Effects of Hemo**ADSORP**tion on **V**ascular **I**ntegrity in Se**P**tic Shock (ADSORP-VIP Trial): Protocol of a Prospective, Randomised, Controlled Trial

NCT: …

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BACKGROUND

Sepsis caused vasoplegic shock accounts for 20% of global deaths (1), and vasoplegia is caused in part by endothelial dysfunction (2). Dysregulated host immune response with uncontrolled production of inflammatory mediators (IMs) plays a central role in the pathophysiology of sepsis, resulting in endothelial dysfunction (3). Extracorporeal hemoadsorption (HA) can reduce the levels of circulating IMs (4), and it is frequently associated with rapid hemodynamic stabilization (5). The association between serum glycocalyx degradation product levels and microcirculation impairment in septic shock is well known (6). Recent in vitro experiments found that HA is able to remove not only IMs but also toxic molecules that can seriously harm the endothelium and the glycocalyx (7). Based on these findings it has recently been hypothesised that HA exerts its potentially beneficial effects, such as hemodynamic stabilisation and improved organ function via endothelial protection (8). However, the link between mediator removal by HA, hemodynamic improvement and endothelial function remain unclear.

HYPOTHESIS

We hypothesize that HA mitigates endothelial and glycocalyx injury by removing inflammatory and other injurious circulating molecules.

AIM OF THE STUDY

To investigate the effects of adjunctive CytoSorb therapy vs standard treatment on endothelial dysfunction in patients with refractory septic shock.

METHODS AND ANALYSIS

Study design

It is a prospective, randomised, controlled, open-label, proof of concept study. The study protocol was constructed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2025 statement. (9)

Settings

The ADSORP-VIP trial is designed as a monocentric clinical investigation. The study is organized and coordinated by the Centre for Translational Medicine at Semmelweis University. The clinical study will be conducted at the Department of Anaesthesiology and Intensive Therapy, Intensive Care Clinic at Semmelweis University, Budapest. This tertiary care unit will serve as the sole site for patient screening, enrolment, and intervention.

Study Duration

The total duration of the study is planned to be 24 months (2 years), commencing from the date of final regulatory and ethical approval. This period encompasses the initiation phase, recruitment, the active treatment intervention, follow-up assessments, and final data analysis.

Data collection

Patient data will be prospectively collected using secure, standardized electronic case report forms (eCRFs) implemented in the REDCap system. All data items will be captured at predefined time points—specifically at baseline (T0), 6, 12, 18, 24 hours after intervention, and then daily until the end of the study period, as well as at the 28-day follow-up visit. Data sources include bedside clinical assessments, laboratory results, hemodynamic monitoring devices, and study-specific sample analyses. All collected data will be entered into REDCap, a widely-used, secure, encrypted, and GDPR-compliant data management platform. Data integrity will be ensured through built-in completeness and range checks, regular study team monitoring, and periodic data cleaning in collaboration with an independent data management board (IDMB). All protocol deviations and adverse events will be documented in the eCRF.

Randomisation

Patients will be enrolled consecutively and randomly assigned in a 1:1 ratio to receive either standard medical therapy alone (Group A) or standard therapy plus CytoSorb hemoadsorption (Group B).

Randomisation will be performed using the randomisation module of the REDCap electronic case report form (eCRF) system. Allocation will be based on a pre-generated sequence table, created before the study initiation and implemented within REDCap. Randomisation will occur after confirmation of eligibility and informed consent. Randomisation is planned to be open-label. The treating clinicians, investigators, and study personnel will be aware of the assigned treatment group immediately after randomisation. The REDCap system will automatically assign the treatment arm and record the allocation in the eCRF. Statistical analyses will be performed by statisticians blinded to treatment allocation.

Blinding

It is not possible for the staff who are providing patient care to be unaware of the group assignments after randomisation. Sham procedures for the control group would be unethical. Statisticians are blinded to treatment assignments. Regarding the analysis, investigators will be blinded to the results until the analysis (*see below in Collection and analysis of samples*).

Time points measurements

Duration per patient: The study starts after randomisation. In the CytoSorb group, measurements, blood sampling, and other recordings are performed immediately prior to the start of CytoSorb therapy (indicated as T_0). In the SMT group, T_0 is defined as the first recording after randomisation. The study period ends (Te) on day 5 after randomisation or at the time of death within this period, whichever happens first. The patients will be followed up on day 28 after randomisation.

Study groups

Patients eligible for the study in terms of the inclusion and exclusion criteria (defined below) will be randomly assigned to one of the two study groups after informed consent. In case the patient is unable to give consent, informed consent will be obtained from the next of kin or his/her legal guardian. Information on the study and the treatment will be provided by the attending physician. Patients in group A will be treated with SMT. Patients in group B will be treated with continuous CytoSorb therapy in addition to SMT.

Patient enrollment

The inclusion and exclusion criteria are mainly based on the DECRISS Trial protocol (10) and the results of previous case series and trials(11–13) and modified accordingly:

Inclusion criteria:

- Septic shock as defined by Sepsis-3 criteria (14).
- Serum lactate levels 2< and <8 mmol/L at screening.
- Fluid unresponsiveness: Objectively confirmed via dynamic tests or fluid challenges following initial resuscitation (15).
- Norepinephrine base equivalent (NEE) requirement ≥0.5 μg/kg/min (15) and already on corticosteroids for at least 30 min.
- Tissue perfusion impairment: Persistently elevated serum lactate AND/OR prolonged capillary refill time (> 3 seconds) despite standard therapy (15).
- Alternative causes of shock (e.g., obstructive or cardiogenic) must be ruled out using critical care ultrasonography (CCUS) (15).
- Arterial, central venous catheters and an invasive hemodynamic device (PiCCO, Getinge) in place for invasive haemodynamic monitoring.
- Inclusion within a maximum of 12 hours after the onset of vasopressor need and after all standard therapeutic measures have been implemented.
- High likelihood of dysregulated immune response, indicated by (AND/OR):
    - PCT ≥ 5 ng/mL (based on a retrospective analysis of own data: n=171 patients treated with septic shock, median: 6.71 IQR: 0.78-31.70 ng/mL; (unpublished data))
    - IL-6 ≥ 1000 pg/mL (16)
    - Ferritin ≥ 1000 ng/mL (17)
- Written informed, retrospective consent from the patient or next of kin.

Exclusion criteria:

- Patients under 18 years of age and over 80.
- Pregnancy
- Unlikely to survive for 24 hours, according to the attending physician.
- SOFA-2 score ≥ 16 at ICU admission.(18)
- Source control is uncertain
- Thrombocytopenia (<20 G/L).
- Criteria of standard guideline-based medical treatment not exhausted (detailed below at SMT).
- If CytoSorb therapy needs to be disconnected for more than 2 hours (i.e.: surgery, CT-transfer), the patient should be excluded from the study.

- End stage organ failure.[1]

Standard medical therapy

Standard medical therapy is provided according to local protocols based on international guidelines. It includes 5-lead ECG, pulse oximetry, continuous invasive blood pressure monitoring, central venous cannulation. Advanced haemodynamic monitoring - generally PiCCO - is used to optimise haemodynamics. The goal is to use the lowest necessary catecholamine support to reach a 65 mm Hg mean arterial pressure, but it should be left to the physician to tailor it to each patient's needs based on other perfusion parameters like diuresis, serum lactate level, and ScvO2. The first choice of vasopressor is norepinephrine — also including steroid support, decided by the attending physician. Vasopressin is the second-line recommended vasopressor. If needed, dobutamine is the suggested first-line inotrope. SMT will be performed according to the 'Surviving Sepsis Campaign' Guidelines (19). Patients in group B will receive a haemodialysis catheter inserted into a central vein (femoral, subclavian or internal jugular, as appropriate). Treatment will be performed as instructed by the manufacturer's user guide.

Cytosorb Therapy

CytoSorb will be placed in the blood circuit for either standalone extracorporeal treatment (13) or a continuous renal replacement treatment (CRRT). If used with CRRT, the device should be used in continuous venovenous hemodiafiltration (CVVHDF) mode. The preferred anticoagulation method is regional citrate anticoagulation (RCA). The target blood flow rate is 1.5 ml/kg/min, and the flow rate will be recorded. The intervention follows a fixed 24-hour hemoadsorption regimen utilizing two sequential cartridges exchanged at the 12-hour mark. Premature discontinuation is restricted solely to technical complications or defined Serious Adverse Events (SAEs, see below).

Collection and analysis of samples

Blood samples for study analyses will be collected at baseline, 6, 12, 18, 24 hours after randomisation and then daily until the end of the study period. Sampling will be performed via existing arterial catheters. All samples will be processed immediately after collection, promptly centrifuged and supernatant obtained. Aliquots will be prepared, labelled and either examined within 2 hours locally according to standard hospital laboratory procedures or stored at -80 °C in cryovials to minimise repeated freeze–thaw cycles. A continuous cold chain will be maintained throughout storage and transport with shipment on dry ice if longer transport. Hemolysed samples will be documented and excluded from microRNA analyses with sensitivity analyses excluding the affected samples.

[1] Chronic renal failure (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m2), Chronic liver failure (MELD Score >30, ChildPugh score class C.), Chronic heart failure (New York Heart Association class IV.); Severe chronic pulmonary disease (Chronic obstructive pulmonary disease: GOLD DEnd-stage)

Primary endpoints

1. Changes in Syndecan-1 serum levels (collected at T_0, T_6, T_{12}, T_{18}, T_{24} and then daily, pre- and postadsorbent samples in CytoSorb group).

Secondary endpoints

1. Changes in laboratory parameters (collected at T_0, T_6, T_{12},, T_{18}, T_{24} and then daily)
    a. Endothel and glycocalyx specific markers: Glypican-1, Heparan-sulfate, MCP-1 (CCL2), sICAM-1, sVCAM-1, VEGF, sE-selectin (soluble E-selectin; CD62E), sP-selectin
    b. Inflammatory parameters: procalcitonin (PCT), C-reactive protein (CRP), White Blood Cell (WBC), Ferritin, TNF-α, IL-1β, IL-6, IL-8 (CXCL8),
    c. miRNAs: miR-126, miR-92a, miR-155, miR-21, miR-23a.
2. Arterial lactate level changes
3. Change in Sequential Organ Failure Assessment (SOFA)-2 score (SOFA-2 score will be assessed at T0, T24 and then daily) (18).
4. Change in EVLWI (T_0, T_6, T_{12}, T_{18}, T_{24} and then daily)
5. Fluid balance.
6. Time to negative fluid balance.
7. MV free days.[2]
8. Vasopressor free days.[2]
9. Change in vasoactive-inotropic score (VIS)(20)
10. CRRT free days
11. Length of stay at the Intensive Care Unit (ICU).
12. Survival (ICU, Hospital, at day 28)
13. Adverse events (AEs) (see below)

AEs and serious AEs: definition and recording

AEs will be collected from the start of the intervention period until follow-up.
All AEs and device deficiencies including all serious AEs (SAEs) are collected and documented in the source document and the AE report form during the entire study period, that is, from the patient's informed consent until the last follow-up visit/call. Dates of the event, the seriousness of the event and the relationship to the study device need to be documented. The AE report form has to be forwarded to the SC and the independent data management board (IDMB). Provided that the AE is confirmed by the SC, the national ethics committee needs to be notified (http://

[2]Adapted from Laterre PF at al, 2019 and Derek A et al, 2020) This exploratory endpoint is defined as the number of days from the inclusion in the study to 28 days or ICU discharge, during which the patient is: 1) alive; 2) free of treatment with intravenous vasopressors; and 3) free of any invasive mechanical ventilation (see definition below). Any patient that dies within this 28-day period is assigned zero P&VFDs, even if there is a period during which the patient is free of both vasopressor treatment and mechanical ventilation. If vasopressors need to be restarted or mechanical ventilation needs to be initiated or restarted, and the use of either is greater than 60 minutes within a 24-hour period, then the clock is reset and the patient is not considered free of vasopressors and / or mechanical ventilation until after those therapies are again finally discontinued. Vasopressor use or mechanical ventilation during – and up to three hours after – surgery / procedure (including bedside) is exempt from this rule (i.e. does not reset the calculation of P&VFDs). The intent is for the endpoint to reflect the speed of recovery from septic shock and respiratory failure, with appropriate penalties for recurrent shock, new or recurrent respiratory failure, and death. Vasopressor use is defined as any intravenous dose of noradrenaline / noradrenaline, phenylephrine, dopamine, epinephrine / adrenaline, vasopressin. Mechanical ventilation is defined as use of endotracheal or tracheostomy tube assisted ventilation (>5 cm H2O continuous positive airway pressure and >5 cm H2O of pressure support from the ventilator in tracheostomy patients). End of mechanical ventilation is defined as: 1) extubation of intubated patients or 2) ≤5 cm H2O continuous positive airway pressure and ≤5 cm H2O of pressure support from the ventilator in tracheostomy patients. If non-invasive ventilation by mask or bag (>5 cm H2O of pressure support) is deployed to avoid (re)intubation, it also counts as mechanical ventilation. However, all other uses of non-invasive ventilation such as chronic night-time use of positive airway pressure for chronic obstructive pulmonary disease (COPD) or sleep apnea does not count as mechanical ventilation (regardless of pressure).

www.ett.hu/tukeb. htm).

Follow-up

A follow-up assessment will be conducted 28 days after randomisation using a follow-up letter/email or a phone call. In case the patient or the next-of-kin cannot be reached, medical records will be used to obtain the needed information. On day 28 survival, need for dialysis and AEs will be assessed.

Sample size calculation

The sample size calculation is based on the difference in Syndecan-1 serum levels between the two study groups, which constitutes the primary endpoint of the trial. Based on published literature comparing Syndecan-1 levels in septic and septic shock patients (21–26), the study is powered to detect a 40% relative decrease in Syndecan-1 serum levels in the treatment arm compared to the standard medical treatment arm.

The primary analysis assumes a continuous endpoint, analyzed using a two-sample t-test on log-transformed data to account for the expected right-skewed distribution of Syndecan-1 concentrations. The assumed standardized effect size is 0.578, reflecting the anticipated treatment effect derived from the literature.

The study is designed as a group sequential trial with a maximum of two analyses (one interim and one final analysis). The overall two-sided significance level is 5%, with a target statistical power of 80%.

An interim analysis is planned after approximately 30 patients have been enrolled and evaluated (corresponding to an information rate of 29.5%). At the interim analysis, a portion of the overall type I error will be spent according to the predefined Hwang-Shih DeCani alpha-spending function (gamma = 0). If the interim efficacy boundary is crossed, the study may be stopped early for efficacy.

If the interim analysis does not demonstrate sufficient evidence for efficacy, the study will continue to the second stage. In this case, an unblinded sample size re-estimation will be performed based on the observed treatment effect and variability at the interim analysis, while preserving control of the overall two-sided type I error rate within the group sequential framework.

The sample size for the second stage will be recalculated accordingly; however, the total number of randomized participants will be capped at 200. This cap is intended to ensure feasibility.

Participants will be randomized in a 1:1 ratio between the treatment and control arms. An anticipated 15% attrition rate (including loss to follow-up, protocol deviations, or withdrawal of consent) is considered in the operational planning of the study.

Analysis plan and statistics

General principles

Deviations from this section, if any, will be justified and documented. Unless stated otherwise; statistical tests will be two-sided; the overall type I error for the single primary endpoint will be controlled at 5%. Confidence intervals (CI) will be presented at the 95% level. Secondary and additional biomarker endpoints are exploratory; multiplicity adjustments will not be applied.

Baseline will be defined as the **T0** sample and assessment timepoint; for the CytoSorb group, T0 corresponds to immediately before the start of CytoSorb; for the control group, T0 corresponds to the first post-randomisation assessment.

Analysis sets

- **Intention-to-treat set (ITT);** all randomized participants who have not withdrawn consent for use of their data and have at least one post-treatment observation for the primary variable. ITT data would be analyzed according to the randomized treatment assignment.
- **Per-protocol set (PP);** all participants without major protocol deviations affecting primary endpoint assessment like exclusion criteria met during the trial; serious adverse effect requiring discontinuation; missing primary endpoint data; serious non-sepsis medical events (e.g., myocardial infarction, stroke); commencement of CytoSorb more than 2 hours after randomization; CytoSorb duration not reaching 24 hours; or death within 24 hours of enrolment.
- **Safety analysis set (Safety);** all enrolled participants for whom any post-enrolment safety information is available; participants will be analyzed according to treatment actually received.

Primary inference will be based on ITT; PPS will be provided as a sensitivity analysis.

Missing data rules and conventions

No imputation will be performed for efficacy endpoints.

For analyses requiring a single post-baseline value within a time window; a complete-case analysis will be applied.

Primary endpoint; definition and estimand

Primary endpoint: change in Syndecan-1 serum concentration over the first 24 hours post baseline.

Primary analysis variable: the log-scale change from baseline to the T24 post-baseline Syndecan-1 value. If the T24 value is missing, the value will be considered missing.

Estimand: treatment effect expressed as a ratio of geometric mean changes (or equivalently, the between-group difference of mean log-changes).

Primary statistical method

Syndecan-1 values will be analysed on the natural logarithmic scale due to expected right skew.

The primary comparison will use a two-sample t-test on the individual log-change values:

$$Y_i = log(Syndecan - 1_{i,last \leq 24h}) - log(Syndecan - 1_{i,T0})$$

The treatment effect will be reported as:

- difference in means on the log scale with 95% CI;
- back-transformed effect as a **geometric mean ratio** of changes between groups; presented as percent relative difference.

Assumptions will be checked using residual diagnostics on the log-scale change variable; if gross violations are evident, a supportive non-parametric comparison (Wilcoxon rank-sum on log-change) will be reported as a sensitivity analysis.

Interim analysis and sample size re-estimation

The study will use a **two-look group sequential design** with one interim and one final analysis for the primary endpoint; implemented using an inverse normal combination test framework.

- **Timing:** interim analysis after approximately **30 participants** have evaluable primary endpoint data (information rate approximately 0.295); final analysis at completion of recruitment and evaluability.
- **Type I error control:** overall one-sided alpha 2.5% (equivalent to two-sided 5%); alpha spending per a Hwang–Shih–DeCani spending function with gamma = 0; resulting stagewise one-sided significance levels approximately 0.0073 at interim and 0.0195 at final (to be recalculated prior to unblinding based on the number of actually evaluable patients).
- **Stopping for efficacy:** if the interim efficacy boundary is crossed; the trial may be stopped early for efficacy; no formal futility stopping is planned unless specified in SAP.
- **Unblinding:** the interim analysis, including any unblinded variance/effect estimates needed for sample size re-estimation, will be conducted by a statistician; interim outputs will be restricted to what is necessary for decision-making; the analysis dataset will remain otherwise controlled.

- **Unblinded sample size re-estimation (SSR):** if early stopping is not triggered; an unblinded SSR will be performed at interim based on observed variability and treatment effect on the primary endpoint; the updated stage-2 sample size will be chosen to maintain target power within the combination test framework; the total number of randomized participants will be capped at **200** for feasibility.

The final confirmatory p-value for the primary endpoint will be derived according to the alpha spending function (final one-sided confidence level expected to be 1.95%) ensuring preservation of the overall type I error rate.

Secondary endpoints analysis approach

All secondary analyses are exploratory; no multiplicity adjustment will be applied; results will be summarised with effect sizes and 95% CI where feasible. Area Under Curve analysed will be carried out where feasible.

Repeated laboratory biomarkers (including endothelial/glycocalyx markers; inflammatory markers; miRNAs):

- Descriptive summaries at each timepoint by group; mean (SD) or median (IQR) as appropriate; plus graphical time profiles.
- For between-group comparisons over time; an exploratory mixed model for repeated measures may be fitted for log-transformed concentrations where appropriate; fixed effects: treatment; time; treatment-by-time interaction; baseline value as covariate; participant as random factor with an appropriate covariance structure; inference considered descriptive.

Physiologic/organ dysfunction endpoints (lactate; SOFA; EVLW; VIS):

- Change from baseline to specified timepoints (e.g., T24 and daily) will be summarized;
- Primary summaries will be based on observed data without imputation; where a single summary is required, only the available values will be used;
- Between-group comparisons will use t-tests on change scores for approximately normal variables, otherwise rank-based methods if residual plots suggest them necessary. Supportive regression adjustment may be used.

Fluid balance; time to negative fluid balance:

- Fluid balance summarized daily and cumulatively;
- Time-to-event methods (Kaplan–Meier; log-rank; Cox model) may be used descriptively for time to negative balance, with censoring at death or ICU discharge as applicable.

Ventilator-free days; vasopressor-free days; CRRT-free days; ICU length of stay:

- Summarized using medians and IQR due to expected non-normality
- Between-group comparisons using rank-based tests; model-based approaches (e.g., negative binomial; zero-inflated models) may be used supportively.

Survival (ICU; hospital; day 28):

- Kaplan–Meier curves and descriptive hazard ratios from Cox regression may be provided.

Safety analyses

Adverse events will be coded and summarised by system organ class and preferred term; severity and relationship to study procedures will be tabulated.
Comparisons of AE rates between groups will be descriptive; selected device-relevant safety signals (e.g., thrombocytopenia; bleeding; circuit issues) will be summarized with time of onset and clinical context.

Software

Analyses will be performed using R. Primary and interim group sequential procedures will be implemented in R using the rpact package. Version and package details will be documented.

Study populations

Safety analysis set (all patients enrolled in the study), PP Set (PPS, all enrolled patients who finished the study conforming to the requirements of the study protocol) and ITT (all randomised participants who start on a treatment, excluding consent withdrawals) will be performed.

Withdrawal of a subject from PPS

Patients will not be included in the per-protocol analysis if: (1) during the trial any exclusion criteria is met; (2) a serious adverse effect occurs; (3) data required for the primary endpoints are missing; or (4) serious medical conditions not related to septic shock occur (eg, myocardial infarction, stroke); (5) commencement of CytoSorb more than 2 hours after randomisation and (6) the duration of CytoSorb therapy did not reach 24 hours or the patient died within 24 hours from enrolment.

ETHICS AND DISSEMINATION

Ethical and legal considerations

This clinical study will be conducted following the Declaration of Helsinki. It will be conducted in compliance with the protocol, Good Clinical Practice (GCP) (2001/20/ EEC, CPMP/ICH/135/95), designated standard operating procedures, and local laws and regulations relevant to the country of conduct. This protocol in its current version was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (BM/11851-1/2026).

Data management

IDMB will handle data, eCRF will be applied. The investigator will guarantee that the data in the eCRF are accurate, complete and clear. Data management plan will detail the data handling during and after the trial. Data from completed eCRFs will be assessed under the direction of the data manager at IDMB according to a data cleaning plan. In case of missing, improbable or inconsistent data in the eCRFs will be referred back to the Investigator using a data query form.

Trial organisation, committees and boards

ADSORP-VIP is designed and coordinated by the Centre for Translational Medicine at Semmelweis University.

Steering committee

The SC will be led by ZM (intensive care specialist). Other members will be TT (intensive care specialist), DMK (intensive care specialist), DK (anesthesiology and intensive care resident), LZ (intensive care specialist), NK (intensive care specialist) and MO (experimental scientist). The SC will discuss all important questions, including adverse events (AEs) and dropouts during the study." SC will discuss all important questions including AEs and the drop-outs during the study.

Participating centres

The ADSORP-VIP trial is designed as a monocentric clinical investigation. The study is organized and coordinated by the Centre for Translational Medicine at Semmelweis University. The clinical study will be conducted at the Department of Anaesthesiology and Intensive Therapy, Intensive Care Clinic at Semmelweis University, Budapest. This tertiary care unit will serve as the sole site for patient screening, enrolment, and intervention.

Significance

To the best of our knowledge, this will be the first study to evaluate the effects of HA on endothelial function in septic shock in a randomized controlled clinical trial. This study aims to clarify whether HA can protect the endothelial glycocalyx in septic shock and may also shine some light on the physiological background of hemodynamic stabilization during HA. Our results could potentially support a more targeted, personalised approach of HA therapy by better selection of patients treated with septic shock who may benefit the most from adjunctive extracorporeal blood purification.

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