green boxplots (always the first of the two boxplots) illustrate the ammonia clearance (mL/min) by the dialyzer and yellow boxplots show the ammonia clearance (mL/min) by Cytosorb®. Red boxplots present the ammonia plasma-concentrations at baseline, after six, and after 12 h with a significant decrease after six and twelve hours. The boxes of the boxplots represent the interquartile-range and the line the median. Whiskers were limited to 1.5 times of the interquartile range. The cross represents the mean

ammonia-clearances of the dialyzer and Cytosorb® and ammonia-concentrations.

The elimination of ammonia was mainly achieved by the dialyzer with a constant clearance over time depending on blood flow and effluent rate [5]. In contrast, we saw no evidence for a relevant ammonia-clearance by Cytosorb®. Both Dominik et al. and Tomescu et al. combined Cytosorb® with hemodialysis. The decreased ammonia plasma-concentration, that was also observed in our population, can most likely be attributed to the dialyzer, and not, as postulated by Dominik et al., to Cytosorb®. One limiting factor of our study is that Cytosorb® was not primarily used for the elimination of ammonia. In addition, potential clinical benefits cannot be determined based on the study design. In conclusion, utilizing Cytosorb® in addition to CKRT is not suitable to lower ammonia concentrations.

Supplementary Information
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Author contributions
CS designed the study and is funded by Else Kröner-Fresenius-Stiftung. CS, UL and MP drafted the manuscript and did the statistical analysis. MP was responsible for laboratory analyses. CG and MZ participated in study design and interpretation of results. All authors meet key authorship requirements and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
All data that are necessary to answer the question are included in this article.

Declarations

Conflicts of interest
Upon manuscript submission, all authors declare they have no competing interests.

Ethics approval and consent to participate
Ethical approval was obtained from the ethical review committee of the Ludwig-Maximilians-Universität (registration number 21-0236).

Consent for publication
Not applicable.

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References

1. Dominik A, Stange J. Similarities, differences, and potential synergies in the mechanism of action of albumin dialysis using the MARS albumin dialysis device and the CytoSorb hemoperfusion device in the treatment of liver failure. Blood Purif 2020; 1–10.
2. Tomescu D, et al. Haemoadsorption by CytoSorb(R) in patients with acute liver failure: A case series. Int J Artif Organs 2020; 391398820981383.
3. Olde Damink SW, Jalan R, Dejong CH (2009) Interorgan ammonia trafficking in liver disease. Metab Brain Dis 24(1):169–181
4. Naorungroj T et al (2021) Extracorporeal ammonia clearance for hyperammonemia in critically ill patients: a scoping review. Blood Purif 50(4–5):453–461
5. Fisher C et al (2022) Ammonia clearance with different continuous renal replacement therapy techniques in patients with liver failure. Blood Purif 51(10):840–846