The effects of haemadsorption on vasoplegic shock reversal in critically ill patients

PhD Thesis

dr. Fatime Hawchar

Doctoral School of Multidisciplinary Medical Science, Doctoral Institute
University of Szeged
Albert Szent-Györgyi Health Center
Department of Anaesthesiology and Intensive Therapy

Supervisor: Prof. Dr. Zsolt Molnár

Szeged
2023

The thesis is based on the following scientific publications:

1. Fatime Hawchar, Cristina Rao, Ali Akil, Yatin Mehta, Christopher Rugg, Joerg Scheier, Harriet Adamson, Efthymios Deliargyris, Zsolt Molnar: The Potential Role of Extracorporeal Cytokine Removal in Haemodynamic Stabilisation in Hyperinflammatory Shock, July 2021, *Biomedicines* 9:768, IF: 4.757. SCImago Journal Rank: Q1.
2. Fatime Hawchar, Ildikó László, Nándor Öveges, Domonkos Trásy, Zoltán Ondrik, Zsolt Molnár: Extracorporeal cytokine adsorption in septic shock: A proof of concept randomised, controlled pilot study, November 2018, *Journal of Critical Care* 49:172-178, IF: 2.685. SCImago Journal Rank: Q1.
3. Fatime Hawchar, Dana Tomescu, Karl Träger, Dominik Joskowiak, Klaus Kogelmann, Jens Soukup, Singrun Friesecke, David Jacob, Jan Gummert, Andreas Faltlhauser, Filippo Aucella, Martijn van Tellingen, Manu L N G Malbrain, Ralph Bogdanski, Günter Weiss, Andreas Herbrich, Stefan Utzolino, Axel Nierhaus, Andreas Baumann, Andreas Hartjes, Dietrich Henzler, Evgeny Grigoryev, Harald Fritz, Friedhelm Bach, Stefan Schröder, Andreas Weyland, Udo Gottschaldt, Matthias Menzel, Olivier Zachariae, Radovan Novak, Jernej Berden, Hendrik Haake, Michael Quintel, Stephan Kloesel, Andreas Kortgen, Stephanie Stecher, Patricia Torti, Frieder Nestler, Markus Nitsch, Detlef Olboeter, Philip Muck, Michael Findeisen, Diane Bitzinger, Jens Kraßler, Martin Benad, Martin Schott, Ulrike Schumacher, Zsolt Molnar, Frank Martin Brunkhorst: Haemoadsorption in the critically ill - final results of the International CytoSorb Registry, October 2022, *PlosOne* 17(10):e0274315, IF: 3.752. SCImago Journal Rank: Q1.

I. Introduction

Sepsis is a potentially life-threatening condition that occurs when the body's immune response to infection becomes dysregulated, leading to organ dysfunction and failure.

The current definition of sepsis has been created in 2016 by the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3). It states that 'sepsis' is a life-threatening organ dysfunction resulting from dysregulated host responses to infection that may lead to subsequential 'septic shock' which is a subset of 'sepsis' when organ dysfunction is present due to severe circulatory, cellular, and metabolic abnormalities.

Septic shock is a clinical picture of a subset of sepsis with severe underlying circulatory and metabolic deteriorations leading to higher mortality. It is practically a picture of sepsis combined with hypotension despite adequate fluid resuscitation, requiring vasopressor therapy to keep MAP $\geq$ 65 mmHg and serum lactate concentration is $\geq$ 2 mmol/L.

Beside the acute consequences, the alertness is expanding about the long-term health consequences of sepsis in survivals: it may affect their physical, psychological, and cognitive status, leading to further healthcare and social compelling and expenditures.

As the pathophysiology of sepsis is gradually better understood, it is now seen as a complex and endogenously amplified host response to a systemic infection. Physicians still expect a single or a limited number of widely available tests with high sensitivity and specificity to diagnose sepsis, however, this solution will probably never appear.

The adaptive and innate immunity work together as a coherent immune system as a highly complex network of cells and molecules, keeping a balance between pro- and antiinflammatory mechanisms. The innate immune system is the 'fast response team' of the immune system, working by releasing pro-inflammatory mediators, cytokines, oxygen free radicals, etc. It is able to recognise a wide spectrum of pathogens via a redundant set of molecules found on the surface of a vast number of pathogens. To keep the process under control and thus the integrity of the body, adaptive immunity-guided antiinflammation is activated at the same time to balance proinflammation. Cytokine storm is a term referred to the state when proinflammatory cytokines and mediators are released in an overwhelming, acute manner, leading to sepsis and septic shock.

One of the novel approaches to improve outcomes is based on the modulation of the immune system and the host's response. Still, the early modulation of the 'cytokine storm' could help regaining control and contribute to improved outcomes. Blood purification reduces the

concentrations of inflammatory mediators in the circulation by non-specific mass removal to attenuate cytokine storm.

Cytokine adsorption is an alternative, relatively novel way of extracorporeal blood purification. CytoSorb® (CytoSorbents, Corporation, New Jersey, USA) is a haemadsorption cartridge that can be routinely used with e.g. blood pumps for renal replacement therapy (RRT). It contains biocompatible, porous polymer polystyrene beads that can adsorb a broad spectrum of molecules between the range of 5-60 kDa molecular weight. This adsorption spectrum is well suitable for cytokine adsorption. Overall, pro-inflammatory cytokines during cytokine storm could be effectively removed from the circulation at the early phase of septic shock to regain control by restoring the balance between pro-, and antiinflammatory cytokines and other molecules that take part in the harmful process of dysregulation. The main clinical benefit may be shown in reversal of vasoplegia and subsequent reduced vasopressor requirements that was found in case studies. Our knowledge so far about the treatment's benefits are relying on the results of some animal experiments, case reports, observational studies, and smaller clinical trials.

II. Aims

After summarising the literature on this topic, we have defined four main goals to find some missing links between haemadsorption and the treatment of septic shock: 1) our aim was to conduct a proof-of-concept, randomised pilot study on haemadsorption on septic shock patients who did not require RRT; 2) we aimed to measure the effectiveness of CytoSorb in reducing the serum levels of inflammatory molecules (procalcitonin, IL-6,8,10 and TNF-α); 3) due to the lack of randomised controlled trials, we planned to perform a systematic review to pool that was published up to date; 4) we summarised the data of the CytoSorb Registry to have a glance at the greater picture in the field of clinical application haemadsorption cartridges.

III. Materials and methods

a) *Extracorporeal cytokine adsorption in septic shock: A proof of concept randomised, controlled pilot study*

Upon inclusion, all patients admitted with septic shock of medical origin were screened between January 2015 and December 2017 at the 36 bedded, level III multidisciplinary intensive care unit of University of Szeged.

A patient was included if after the first six hours of adequate fluid resuscitation and antibiotic therapy there was no improvement in clinical condition, mostly indicated by steady or increased vasopressor need. The treatment was commenced within the first 24 hours after ICU admission or the onset of septic shock.

Included patients were randomised into CytoSorb or Control groups. Patients of both groups received standard treatment according to the institutional adaptation of the Surviving Sepsis Guidelines. Routine monitoring as per institutional protocol (5-lead ECG, pulse oximetry, invasive arterial blood pressure measurement, hourly diuresis, temperature, end-tidal CO2, airway pressures, etc.) was combined with invasive haemodynamic monitoring (PiCCO, PULSION-Maquet, Germany) to guide adequate fluid resuscitation and vasopressor treatment: cardiac index (CI), pulse pressure variation (PPV), systemic vascular resistance index (SVRI) and extravascular lung water index (ELWI) were assessed. CytoSorb treatment was introduced as instructed by the company's guide via a haemodialysis catheter inserted into a central vein as per institutional protocol (femoral, subclavian, or internal jugular, as appropriate): the adsorber was connected into a renal replacement device (MultiFiltrate, Fresenius Medical Care, Bad Homburg von der Höhe, Germany), with heparin anticoagulation and a blood flow rate of 250–400 mL/min.

T_0 values were recorded at the time of inclusion in case of the control group and at the time of commencement of extracorporeal cytokine adsorption therapy in the CytoSorb group. Subsequent measurements were performed 12, 24 and 48 hours later (T_{12}, T_{24}, T_{48}): blood sampling for laboratory parameters (C-reactive protein (CRP), procalcitonin (PCT), big endothelin-1 (BigET-1)) and blood gas analysis, complete haemodynamic measurements as well as calculation of SOFA scores to monitor organ dysfunction.

As our study was a proof-of-concept pilot study, our aim was to investigate the potential clinical effects of cytokine adsorption on 20 patients.

b) The Potential Role of Extracorporeal Cytokine Removal in Haemodynamic Stabilisation in Hyperinflammatory Shock

This systematic review is based on a literature search (PubMed, https://pubmed.ncbi.nlm.nih.gov/, accessed on 10 March 2021) on the key word 'Cytosorb'. In terms of study design, no restrictions were applied. Our aim was to select papers that report norepinephrine doses required in patients with vasoplegic shock and receiving CytoSorb treatment. Only those studies were involved where norepinephrine doses were given in µg/kg/min and where data were shown before and after CytoSorb treatment. After retrieving

data, descriptive and pooled comparative analysis were conducted, the standardised mean difference between baseline and 24-hour data on the relative reduction in vasopressor support was determined.

c) *Hemoadsorption in the critically ill – final results of the International CytoSorb Registry*

The protocol of the registry was registered on 9 December 2014 on ClinicalTrials (NCT02312024). It has also been submitted to the Institutional Review Board of the Faculty of Medicine at Friedrich Schiller University, Jena. The study sites were involved after voluntary registration and local ethics approval. Patients who fulfilled the inclusion criteria (use of CytoSorb adsorber, age ≥18 years and signed informed consent) were involved and data collection was commenced. There were no exclusion criteria.

The patients were divided into four study groups: Sepsis, septic shock ('Sepsis'), Cardiac surgery with cardio-pulmonary bypass (CBP), treated with CytoSorb intraoperatively ('Preemptive'), Treated with CytoSorb in the postoperative period of cardiac surgery on the intensive care unit (ICU) ('Postoperative'), Any other indication of CytoSorb treatment ('Other').

Haemadsorption was applied according to the instructions of the company: the adsorbent is to be inserted into an extracorporeal circuit either on its own or combined with RRT, cardiopulmonary bypass, or extracorporeal membrane oxygenation. One cartridge was recommended to be used for 24 hours. Electronic case reports forms (eCRF) were used to record data at four timepoints.

OpenClinica study management software was used to save data on the servers of the Center for Clinical Studies (Jena University Hospital).

The primary endpoint, as recommended for registries, was the difference between predicted mortality by APACHE II score and actual mortality after intervention.

The secondary endpoints were: organ function as indicated by a change in SOFA score before and after treatment (T2-T1), concentration changes of biomarkers: IL-6, CRP, PCT, myoglobin, free haemoglobin (T2-T1), length of ICU and hospital stay (days), duration of mechanical ventilation (days), duration of RRT (days), duration of vasopressor therapy (days), subjective assessment of the change of the patients' condition by the attending physician using a scale from 'very much improved' to 'very much worse'. Besides the abovementioned

endpoints, the aim of the Registry was to record and highlight possible adverse events related to haemadsorption as well.

Descriptive statistics was applied to all displayed data. Mortality with APACHE II score was evaluated based on the work of Knaus et al.: the rate of predicted and true mortality was compared by a logistic regression model. The level of significance was α=0.05. We described SAPS II score likewise. A linear model using baseline level as a covariate and t-test were both used to evaluate changes in the SOFA scores.

IV. Results

a) Extracorporeal cytokine adsorption in septic shock: A proof of concept randomised, controlled pilot study

The inclusion of patients lasted from January 2015 to December 2017. Figure 1. shows our flowchart on screening of eligibility and inclusion.

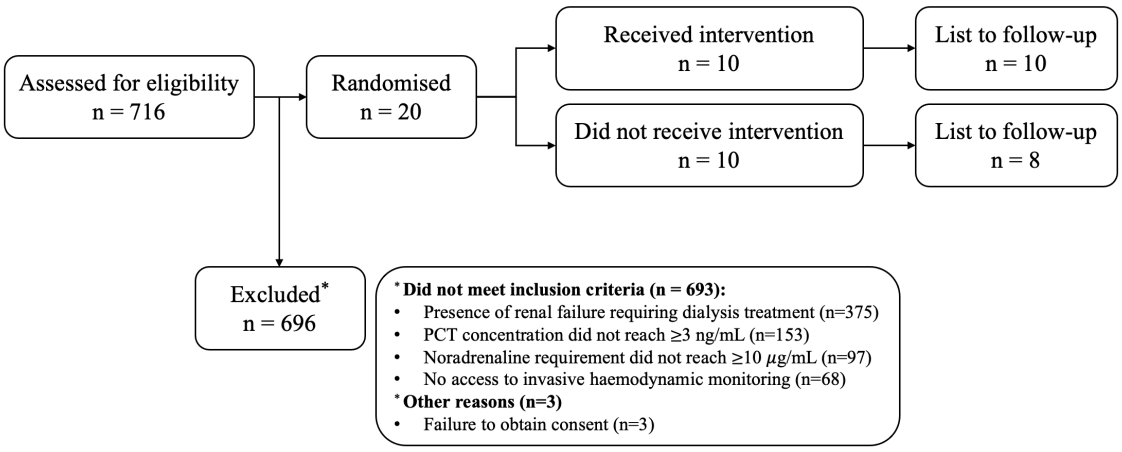

Figure 1. Flowchart of patient screening and involvement

Patients in both CytoSorb and Control groups were similar regarding age, body mass index, days spent on the ICU and APACHE II scores. All 20 patients survived the first 24 hours from the inclusion, however, two patients passed away before the end of the 48-hour period in the Control group. There was no difference in the SOFA scores of the CytoSorb group (T_0 = 13.6 ± 3.2; T_{12} = 13.1 ± 3.6; T_{24}= 13 ± 5.4; T_{48}= 11.6 ± 6.3) and the Control group (T_0 = 12.8 ± 3.9; T_{12} = 12.9 ± 5.0; T_{24} = 12.6 ± 5.9; T_{48} = 11.0 ± 6.3).

We found no significant differences neither within, nor between the study groups regarding mean arterial pressure (MAP), heart rate (HR), cardiac index (CI) and pulse pressure

variability (PPV), extravascular lung water index (ELWI) and systemic vascular resistance (SVRI).

There was a significant, compared to baseline, almost 70% decrease in norepinephrine need in the CytoSorb group while in the Control group it remained steady. The fluid balance was similar in the two groups. Regarding blood gas parameters, initially higher lactate levels were dropped in both groups, while statistically non-significant tendency of central venous to arterial CO_2-gap (pCO_2-gap) was decreasing in the CytoSorb and increasing in the Control group. $ScvO_2$ remained steady in both groups. Oxygenation indicated by PaO_2/FiO_2 showed no significant changes either.

Concerning biomarkers, CRP concentration showed no statistically different values, while PCT decreased significantly in both groups, however, showed different kinetics: in the Control group, a significant drop in PCT was detected at T_{48} ($p = 0.04$ vs. T_0), while in the CytoSorb group this decrease was more pronounced and significant earlier, already at T_{24} and stayed on this track by T_{48}. A less commonly used biomarker, big endothelin-1 (BigET-1) was significantly decreased in the CytoSorb group by T_{12} and further decreased until T_{24} compared to T_0 while remained almost unchanged in the Control group.

No adverse effects were recorded in connection with haemadsorption therapy.

b) The Potential Role of Extracorporeal Cytokine Removal in Haemodynamic Stabilisation in Hyperinflammatory Shock

In our review study we performed a PubMed search to pool data from publications that cover the topic of change of vasopressor need on CytoSorb-treated vasoplegic shock patients. 163 scientific papers mentioned CytoSorb and out of them, 58 included ‘catecholamines and/or vasopressors. 25 of 58 were excluded due to various reasons. Finally, 33 articles with 353 patients were included with various study designs and treatment duration.

Norepinephrine doses (highest and lowest) 24, 48, 72 and 96 hours after commencing haemadsorption treatment were recorded. Our descriptive report involved 21 case reports, 11 case series and one randomised study. The number of adsorbents and the duration of treatment were not taken into account. 14 studies reported that norepinephrine need was completely diminished after CytoSorb treatment. One case report and two case series showed a vasopressor need higher than 0.5 μg/kg/min at the end of the adsorption therapy. The norepinephrine dose showed a marked decrease by the end of CytoSorb treatment which conforms with the evidence available. A subgroup of the publications was analysed separately as they involved control patients beside those who received haemadsorption therapy. Four papers were further analysed

after pooling as these publications involved both treated and control patients. Out of the four studies, three included septic shock patients and one aortic surgery patients. In the case of septic shock, haemadsorption was associated with haemodynamic stabilisation, shown as early reduction of norepinephrine need. In a pilot trial with 20 involved patients, although the dose of vasopressor decreased in both treated and control groups, by 48 hours after the start of haemadsorption, the treated patients were significantly more haemodynamically stable. CytoSorb versus control group also showed a significantly more marked change in norepinephrine requirements between baseline and 48 h (0.67 µg/kg/min vs. 0.10 µg/kg/min; p = 0.047). CytoSorb treatment led to lower vasopressor dose administration after 24 hours of surgery in patients who had aortic surgery and were on cardio-pulmonary bypass. Akil et al. prospectively investigated 13 ARDS patients on ECMO and haemadsorption and compared them with 7 pulmonary sepsis patients on ECMO alone. In their study, all of the treated patients reached haemodynamic stability after 72 hours, in contrast, the control group still required vasopressor. Rugg et al. retrospectively 42 patients who received CRRT and haemadsorption with 42 patients who only had CRRT. Initially, CytoSorb+CRRT patients required higher doses of vasopressor compared to CRRT-only patients. After 24 hours of haemadsorption, the former group needed less norepinephrine while the need of the control group remained steady. After 96 hours both groups showed similar norepinephrine requirements, however, in the case of the control patients, the reduction was moderate.

During our analysis, the results of the four publications above were pooled for effect size estimation. We focused on the reduction of norepinephrine need by CytoSorb haemadsorption.

c) *Hemoadsorption in the critically ill – final results of the International CytoSorb Registry*

1434 patients were registered in the Registry from 18 May 2015 to 29 January 2021 from 46 centres, of which 19 were university hospitals, 18 were academic teaching hospitals, and 9 were general or acute care hospitals. The flowchart lists the number of patients treated for various conditions (Figure 2).

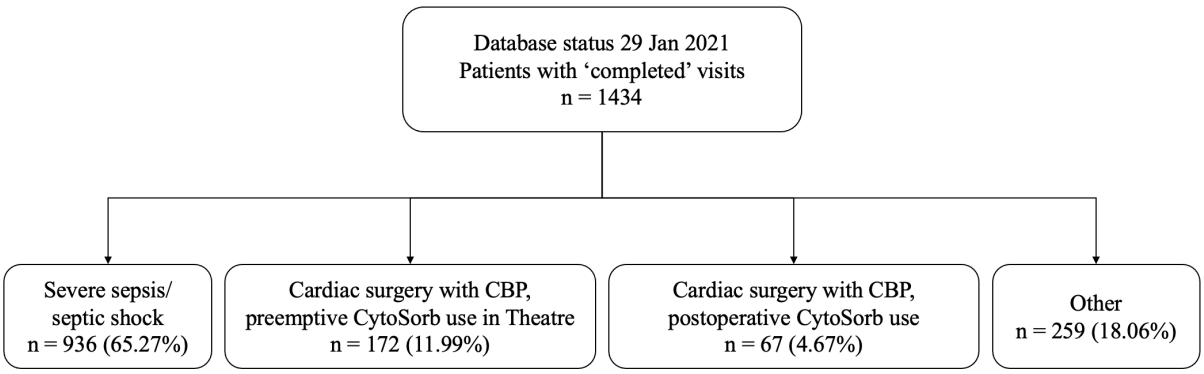

Figure 2. The number of patients by indication.
CBP: cardio-pulmonary bypass.

Whole cohort

43.7% of patients (43.7%) only received one therapy, whereas 88.4% of patients had up to five treatments. In 96% of cases, CytoSorb was used in conjunction with RRT. Actual hospital mortality was 50.1%, while ICU mortality was 47.8%. The main result was the discrepancy between observed and anticipated mortality.

Overall, there was little to no difference between actual and anticipated mortality. In the APACHE II range of 15-20, observed mortality was substantially higher than predicted; whereas, when APACHE II was 30 or above, observed mortality was significantly lower. Between T1 and T2, the overall SOFA ratings did not significantly change. The respiratory and cardiovascular subscores, however, displayed significant variations by T2.

In terms of inflammatory markers, interleukin (IL)-6 was tested in 34.1% of patients, procalcitonin (PCT) in 70.4%, and C-reactive protein (CRP) in 91.6% of patients. From T1 to T2, CRP and PCT dramatically decreased across the entire sample. In terms of the doctors' subjective evaluation of the effectiveness of haemadsorption therapy, altogether 53.8% of patients showed improvement, in 30.2% there was no change, and in 4.0% there was deterioration.

Sepsis group

With 936 (65.3%) patients, this is the Registry's largest cohort. The characteristics of the treatment are quite similar to those of the entire research population. Within 35.5 [min: 0; max: 720] hours after the beginning of sepsis, treatment was initiated. 80.6% of the patients were still alive after haemadsorption. The actual hospital mortality did not differ significantly from the expected mortality, nevertheless. APACHE II's projected mortality and actual mortality exhibited a similar connection and pattern to those of the group. 83% of patients

were treated with norepinephrine, 43.2% with dobutamine, 37.1% got epinephrine, 40.7% vasopressin, 7.5% dopamine. Out of this group, 48.9% of the patients have already been given given hydrocortisone by the time haemadsorption was started.

Like the entire group, both the pulmonary and cardiovascular subscores showed significant improvements. The values of every inflammatory marker examined were higher than for the entire study population. Changes in CRP (67.5%), PCT (45.5%), and IL-6 (20.0%) could be identified. By the time CytoSorb therapy was finished, CRP and PCT levels had dramatically dropped.

Cardiac surgery

In the cardiac surgery registry, there are two distinct datasets according to indication: those who received treatment intraoperatively (the 'Preemptive' group, n=172), and those who received haemadsorption following CPB in the ICU postoperatively (the 'Postoperative' group, n=67). The median EUROscore II [IQR] for preemptive patients was 5.1 [2.6-14.2] and for postoperative patients, it was 9.7 [5.0-21.5].

The majority of patients in the preemptive group underwent coronary artery surgery (n=40, 23.3%) and/or heart valve surgery (n=137, 79.7%). This distribution was 61.2% and 41.8%, respectively, in the postoperative group. Contrary to the other groups, intraoperative treatment was unique in that it was limited in duration to a few hours.

At the termination of the therapy, survival rates were 98.8% ('Preemptive' group) and 94.0% ('Postoperative' group). ICU/hospital mortality in the Pre-emptive group was 9.9% and 10.5%, but in the Postoperative group it was 25.8%.

Patients in this group, like those in the other groups, were already receiving vasopressor support when haemadsorption began. Norepinephrine and epinephrine were the vasopressors that were used the most frequently (preemptive group: 73.3%, postoperative group: 78.2%), while hydrocortisone was given to 53.0% and 57.8% of patients, respectively.

In terms of inflammatory markers, CRP considerably increased in both groups – exactly the opposite of what was observed in the sepsis cohort. IL-6, which was identified in 46.3% of patients in the postoperative group, dramatically decreased from T1 to T2 in these patients.

Within the whole trial population, the Preemptive group showed the least improvement (35.6%), while the Postoperative group showed the most improvement (77.3%), according to the physicians' subjective assessments.

Other indications

Patients in the final cohort received CytoSorb therapy for a diverse range of pathologies. Their actual mortality, which was close to 50%, was consistent with APACHE-II predictions. The cardiovascular subscore saw a considerable improvement in SOFA values as well. A substantial decrease in PCT and IL-6 levels was found in 38.2 and 26.6% of patients, respectively. 26 patients in this group had their myoglobin levels tested, and the results revealed a substantial decrease between T2-T1: -11.578 [-20.594 to -2.562] μg/L. The highest serum bilirubin levels were seen in this group, and although there was a general decline (found in 201 instances), statistical significance was not attained. -1.81 [-2.72;-0.9] mg/L.

With 69.9% indicating improvement, physicians' satisfaction was similar to that of the group as a whole.

Safety issues

The platelet count of the registry patients (minimum value over 24 hours) significantly decreased in the whole study group as well as in all subgroups following therapy, which was the only significant change in routinely recorded laboratory parameters during treatment. There were no known treatment-related problems in 1403 individuals (97.8%). 31 patients had issues while receiving therapy.

Limitations

Our pilot study suffers from a number of shortcomings: the sample size is much too little to arrive at any definitive conclusions on the influence of the treatment on the organ function or the result. In addition, it is possible that our findings cannot be generalised to other institutions since those other institutions may have different patient demographics or therapeutic procedures as well as our results do not include any data on long term adverse events (also known as safety) and outcome. It took us more than two years to include 20 of the 716 people who were screened for the study. In addition, despite all of the efforts that were made, heterogeneity was still present, as seen by the extremely wide range of biomarker concentrations, and patients in the CytoSorb group appeared to be in a worse state of health.

The limitation of the review article is the fact that we had to pool data from studies with several different study design.

The Registry is the largest one ever published regarding haemadsorption therapy. 80.4% of the participating centres are affiliated with academic institutions. A total of 1434 patients were enrolled throughout the 46 trial sites; of these, 1432 gave data for T1, 1427 provided data

on the treatment phase, 1421 provided data for T2, and 1421 provided follow-up data. Even though a sizable quantity of data was undoubtedly missing at T2, particularly in the case of inflammatory markers (CRP, PCT, IL-6), we still had hundreds of samples to analyse.

These patients were extremely ill and most likely received haemadsorption as an adjunctive rescue therapy in a refractory disease state.

V. Discussion

During the early stages of treatment-resistant septic shock, our proof-of-concept pilot trial described that supplementary therapy with standalone extracorporeal cytokine removal for 24 hours was both safe and had some noticeable improvements in comparison to the control group. Although there were no significant changes in SOFA scores between the groups at T24, longer-term improvements in overall organ function may need a higher number of treatments since this outcome measure may be too robust over such a short time. Future research will be crucial in determining the length and frequency of an extracorporeal cytokine adsorption therapy. The considerable decrease in the need for vasopressor support, which was not present in the Control group, was one of the most notable outcomes of extracorporeal cytokine elimination therapy seen in the current investigation.

In the field of biomarkers and cytokines, it is possible to assess a wide variety of them, however, only one or two are regularly utilised in clinical practice. The most notable impact of cytokine adsorption therapy in comparison to Controls was on PCT concentrations, which was in addition to a decrease in the need for vasopressors. Due to procalcitonin's molecular weight, CytoSorb may directly adsorb PCT. In line with the hypothesis, a significant drop in PCT concentrations was seen in the treatment group over the first 24 hours but not in the control group. When standard treatment is effective, PCT declined markedly in both groups by T_{48}, a pattern that has been shown in other investigations. This explains why the PCT decline in the current study's CytoSorb group was more pronounced. These findings further imply that the PCT kinetics that we have previously established to forecast the suitability of an antibiotic treatment during extracorporeal cytokine adsorption, cannot be used, however, the pathophysiological function of PCT in sepsis is still not completely understood. PCT may be a crucial biomarker for cytokine storm, but it also has the potential to be a hazardous mediator in sepsis.

In our investigation, extracorporeal cytokine adsorption treatment had no effect on CRP levels. The fact that CRP is typically present as a pentamer, although having a molecular weight

of about 25 kDa as a monomer, may be one of the causes. As such, it cannot be adsorbed by CytoSorb as effectively as PCT. Additionally, because CRP has a relatively long half-life and has an about 48h delay when following the inflammatory process, its application in determining the effectiveness of a treatment or tracking the progression of a disease within a narrow window of time (12–24 h) may be constrained.

Serum BigET-1 level, natural precursor of endothelin-1 was previously shown to rise in patients with severe sepsis compared to healthy volunteers. Its higher concentrations were associated with elevated serum levels of IL-6 and IL-8 as well as renal failure. In our study, the serum BigET-1 level dropped in the CytoSorb group between T_0 and T_{12}, T_{24}. According to these and our findings, there may be a connection between the lower BigET-1 concentrations and the higher SVRI and lower norepinephrine need, however, further studies are required.

These results highlight the necessity of shock reversal with concurrent 'de-catecholaminisation', which should be carried out as soon as possible. Our review has analysed pooled data from studies that described change in vasopressor need during haemadsorption treatment and have concluded a significant reduction in applied dose of vasopressor in critically ill patients following the therapy.

The data of the International Registry showed that actual mortality was higher in the lower ranges of APACHE II scores (15 to 20), while sicker patients with higher APACHE II scores (30) had better survival, however, the registry's findings did not support a statistically significant reduction in mortality across the entire cohort. It is more challenging to explain the result that patients at lower risk appear to have worse outcomes than anticipated. Patients who received high severity scores upon entry are almost universally unwell. The assessment is typically not repeated within the following 24 hours, however individuals who are hospitalised with lower ratings could develop worse in a matter of hours.

Haemodynamic stabilisation was shown in all subgroups, except for those who had preemptive haemadsorption treatment before heart surgery. These data highlight that there is a rationale in using haemodynamic stability and/or 'shock reversal' of using as major outcomes in subsequent haemadsorption studies.

Our data adds to the body of research showing that levels of inflammatory markers PCT and IL-6 considerably decreased during haemadsorption therapy, as shown similarly by previous randomised controlled trials. Consequently, it may be relevant to evaluate the removal of these two biomarkers via haemadsorption in subsequent research.

The sepsis/septic shock group was the largest cohort, indicating that doctors still consider sepsis as the most crucial indication. Patients with refractory septic shock, particularly

those in whom there is also an indication for RRT, are most likely to benefit, according to the Registry's most recent findings.

The fact that CPB triggers an inflammatory response that may lead to postoperative organ failure has been extensively recognised. Thus, it is hardly unexpected that nearly three times as many patients received CytoSorb before surgery than after. However, the pre-emptive group showed the least improvement, which was also backed by clinical data. This is consistent with the findings of three recent small randomised clinical trials in which haemadsorption was used without obvious outcome advantage. Contrarily, both clinical improvement and reduction of the inflammatory response are reduced when haemadsorption was used in patients with infective endocarditis, aortic surgery, and heart transplantation.

The Registry is unable to answer all safety-related questions, such as changes in platelet count, removal of particular medicines, etc., which must be addressed in future randomised trials.

Medical registries are essential for integrating research findings into clinical practice, as they provide crucial information for quality assurance and therapy optimization.

VI. Conclusions

To the best of our knowledge, our pilot study is the first controlled trial in which a 24-hour extracorporeal cytokine adsorption therapy was evaluated without being in conjunction with other extracorporeal renal replacement therapies. As seen by reductions in norepinephrine needs, serum PCT, and BigET-1 in comparison to the Controls, the treatment was safe, and even a single treatment exhibited some positive effects. Clinical investigations aiming to determine the effects of cytokine elimination in patients with septic shock could use these findings to identify the relevant study endpoints and sample size calculations. The review paper has shown that haemadsorption treatment may play a role in vasoplegic shock reversal. The Registry article highlights the results of comprehensive data collecting on the biggest series of patients treated with extracorporeal cytokine adsorption using CytoSorb to date. There was no significant difference in the primary endpoint of death, but cardiovascular and pulmonary SOFA scores improved, and PCT, CRP, and IL-6 levels decreased. Randomised trials are required to determine whether these effects transfer into a positive overall outcome.

One of the most dynamic specialties in medicine is intensive care medicine, which is always growing in terms of both the understanding of illness condition and the breakthroughs in therapeutic advancements. The role of a "dysregulated immune response" is emphasised in

the new definition of sepsis, and other new terminology that are increasingly employed in this clinical scenario include hyperinflammation, cytokine storm, vasoplegic shock, refractory shock, and shock reversal. These notions more precisely represent the better knowledge of the underlying pathophysiologic mechanisms, and as such, they might also assist set priorities and clinical objectives in the design of future clinical studies.

VII. Acknowledgements

I would like to express my special appreciation and thanks to my supervisor Prof. Dr. Zsolt Molnár. Your advice on both research as well as on my career have been invaluable. I would also like to thank my dear colleagues and friends, dr. Nándor Öveges, dr. Ildikó László and Dr. Domonkos Trásy for their company, guidance, and legacy. I would especially like to thank physicians, nurses, and nurse aids in the intensive care unit of SZAKK AITI as well as Tünde Bodnár, who helped me through all the paperwork and Dr. József Kaszaki, who was always kind to answer any questions. A special thanks to my family and close friends. Thank you for supporting me, especially my fiancé, Mátyás Budavári, who encouraged me throughout this path.