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LETTER TO THE EDITOR

The procalcitonin kinetics paradox in hemoadsorption therapy for septic shock: Infection source, immunomodulation, and biomarker reliability

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Dear Editor,

We read with great interest the study by Gül et al., published in Turk J Intensive Care, which evaluated protocol-based HA330 hemoadsorption therapy (1). The authors demonstrated that early hemoadsorption in patients with refractory septic shock reduced 28-day mortality (30.8% vs. 49.3%; p=0.037) and improved SOFA scores on day 3, providing valuable real-world data in this controversial field. When considered alongside the retrospective analysis by Efe et al. and the Bayesian network meta-analysis by Meco et al., these findings support the potential benefit of hemoadsorption, particularly in the hyperinflammatory phenotype (2,3). This observation is also consistent with the biphasic immune trajectory of sepsis; hemoadsorption applied during the early hyperinflammatory phase may confer greater clinical benefit compared to the late phase, when the compensatory anti-inflammatory response predominates (4).

However, a clinically important paradox is noteworthy in this study: despite improvements in clinical status and organ function in the hemoadsorption group, procalcitonin (PCT) levels remained significantly higher compared to the control group on days 2 and 3 (day 2: 7.38 vs. 1.85 ng/mL; day 3: 6.40 vs. 2.0 ng/mL; p<0.001). This finding suggests a marked dissociation between clinical improvement and biomarker response, raising questions about the reliability of PCT as a marker of treatment response.

The most likely explanation for this paradoxical finding lies in differences in infection sources and pathogen distributions between groups. Bacteremia was significantly more frequent in the hemoadsorption group (26.9% vs. 8.0%; p=0.004), whereas pneumonia was predominant in the control group (58.7% vs. 23.1%; p<0.001). This is clinically relevant, as it is well established that PCT concentrations are substantially higher in bacteremic patients compared to those with pulmonary-source sepsis, regardless of pathogen type, while CRP levels remain similar (5). Furthermore, considering that the "other Gram-negative" organisms, which were significantly more frequent in the hemoadsorption group (34.6% vs. 9.3%; p<0.001), may include enteric-source pathogens carrying a high endotoxin burden, cytokine-independent stimulation of PCT production may have been further amplified. We therefore suggest that sharing the pathogen distribution within this category in a supplementary analysis would provide valuable insight; however, since this distribution was not detailed in the article, this interpretation remains speculative. The observation that CRP levels were similar between groups across all time points (p>0.05) strongly supports the notion that the elevated PCT levels may reflect patient profile

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rather than a selective biomarker shift. Additionally, the significantly higher and more prolonged use of continuous renal replacement therapy (CRRT) in the hemoadsorption group (71.2% vs. 26.7%; p<0.001; median duration 10 vs. 5 days; p=0.016) warrants consideration. In the setting of acute kidney injury, reduced renal PCT clearance may accelerate PCT accumulation; conversely, although CRRT can eliminate PCT, persistently elevated levels in this group further reflect a higher baseline burden of bacteremic infection. Taken together, these findings suggest that the elevated PCT levels in the hemoadsorption group more likely reflect a more severe baseline infection profile rather than a treatment-related alteration in biomarker kinetics.

The potential impact of immunomodulation on PCT kinetics should also not be overlooked. Despite the cytokine-lowering effect of hemoadsorption, cytokine-independent stimuli such as endotoxin burden and immune dysfunction may sustain PCT production (6). This may render biomarker interpretation particularly complex in immunomodulated septic shock. Prospective data incorporating cytokine levels and immune status markers (e.g., HLA-DR expression) are needed to validate this hypothesis (7).

These findings suggest that PCT may be insufficient for monitoring treatment response in patients undergoing hemoadsorption, and that alternative biomarkers less influenced by the site of infection may be required. Presepsin (sCD14-ST) emerges as a promising candidate in this context due to its specificity for bacterial infection and its relatively infection-driven kinetic profile; however, whether presepsin is adsorbed by the HA330 cartridge has not yet been systematically investigated, and its kinetic reliability in the hemoadsorption setting requires prospective validation (8). IL-6, while of interest for real-time monitoring of treatment efficacy, is directly adsorbed by the cartridge; therefore, measured levels may reflect adsorption capacity rather than infection burden, and its use as a standalone monitoring biomarker is not recommended (9).

In conclusion, despite growing evidence supporting the clinical benefit of hemoadsorption, the interpretability of biomarkers remains a key source of uncertainty. Future multicenter, prospective studies incorporating biomarker-based patient phenotyping, stratified analysis of PCT kinetics by infection source, and simultaneous immune marker measurements will enable more accurate and clinically meaningful assessment of both diagnosis and treatment response. In this context, it should be considered that PCT levels in patients with septic shock undergoing hemoadsorption may reflect underlying infection characteristics rather than treatment response. We therefore believe that interpreting biomarkers independently of clinical context may lead to misleading conclusions and should be approached with caution in patients undergoing hemoadsorption.

Yours sincerely,

Author contribution

Study conception and design: Hİ, Vİ; data collection: Hİ, Vİ; analysis and interpretation of results: Hİ, Vİ; draft manuscript preparation: Hİ, Vİ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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