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LETTER

Adjuvant therapeutic plasma exchange in septic shock

Sascha David[1,2*], Christian Bode[3], Christian Putensen[3], Tobias Welte[4], Klaus Stahl[5] and The EXCHANGE study group

Dear Editor,

The hallmark of sepsis is a pathological host response to an infection that may lead to organ dysfunction, shock and high mortality. Besides numerous circulating mediators initiating inflammation, vascular barrier breakdown and microvascular hypoperfusion, the consumption and subsequent lack of protective plasmatic factors additionally contribute to sepsis pathophysiology. Immunotherapy is complex and selective inhibition of key molecules, such as TNFα or inflammatory pathways, including Toll-like receptor 4 signaling was so far not effective in men [1]. Therapeutic plasma exchange (TPE) might eliminate circulating injurious mediators in a short intervention and simultaneously replace essential but already consumed protective factors. We have recently demonstrated safety and feasibility of TPE in septic shock in a prospective observational study (POS) [2]. Although uncontrolled by design, efficacy endpoints, such as norepinephrine (NE) requirement, suggested protective effects in these extremely sick patients. Previous studies using TPE in heterogeneous sepsis groups have even implicated potential survival benefits [3–5]. Based on these findings, we hypothesized that a single adjuvant TPE performed within 24 h after onset of septic shock might lead to rapid hemodynamic improvement and therefore performed a pilot bicentric randomized controlled trial (RCT) to test this (Identifier: NCT04231994).

We screened patients at two university hospitals for septic shock of < 24 h (+NE requirement > 0.4 µg/kg/min despite adequate fluid resuscitation), comparing standard of care (SOC) vs SOC + one single additional TPE (performed immediately following 1:1 envelope-based randomization). TPE was performed against fresh frozen plasma (FFP), exchanging a fixed dose of 12 units of human plasma (3262 ± 350 ml equal to 1 ± 0.3 times plasma volume) within 121 ± 37 min treatment time.

Forty patients were randomized based on a power analysis from our earlier POS ($n = 20$/group, 34 in Hannover, 6 in Bonn). Supplemental Table 1 shows the clinical characteristics highlighting the well-matched cohorts with a comparable severity of disease. The primary endpoint was early hemodynamic improvement (indicated by NE reduction between randomization and 6 h). Despite standard sepsis treatment, the NE dose in the SOC group did not change between randomization and 6 h (NE dose: 0.58 [0.46–0.84] vs 0.48 [0.36–0.84] µg/kg/min, $p = 0.15$). In contrast, the NE dose fell significantly in the TPE group (0.60 [0.55–0.87] vs 0.34 [0.21–0.44] µg/kg/min, $p < 0.0001$, and between-group difference at 6 h: $p = 0.004$, Fig. 1a). These absolute changes are consistent with a relative NE reduction of − 10% in the SOC group vs − 48% in the TPE group ($p = 0.001$). The ratio of mean arterial pressure (MAP) to NE dose (MAP/NE) increased within the TPE group ($p < 0.0001$), while it remained unchanged in the SOC group ($p = 0.123$) (Fig. 1b), as MAP even increased in the TPE group ($p = 0.03$) despite profound NE dose reduction, while it was unchanged in the SOC patients ($p = 0.52$). With regard to key secondary endpoints, the median SOFA score over 9 days (SOC 19 [15–24] vs TPE 16.5 [12–20.5], $p = 0.19$) and the 28-day survival (SOC 50% vs TPE 60%, $p = 0.44$) were both not different (Fig. 1c, d). Analysis of predefined secondary

*Correspondence: sascha.david@usz.ch; david.sascha@mh-hannover.de
[2] Department of Nephrology and Hypertension, Medical School Hannover, Carl-Neuberg-Street 1, 30625 Hannover, Germany
Full author information is available at the end of the article

Sascha David and Christian Bode contributed equally to this work.

The members of The EXCHANGE study are listed in acknowledgements.

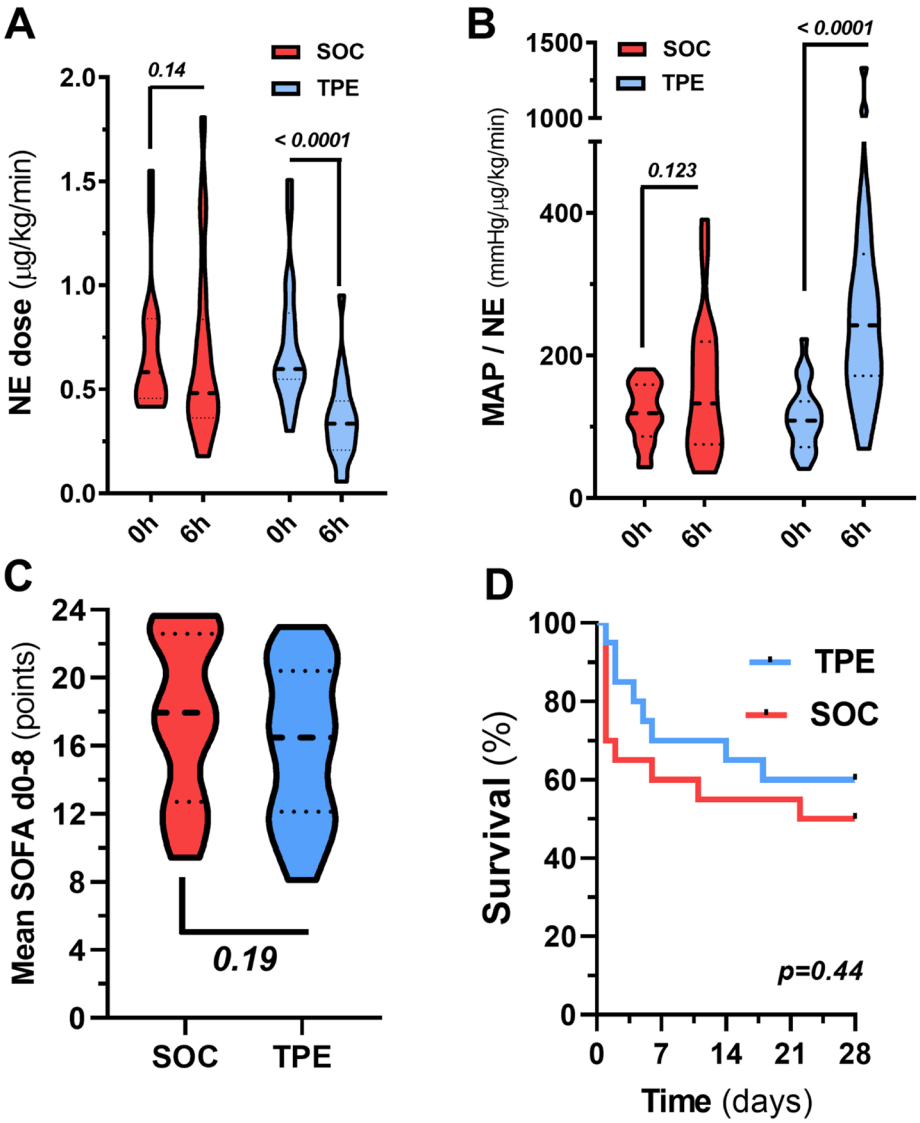

Fig. 1 Primary and key secondary endpoints. Violin blots showing (**A**) absolute norepinephrine (NE) doses in standard of care (SOC) and the therapeutic plasma exchange (TPE) group at randomization (0) and after 6 h. Wilcoxon-test was used to compare the paired longitudinal values, SOC 0 vs 6 h, $p=0.16$; and TPE 0 vs 6 h, $p<0.0001$). Mann–Whitney test was used to compare between groups: SOC 0 h vs TPE 0 h, $p=0.63$; SOC 6 h vs TPE 6 h, $p=0.004$). **B** Mean arterial pressure (MAP)/NE ratio at 0 and 6 h in SOC and the TPE group. Wilcoxon-test was used to compare the paired longitudinal values, SOC 0 vs 6 h, $p=0.123$; and TPE 0 vs 6 h, $p<0.0001$). Mann–Whitney test for between-group comparison (SOC 0 h vs TPE 0 h, $p=0.57$; SOC 6 h vs TPE 6 h, $p=0.005$) **C** Mean sequential organ failure assessment (SOFA) score calculated over nine consecutive days in the SOC and TPE group. **D** Kaplan–Meier survival graph for individuals in the SOC and TPE arm showing no statistical significant difference (log-rank test 0.437)

endpoints showed relevant changes with regard to coagulopathy and permeability in the TPE group (Supplemental Table 2). Of note, no adverse events occurred during the procedures.

In summary, our data show in a randomized controlled design that TPE in a subgroup of patients with septic shock leads to rapid hemodynamic improvement. Although most intensivists would probably agree that high doses of vasopressors might be injurious to our patients, it is of immense clinical relevance to test if this finding ultimately translates into a better outcome in an adequately powered multicenter RCT.

Supplementary Information
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Author details
[1] Institute of Intensive Care Medicine, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. [2] Department of Nephrology and Hypertension, Medical School Hannover, Carl-Neuberg-Street 1, 30625 Hannover, Germany. [3] Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany. [4] Department of Pulmonology, Medical School Hannover, Carl-Neuberg-Street 1, 30625 Hannover, Germany. [5] Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Carl-Neuberg-Street 1, 30625 Hannover, Germany.

Acknowledgements
The EXCHANGE study group exists of: All authors on the byline above and (in alphabetic order): 1. Markus Busch (Medical School Hannover, Department of Gastroenterology, Hepatology and Endocrinology). 2. Hermann Haller (Medical School Hannover, Department of Nephrology). 3. Marius M Hoeper (Medical School Hannover, Department of Pulmonology). 4. Felix Lehmann (University Hospital Bonn, Department of Anesthesiology and Intensive Care Medicine). 5. Julius J Schmidt (Medical School Hannover, Department of Nephrology). 6. Bernhard M.W. Schmidt (Medical School Hannover, Department of Nephrology). 7. Benjamin Seeliger (Medical School Hannover, Department of Pulmonology). 8. Andrea Sauer (University Hospital Bonn, Department of Anesthesiology and Intensive Care Medicine). 9. Philipp Wand (Medical School Hannover, Department of Nephrology). 10. Olaf Wiesner (Medical School Hannover, Department of Pulmonology). 11. Heiner Wedemeyer (Medical School Hannover, Department of Gastroenterology, Hepatology and Endocrinology).

Compliance with ethical standards

Conflicts of interest
SD has received fees from Baxter for expert advice and talks about plasma exchange in sepsis. SD has received support from Terumo to study plasma exchange in COVID-19, and by the German Research foundation (DA1209/4-3). SD, CB and KS have applied for support of a multicenter RCT from the German Research Foundation (DA1209/6-1). Otherwise, the authors have no conflict of interest related to the topic.

Ethical approval
The study was approved by local ethical committees at Hannover and Bonn, Germany.

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