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

PhD Thesis

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The thesis is based on the following scientific publications:

a) Peer reviewed publications

I. 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.

II. Fatime Hawchar, Zsolt Molnár: Interpreting biomarkers in infectious diseases in intensive care unit: the potential role of procalcitonin, December 2018, *Journal of Emergency and Critical Care Medicine* 2:107, IF: 0. SCImago Journal Rank: 0.

III. 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.

IV. 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.

b) Book chapters, non-peer-reviewed publications, lectures

I. Fatime Hawchar, Zsolt Molnár: Blood purification in sepsis: clinical evidence, *Blood purification in critically ill patients*, Pappalardo and Montisci, 2021.
II. Hawchar Fatime, Molnár Zsolt: Molekulaadszorpciós kezelések kritikus állapotú betegekben, *Aneszteziológia és Intenzív Terápia 4. bővített kiadás*, Bogár Lajos, 2021.
III. Fatime Hawchar, Nándor Öveges, Zsolt Molnár: Extracorporeal Cytokine Removal in Septic Shock Chapter, *Annual Update in Intensive Care and Emergency Medicine* 2019.
IV. Fatime Hawchar: An international registry on the use of extracorporeal adsorption – E-SMART conference 2020.
V. Hawchar Fatime, Molnár Zsolt: A citokin vihar és kezelése kritikus állapotú betegeknél, *Magyar Mentésügy*, 2020.
VI. Hawchar Fatime, Molnár Zsolt: CytoSorb®-bal végzett vértisztító eljárás, *Interdiszciplináris Magyar Egészségügy*, 2019. május.

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Abbreviations

ANOVA Analysis of variance

APACHE II Acute physiology and chronic health evaluation II

BigET-1 Big endothelin-1

CBP Cardio-pulmonary bypass

CI Cardiac index

CRP C-reactive protein

DAMP Damage associated molecular patterns

eCRF Electronic case reports forms

ELWI Extravascular lung water index

ICU Intensive care unit

IL Interleukin

LOS Length of stay

MAP Mean arterial pressure

MV Mechanical ventilation

PAMP Pathogen associated molecular patterns

PCT Procalcitonin

PPV Pulse pressure variation

qSOFA quick SOFA

RRT Renal replacement therapy

SAPS II Simplified acute physiology score II

SIRS Systemic inflammatory response syndrome

SOFA Sequential organ failure assessment

SVRI Systemic vascular resistance index

TNF Tumour necrosis factor

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. Patients with sepsis often require admission to intensive care units (ICUs) for close monitoring and aggressive treatment. Despite advances in critical care, sepsis remains a significant cause of morbidity and mortality in ICUs worldwide and it is substantially higher when patients develop septic shock. According to a recent meta-analysis, the mortality of septic shock in Europe and in North America is high, around 38% [1]. The management of sepsis in ICU requires a multidisciplinary approach, including prompt identification and treatment of the underlying infection, administration of appropriate antimicrobial therapy, haemodynamic support, and respiratory management. Despite it is one of the most challenging fields of intensive care, sepsis is not a definitive disease, and its definition has changed several times over the last 40 years.

a) Current definition of sepsis and septic shock and the evolution of its definition

The current definition of sepsis has been created in 2016 by the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) [2]. 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. The focus of the latest definition is on the 'non-homeostatic' host response triggered by an infection that is potentially leading to death if not recognised in time.

Defining and diagnosing sepsis has never been easy. The term 'sepsis syndrome' was first introduced in Las Vegas in 1980 as Roger Bone and his colleagues were designing the first prospective randomised trial in sepsis [3]. The trial itself has not concluded any significant findings, however, based on their experience, a statement paper was later published by the same authors titled 'Sepsis syndrome: a valid clinical entity' [4].

After the first observation of a maladaptive systemic manifestation of an infection in the 1980's, the first consensus conference in 1991 brought the initial sepsis definitions to life focused on the host's systemic inflammatory response syndrome (SIRS) to infection (Figure 1) [2].

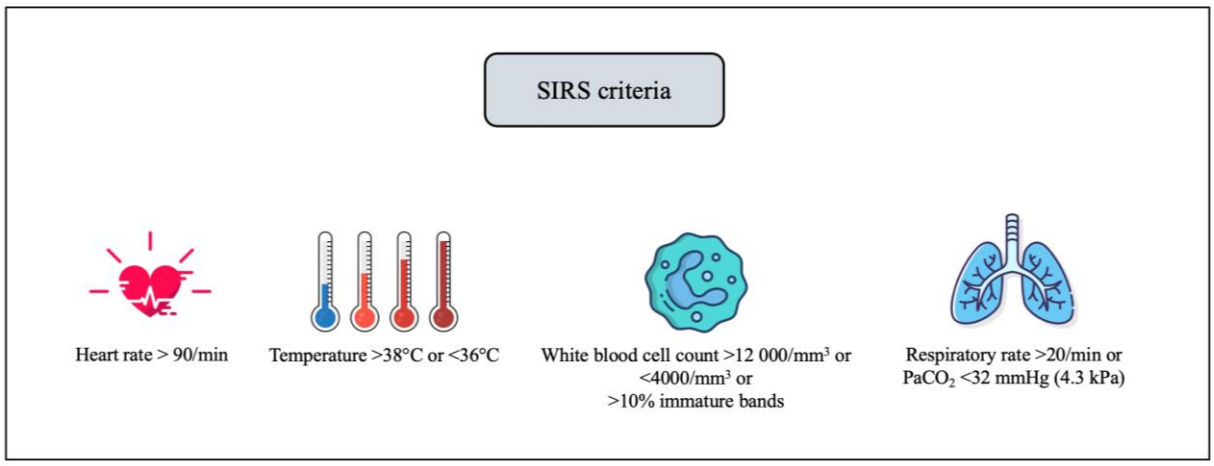

Figure 1. SIRS criteria

The terms ’severe sepsis’ and ’septic shock’ are referred to sepsis with complications. [5] Severe sepsis meant sepsis accompanied by organ dysfunction which may progress to septic shock due to lactatemia and ‘sepsis-induced hypotension persisting despite adequate fluid resuscitation’ [2].

The limitations of these definitions were recognised and in 2001, the list of the diagnostic criteria was revised by the task force, however, the definitions were left untouched due to the lack of evidence until 2016.

The latest definition of sepsis relocated the focus from the SIRS to codification of organ dysfunction [2,5]. Thus, sepsis is no longer considered to be an inflammatory disorder despite being a dysregulated host response due to the imbalance between pro- and anti-inflammatory forces. The term ‘severe sepsis’ was found to be redundant and was removed, simplifying the previous classification to ‘infection’, ‘sepsis’ and ‘septic shock’. Sequential Organ Failure Assessment (SOFA) score is recommended to define organ dysfunction (Table 1).

System	SOFA score [2]				
	0	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2, mmHg)	≥ 400	< 400	< 300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation (Platelets, $x10^3/\mu L$)	≥ 150	< 150	< 100	< 50	<20
Liver (bilirubin, g/dL)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12.0
Cardiovascular (MAP, mmHg and catecholamines as μg/kg/min for at least 1 hour)	≥ 70	< 70	Dopamine <5/ dobutamine (any dose)	Dopamine 5.1-15/ epinephrine ≤0.1/ norepinephrine ≤0.1	Dopamine >15/ epinephrine >0.1/ norepinephrine>0.1
Central nervous system (GCS)	15	13 – 14	10 – 12	6 – 9	< 6
Renal (creatinine, mg/dL and Urine output, mL/day)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 UO: <500	> 5.0 UO: <200

Table 1. SOFA score calculation.

Another scoring, the 'quick SOFA' (qSOFA) was also introduced which may identify hospitalised patients at a high risk of death, found to be more specific than SIRS criteria. The variables are three clinical criteria and meeting at least two of them highlights that the patient may be considered 'high risk'.

The criteria are alteration in mental status, systolic blood pressure of less than 100 mmHg, or a respiratory rate of more than 22 breaths per minute, however, not meeting the criteria does not overwrite the clinician's suspicion for sepsis. [6,7]

qSOFA score
Respiratory rate ≥ 22/min
Altered mentation
Systolic blood pressure ≤ 100 mmHg

Table 2. qSOFA criteria.

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 ≥ 65 mmHg and serum lactate concentration is ≥ 2 mmol/L [2,8].

b) Epidemiology

According to the third sepsis consensus published in 2016, sepsis is a complex infection-induced syndrome with physiologic, pathologic, and biochemical abnormalities. In 2011, it accounted for more than 5% of total hospital costs in the USA. Since then, the number of cases is increasing possibly due to better recognition of sepsis, the aging of the population and increasing incidence of several comorbidities, making sepsis a serious economic and healthcare issue and the leading cause of mortality and critical illness all around the world (Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations). [9–11] The Surviving Sepsis Campaign guideline states that early recognition of infection, adequate antimicrobial therapy and fluid resuscitation may contribute to survival benefit and better outcomes [7]. Despite undoubtably effective steps towards early recognition, adequate resuscitation, organ support, appropriate antibiotic therapy and source control, mortality rates still could not drop below 20-50% [12,13]. Timing is crucial as even a commencing organ dysfunction is associated with an increased mortality. The level of organ dysfunction is codified by SOFA score as recommended by Sepsis-3 [8].

Even though SIRS criteria solely are considered as outdated in diagnosing sepsis, they may add crucial information to evaluate the general clinical picture as well as the symptoms that may focus our attention on the most likely anatomical sources and most likely pathogens.

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.

c) Pathophysiology

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 [2]. Earlier, sepsis was thought to show at least two out of the four SIRS criteria as the definition was only focused on the process of inflammation. This concept has been debated and sepsis is now rather identified as an early activation of pro- and anti-inflammatory responses as well as major alterations in several so-called ‘nonimmunologic’ pathways (e.g. cardiovascular, hormonal etc.) [2]. The multifaceted syndrome is complicated by the heterogeneity of the affected patients as they are showing a broad spectrum of age, comorbidities, injuries or surgical interventions, and source of infection [14]. This leads to the situation that no models are capable of appropriate simulation of sepsis, making it even more difficult to map the underlying pathways and develop a ‘Swiss

army knife' of sepsis treatment [15]. 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. New-generation data-processing techniques such as transcriptomics, metabolomics and proteomics may lead to specify population subsets and different schemes of effective treatment and to better differentiate between septic patients and patients showing the characteristics of sepsis without an infectious background [16,17].

What does 'dysregulated host response' actually mean? Janos Selye discovered a syndrome which he later named 'stress' in 1936. He exposed animals to several different acute non-specific harmful injuries such as surgery, cold, or heat, and he observed the same pattern of physiological changes independent of the type of damage [18]. Our knowledge on this non-specific response connects this phenomenon to the convergent mechanisms of the immune system, which leads to the same syndrome after an either infectious or non-infectious harm reflecting an individual response to numerous different kinds of injuries.

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.

These molecules are the so-called 'pathogen associated molecular patterns' or PAMPs which activate a proinflammatory response to the pathogens. To keep the process under control and thus the integrity of the body, adaptive immunity-guided anti-inflammation is activated at the same time to balance proinflammation (Figure 2).

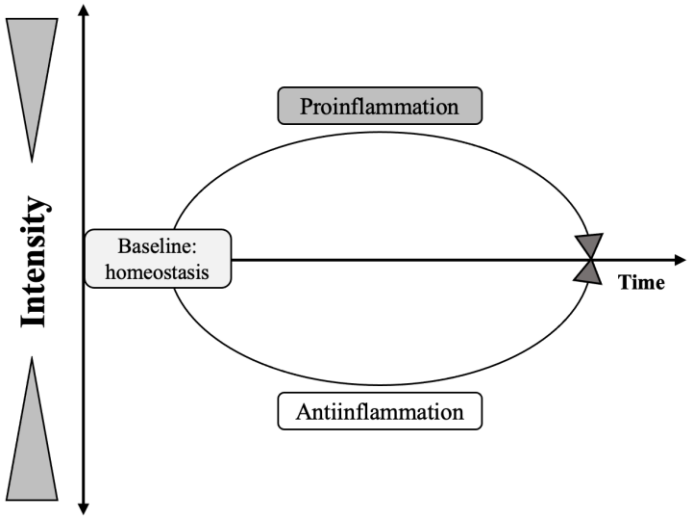

Figure 2. Balance of pro- and antiinflammation.

The discovery of ‘damage-associated molecular patterns’ or DAMPs opened an exciting new point of view as it was found that mechanical tissue damage (trauma, ischaemia-reperfusion, burns, major surgery etc.) may also lead to the same syndrome as infectious agents due to the common genetic background of bacteria and mitochondria [19]. The antagonistic forces of pro- and antiinflammation in a healthy individual can keep the balance and control the process of elimination of harmful agents without this costing the integrity of the host organism as normally these abovementioned functions are in a steady-state baseline level. In the case of any kinds of illness, pro- and anti-inflammatory effects are activated to keep the inflammatory response in control and after the elimination of the dangerous agents, recovery is possible in a few days, and the activity of both systems return to the baseline levels [20]. The reason why the concept of SIRS as the underlying mechanism of sepsis has failed is that SIRS is a normal physiological process in response to DAMPs or PAMPs while in the case of sepsis, the proinflammatory effects outgrow the antiinflammatory system, leading to an uncontrolled inflammatory response, resulting in a fulminant septic shock [21]. This condition presents as increased vascular permeability and subsequent organ dysfunction. Cytokine storm is a term referred to the state when pro-inflammatory cytokines and mediators are released in an overwhelming, acute manner. As a result, over time the pro-inflammatory activity is getting depleted, leading to overwhelming anti-inflammatory effects and over time to persistent immunoparalysis, thus the patients become susceptible to further infections.

One of the novel approaches to improve outcomes is based on the modulation of the immune system and the host’s response. The emergence of antiinflammatory therapies, such as anti-cytokines, anti-oxidants, however, was not able to bring a breakthrough [22,23]. Still, the early modulation of the ‘cytokine storm’ could help regaining control and contribute to improved outcomes [24].

d) Cytokine adsorption as a mean of adjuvant therapy in septic shock

Considering the abovementioned role of disbalance of inflammation and the role of the cytokine storm in sepsis, it seems to make sense that removal of these molecules from the bloodstream may reduce the devastating effects of the dysregulated host response, regaining control and balance in the inflammatory process, leading to enhanced recovery. Blood purification reduces the concentrations of inflammatory mediators in the circulation by non-specific mass removal to attenuate cytokine storm [25]. Haemofiltration, and high-volume haemofiltration were introduced to reach this goal, however, no multicentre studies could demonstrate the survival

benefit [24,26–28]. Furthermore, Polymyxin B was a promising method of extracorporeal haemadsorption, however, trials could not prove its efficacy [29,30].

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 [31–33]. The volume of the cartridge is 300 mL and has a filling blood volume of 120 mL. It contains biocompatible, porous polymer polystyrene beads. These beads 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. One device has a surface area of about 40.000 m^2 which is enormous compared to conventional haemodialysis membranes that usually bear a surface area of 2-2.5 m^2 [34]. CytoSorb can be applied as a stand-alone haemoperfusion treatment or possibly be combined with renal replacement therapy, heart-lung machines, or extracorporeal membrane oxygenation. As it was already mentioned, during the dysregulated immune response the pro-inflammatory response is more pronounced, however, antiinflammatory molecules are also released. The haemadsorption cartridge is able to adsorb cytokines irreversibly from the blood by mass removal, thus, more are adsorbed from the more prevalent molecules. 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 early use of treatment in septic shock seems to be crucial to reach potential clinical benefit as it is reported to be most effective within the first 24 hours of septic shock [35]. In addition to pro- and antiinflammatory molecule adsorption, the adsorption spectrum involves other inflammatory biomarkers such as procalcitonin. The main clinical benefit may be shown in reversal of vasoplegia and subsequent reduced vasopressor requirements that was found in case studies [35]. Kellum et al. performed a feasibility study of haemadsorption on brain-dead patients. There findings showed that the removal of tumour necrosis factor (TNF), interleukin (IL)-6, and -10 was feasible and safe [36]. However, no randomised controlled trials were done on septic shock patients to date. 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. There are currently 14 studies on CytoSorb on ClinicalTrials that recruit patients, and 15 studies are marked as 'finished'.

e) 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 renal replacement therapy; 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.

II. Materials and methods

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

The study protocol was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged, Hungary (Approval number: SZTESZAKKREG.KUTETIKA 199/ 2016-SZTE). The study was registered on ClinicalTrials.gov, under the registration number of NCT02288975 (registered 13th November 2014) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all subjects or from their relatives.

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.
The inclusion criteria were the following:

- intubated, mechanically ventilated patients with suspected septic shock of medical origin,
- invasive haemodynamic monitoring,
- invasive haemodynamic monitoring-guided demand for norepinephrine > 10 μg/min,
- plasma lactate concentration > 2.0 mmol/L,
- procalcitonin concentration ≥ 3 ng/mL.

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.

Exclusion criteria were the following:

- age < 18 years,
- acute or chronic renal insufficiency requiring renal replacement therapy,
- pregnancy (β-hCG test positivity),
- operation in connection with the septic condition of the patient,
- end-stage cardiomyopathy,
- acute coronary syndrome,
- cardiogenic shock,
- haemato-oncological diseases,
- admission after cardiac arrest,
- immune-compromised patients due to HIV positivity and active AIDS or organ transplantation or on chronic steroid treatment (>10 mg/day prednisolone),
- thrombocytopaenia (<20 G/L),
- other coagulopathies contraindicating extracorporeal therapies.

Included patients were randomised into CytoSorb or Control groups. Randomised closed envelopes were numbered and were opened one by one when including a patient, dividing them into two groups. Patients of both groups received standard treatment according to the institutional adaptation of the Surviving Sepsis Guidelines [31]. 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 [37].

Our dataset was primarily recorded in Microsoft Excel 2016 on computers secured with proper password only accessible by authorised personnel. 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. Power analysis was not possible as there were no similar studies at the literature at the time the protocol was written to estimate differences. Indeed, this study was meant to help design further studies to have relevant data to calculate power. IBM SPSS 23.0 (Armonk, NY, USA) and Systat Software Inc. SigmaPlot 12.5 (London, UK) were used to analyse data: we tested normality with Shapiro-Wilk test. In case of demographic data, Student t-test or Mann-Whitney U test was applied as appropriate. Analysis of variance (ANOVA) with Bonferroni post hoc test was used to compare the groups. The level of significance was defined as $p < 0.05$.

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 septic 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. The analysis of data was conducted using Microsoft Excel version 16 (Microsoft Corporation. 2019. Redmond, WA, USA) and STATA statistical software, release 16 (StataCorp LLC. 2019. College Station, TX, USA).

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 review board has approved the study protocol and was in charge. 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:

1. Sepsis, septic shock ('Sepsis') [38],
2. Cardiac surgery with cardio-pulmonary bypass (CBP), treated with CytoSorb intraoperatively ('Preemptive'),
3. Treated with CytoSorb in the postoperative period of cardiac surgery on the intensive care unit (ICU) ('Postoperative'),
4. 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 renal replacement therapy, cardiopulmonary bypass, or extracorporeal membrane oxygenation. One cartridge is recommended to be used for 24 hours. Electronic case reports forms (eCRF) were used by dedicated staff trained by CytoSorb Registry project manager to record data at four timepoints as following:

- T0: baseline (within 24 hours before commencing haemadsorption therapy) demographics, indications, severity scores,
- T1: physiological and laboratory data right before the start of haemadsorption therapy,
- T2: physiological and laboratory data up to 24 hours after the last cartridge,
- T3: follow-up on discharge from the hospital.

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, for patient outcome evaluation the difference between predicted mortality by APACHE II score and actual mortality after intervention was our primary endpoint [39].

Our study group has defined the secondary endpoints listed below:

- 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 renal replacement therapy (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' (for details please see the results).

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

Appropriate descriptive statistics was applied to all displayed data: at least number of non-missing values, number of missing values, mean, standard deviation, minimum, quartiles, median, interquartile ranges and maximum for metric data and frequencies for categorial data. Mortality with APACHE II score was evaluated based on the work of Knaus et al.: the rate of predicted and true mortality were compared by a logistic regression model [40]. 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.

III. 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 3. shows our flowchart on screening of eligibility and inclusion.

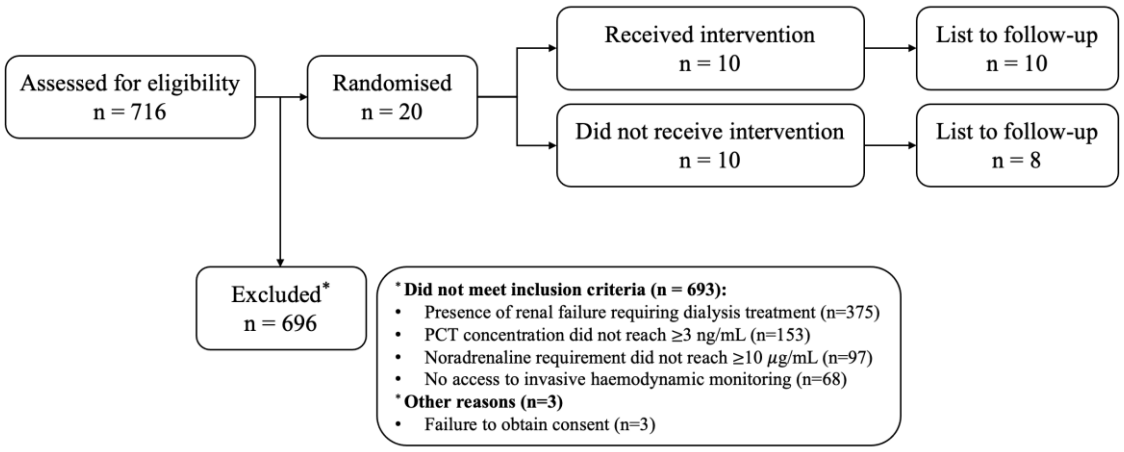

Figure 3. Flowchart of patient screening and involvement.

Table 3 shows the summary of demographic data. 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.

Parameters	All	CytoSorb	Control
N (male/female)	20 (13/7)	10 (7/3)	10 (6/4)
Age (years)	65.6 ± 12.9	60 ± 10	71 ± 14
Body Mass Index	28.8 ± 8.0	30.5 ± 10.2	26.9 ± 4.4
ICU length of stay (days)	10.1 ± 6.5	10.2 ± 8.5	10.0 ± 4.3
APACHE II	28 ± 7	26 ± 9	30 ± 6
Mortality within 48	2	0	2
Etiology (n)		pneumonia (7) pancreatitis (1) toxic shock syndrome (1) urosepsis (1)	pneumonia (6) meningococcus sepsis (2) cholangiosepsis (1) dermatomyositis (1)

Table 3. Demographic data.

N: number of subjects, ICU: Intensive Care Unit, APACHE II: Acute Physiology and Chronic Health Evaluation II score. Data are presented as mean ± standard deviation.

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).

Table 5 summarizes the results of the haemodynamic measurements, laboratory parameters and fluid balance.

	Group	T_0	T_{12}	T_{24}	T_{48}
MAP (mmHg)	*CytoSorb*	80 ± 10	74 ± 9	76 ± 9	81 ± 15
	Control	83 ± 8	82 ± 8	79 ± 10	84 ± 10
HR (1/min)	*CytoSorb*	69 ± 12	69 ± 26	73 ± 28	59 ± 14
	Control	62 ± 13	76 ± 24	67 ± 12	71 ± 12
CI (l/min/m^2)	*CytoSorb*	3.2 ± 1.1	3.1 ± 1.2	3.2 ± 1.5	3.4 ± 1.1
	Control	3.0 ± 0.8	3.8 ± 0.5	3.8 ± 0.7	3.5 ± 0.9
PPV (%)	*CytoSorb*	12.2 ± 5.3	14.9 ± 6.1	12.1 ± 6.2	12.6 ± 5.6
	Control	11.8 ± 5.7	13.9 ± 7.4	12.1 ± 6.9	13.7 ± 4.9
EVLWI (mL/kg)	*CytoSorb*	16.4 ± 10.1	14.6 ± 6.0	13.6 ± 6.1	13.1 ± 5.0
	Control	8.7 ± 3.7	7.8 ± 2.5	7.8 ± 3.0	7.1 ± 1.7
SVRI	*CytoSorb*	1909 ± 497	2030 ± 755	1946 ± 598	1806 ± 494
(dyn × s/cm^5/m^2)	*Control*	2314 ± 812	1656 ± 252	1588 ± 300	1852 ± 377
Cumulative total i.v. fluid (mL)	*CytoSorb*	–	2195.8 ± 1319.0	3922.1 ± 1634.2	6861.6 ± 1488.3
	Control	–	2370.3 ± 816.6	4639.2 ± 2477.1	7648.3 ± 2988.3
Lactate (mmol/L)	*CytoSorb*	3.6 ± 3.9	4.4 ± 4.7	3.1 ± 3.3	2.4 ± 2.9
	Control	3.0 ± 2.4	2.1 ± 1.2	1.6 ± 0.7	1.4 ± 0.5
CO_2 gap (mmHg)	*CytoSorb*	7.8 ± 3.5	7.0 ± 3.4	6.1 ± 3.6	4.1 ± 4.7
	Control	2.8 ± 5.4	4.8 ± 2.8	4.7 ± 1.8	6.6 ± 1.6
$ScvO_2$ (%)	*CytoSorb*	75.8 ± 9.6	78.4 ± 8.2	76.3 ± 5.4	77.9 ± 5.0
	Control	80.9 ± 5.7	82.1 ± 4.2	81.1 ± 3.5	78.2 ± 6.0
PaO_2 /FiO_2	*CytoSorb*	173.2 ± 64.2	212.7 ± 99.2	293.9 ± 207.1	243.9 ± 116.8
(mmHg)	*Control*	249.5 ± 127.6	215.5 ± 81.0	227.5 ± 100.4	244.0 ± 83.0
CRP (mg/L)	*CytoSorb*	238.1 ± 95.5	226.8 ± 109.2	220.3 ± 104.0	169.54 ± 86.4
	Control	307.4 ± 116.7	307.7 ± 104.2	280.4 ± 80.8	189.9 ± 48.5
BigET-1 (pmol/L)	*CytoSorb*	1.3 ± 0.6	0.9 ± 0.3#	1.0 ± 0.4#	1.4 ± 0.8
	Control	1.1 ± 0.7	1.0 ± 0.5	1.1 ± 0.6	1.2 ± 0.6
eGFR (mL/min/m^2)	*CytoSorb*	31.0 ± 19.4	30.0 ± 14.9	35.3 ± 19.5	34.0 ± 21.6
	Control	41.3 ± 15.7	40.6 ± 19.2	44.9 ± 25.6	45.4 ± 26.3
Creatinine (μmol/L)	*CytoSorb*	215.7 ± 187.5	181.5 ± 124.6	164.3 ± 123.68	177.1 ± 166.0
	Control	141.4 ± 87.9	181.8 ± 105.1	186.3 ± 158.7	147.6 ± 138.8
Fluid balance (mL/24 h)	*CytoSorb*	–	1454.7 ± 1382.2	1089.6 ± 861.1	1475.1 ± 1262.7
	Control	–	1210.2 ± 940.8	1239.1 ± 1829.6	1166.7 ± 1258.3

MAP: mean arterial pressure, HR: heart rate, CI: cardiac index, PPV: pulse pressure variation, EVLWI: extravascular lung water index, SVRI: systemic vascular resistance index, $ScvO_2$: central venous oxygen saturation, PaO_2: partial arterial oxygen pressure, FiO_2: fraction of inspired oxygen, CRP: C-reactive protein, BigET-1: big endothelin-1. Data are presented as mean ± standard deviation; #: $p < .05$ vs.T_0.

Table 4. Haemodynamic and laboratory parameters.

We found no tendencies and 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) showed a decreasing, but statistically non-significant decreasing tendency in CytoSorb group. Systemic vascular resistance (SVRI) was gradually decreasing in Control group in the first 24 hours, while it increased in the CytoSorb group during the treatment, however, statistical significance was not shown in either case.

There was a significant, compared to baseline, almost 70% decrease in norepinephrine need in the CytoSorb group while in the Control group it was steady (Figure 4). The fluid balance was similar in the two groups.

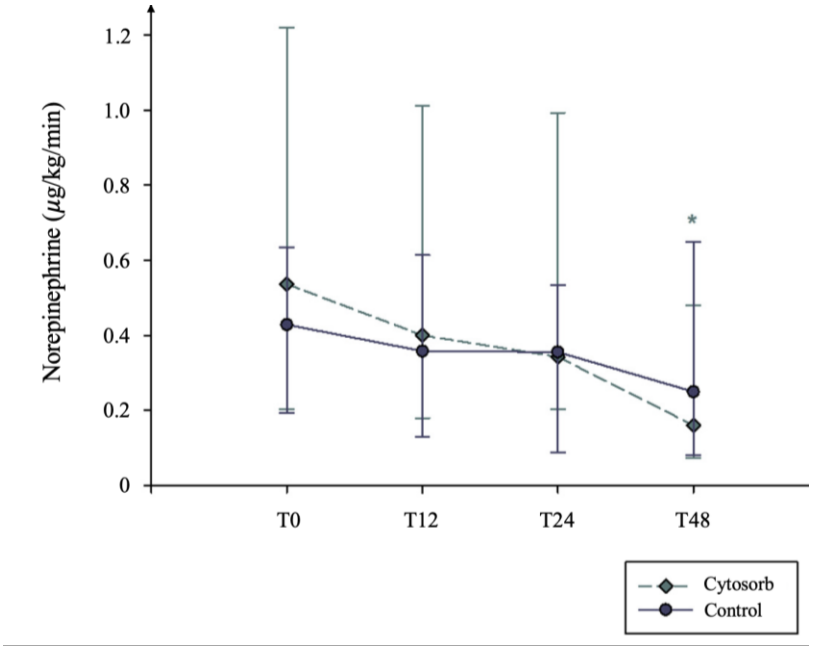

Figure 4. Kinetics of norepinephrine need in the CytoSorb and in the Control group.
*Data are shown as median and interquartile ranges. *p <0.05 vs. T0.*

Regarding blood gas parameters (*Table 5*), 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 (*Figure 5*) 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}.

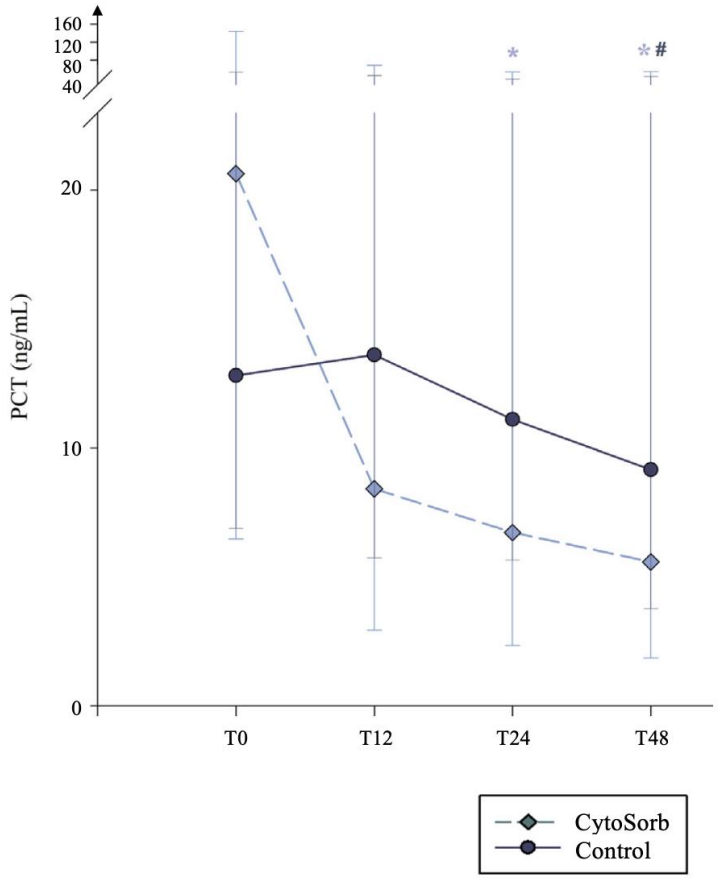

Figure 5. Procalcitonin kinetics in the CytoSorb and in the Control group.
*Data are presented as median and interquartile ranges. *p <0.05 vs. $T_{0CytoSorb}$, #p <0.05 vs. $T_{0Control}$.*

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 septic shock patients. 163 scientific papers mentioned CytoSorb and out of them, 58 included ‘catecholamines and/or vasopressors. 25 of 58 were excluded: 12 because of their scales were non-comparable, [35,41–48] [49–51] 4 papers did not specify the type and dose of vasopressor used [52–55], 1 showed combined norepinephrine and epinephrine doses [56], 1 study only published data on survival patients [57], 7 publications involved no measurements in the same patient before and after the

adsorption therapy [58–64]. Finally, 33 articles with 353 patients were included with various study designs and treatment duration [65–96].

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. Figure 6. summarises our analysis. 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 [82,86,97]. The norepinephrine dose showed a marked decrease by the end of CytoSorb treatment which conforms with the evidence available.

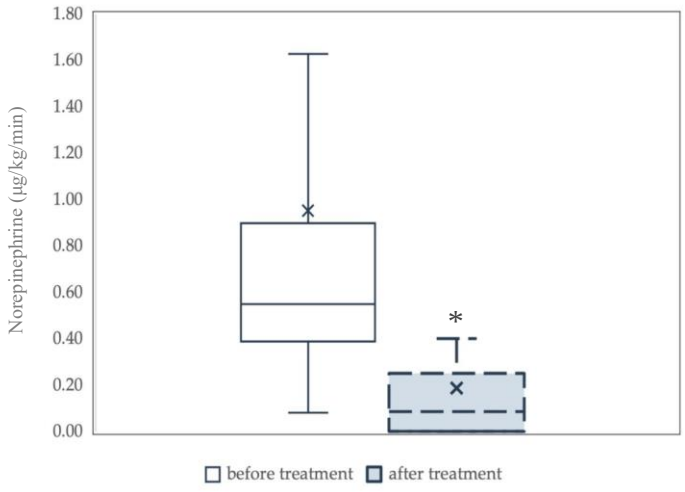

Figure 6. Norepinephrine requirements before and after treatment with CytoSorb.
*Data are summarised as boxplots. The "x" in the box represents the mean value. There is a significant decline in median norepinephrine requirements before and after haemadsorption with CytoSorb (from 0.55 (0.39–0.9) μg/kg/min to 0.09 (0.0–0.25) μg/kg/min, *p < 0.001).*

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 (Table 5) [83,85,87,98].

Study	Design	Indication	CytoSorb (n)	Control (n)	Total (n)
Mehta et al. [85]	Observational	Aortic surgery	8	8	16
Hawchar et al. [98]	Randomised	Septic shock	10	10	20
Akil et al. [83]	Observational	Septic shock	13	7	20
Rugg et al. [87]	Observational	Septic shock	42	42	84
Total			73	67	140

Table 5. Studies with CytoSorb and control cohorts.

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 [71,83]. 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 [85]. Akil et al. prospectively investigated 13 ARDS patients on ECMO and haemadsorption and compared them with 7 pulmonary sepsis patients on ECMO alone [83]. 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 [87]. 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.

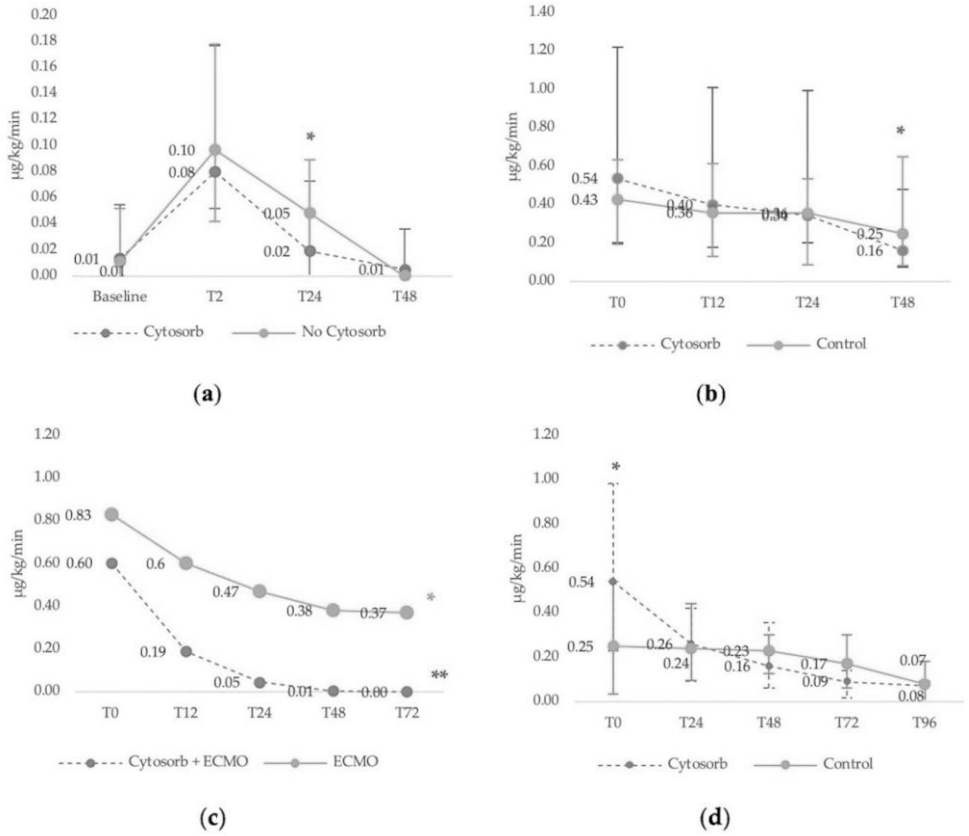

Figure 7. Median vasopressor therapy requirements in CytoSorb and control cohorts.
*(a) Median vasopressor therapy requirements in aortic surgery patients. Based on Mehta et al. [86]. * p <0.05 for norepinephrine dose of CytoSorb vs. no CytoSorb at T24. (b) Median vasopressor therapy requirements in septic patients. Based on Hawchar et al. [41]. T0 is measured right after inclusion (control) or start of haemadsorption. T12, T24 and T48 were measured 12, 24 and 48 h later. * p <0.05 vs. T0 in the CytoSorb group. (c) Mean vasopressor therapy requirements in patient with pneumonia-derived sepsis. Based on Akil et al. [84]. Timepoints represent hours after the initial dose administered at the entrance into the ICU. * p = 0.05 at T48 and T72 in the ECMO group. ** p <0.005 at T12, T24, T48 and T72 in the CytoSorb group. (d) Median vasopressor therapy requirements in septic shock patients requiring CRRT. Based on Rugg et al. [88]. Baseline is defined as the day of Cytosorb mounting in the treatment group. Data are presented as median and interquartile ranges. * p = 0.014 as compared to baseline. For explanation see text.*

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. STATA 16 software was used to apply meta-analysis by its 'meta' command [99]. We estimated the effect size as follows: standardised mean difference from baseline to the 24-hour value was calculated of the relative reduction in vasopressor dose. As our cohort has a small sample, we applied Hedge's g statistical method. According to this, small effect = 0.2; medium effect = 0.5 and large effect = 0.8. I^2 shows heterogeneity among the involved studies. The result of the pooled analysis is shown in Figure 8.

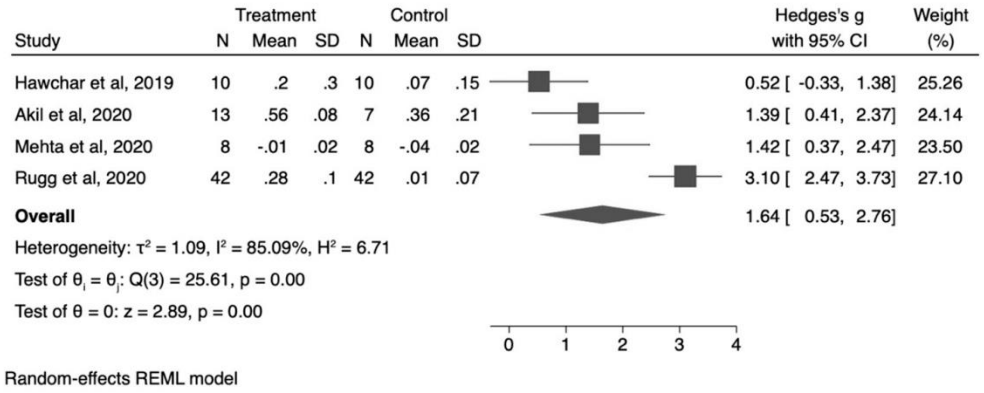

Figure 8. Forest plot for efficacy of CytoSorb therapy to reduce norepinephrine requirements at 24h.

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 flow chart lists the number of patients treated for various conditions (Figure 9).

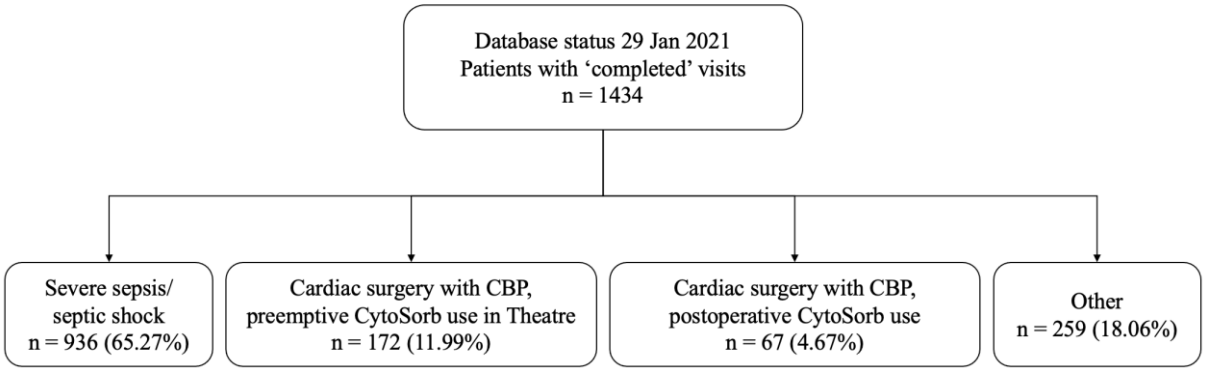

Figure 9. The number of patients by indication.
CBP: cardio-pulmonary bypass.

Whole cohort

Table 6 provides an overview of demographic, baseline, and treatment variables and lists any missing information in the 'N' columns. 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 renal replacement therapy (RRT). Additional information is shown in Table 6.

Parameter	Sepsis / septic shock		Cardiac surgery with CPB – preemptive		Cardiac surgery with CPB – postoperative		Other indication		Total	
	Mean±Std. Median [IQR]	N (936)	Mean±Std. Median [IQR]	N (172)	Mean±Std. Median [IQR]	N (67)	Mean±Std, Median [IQR]	N (259)	Mean±Std, Median [IQR]	N (1434)
Age [years]	62.2 ± 14.3	936	61.0 ± 13.5	172	64.7 ± 12.5	67	54.7 ± 16.4	259	60.8 ± 14.8	1434
Male/Female	610/326	936	126/46	172	59/8	67	165/94	259	960/474	1434
APACHE II score	28.2 ± 8.6	811	N.A.	N.A.	25.5 ± 8.2	60	24.1 ± 10.0	213	27.2 ± 9.0	1084
Predicted mortality [%]	66.4 ± 22.5	811	N.A.	N.A.	42.5 ± 25.0	60	50.8 ± 27.2	213	62.0 ± 24.8	1084
SOFA score	14.3 ± 3.8	805	9.6 ± 3.3	119	14.7 ± 3.0	63	13.2 ± 4.8	217	13.7 ± 4.1	1204
Number of adsorbers	2 [1 – 39]	931	1 [1-9]	172	1 [1-11]	67	2 [1-25]	257	2 [1-39]	1427
Total duration of treatment (h)	43 [0.3-792]	931	2.9 [1-169]	172	38.8 [2.8-234]	67	47.4 [0.7-484]	257	37.7 [0.3-792]	1427
Treatment time per adsorber (h)	20 [0.1-105]	3329	3 [0.8-72]	202	24 [0.5-78]	133	24 [0.2-267]	678	20 [0.1-267]	4342
Time between treatments (h)	2.6 [0.1-7.7]	2398	2.9 [0.8-19.2]	30	0.8 [0.0.-5.6]	66	0.17 [0.0-8.0]	421	2.3 [0.1-7.7]	2915
Blood pump flow rate (mL/min)	150 [130-180]	3327	300 [180-400]	202	120 [100-160]	133	140 [100-160]	678	150 [120-180]	4340
Combined with RRT, n [%]	3216 [97]	3323	60 [30]	201	122 [92]	133	642 [96]	672	4040 [93]	4329
HCO_3 – min (mmol/L)	18.6 ± 5.1	836	NA	NA	18.7 ± 3.8	64	19.2 ± 5.5	245	18.7 ± 5.1	1145
Creatinine – max (mg/dL)	2.4 ± 1.4	383	1.5 ± 0.7	28	2.0 ± 0.7	42	2.7 ± 2.1	88	2.3 ± 1.5	541
Blood urea nitrogen (pg/mL)	15.2 ± 10.5	896	NA	NA	12.0 ± 7.1	67	14.3 ± 10.8	250	14.8 ± 10.5	1213
Total bilirubin (mg/dL)	1.6 [0.8 – 3.5]	849	0.7 [0.4-1.0]	145	1.6 [1.0-2.3]	66	2.8 [1.0-11]	246	1.5 [0.7-3.6]	1306
Leukocytes – min (G/L)	13.4 ± 11.3	929	NA	NA	13.1 ± 8.3	66	13.9 ± 9.0	253	13.5 ± 10.7	1248
Leukocytes – max (G/L)	18.2 ± 17.6	588	NA	NA	19.8 ± 8.8	49	18.6 ± 10.7	101	18.3 ± 16.33	738
Platelets – min (G/L)	150.1 ± 111.5	928	222.8 ± 91.0	163	126.6 ± 55.5	67	131.8 ± 92.6	254	154.1 ± 107.2	1412
Platelets – max (G/L)	181.5 ± 115.9	582	312.3 ± 339.3	29	165.8 ± 64.9	49	178.9 ± 121.2	104	185.1 ± 131.8	764
CRP at T1 (mg/L) (Mean ± Std [Range])	179.6 ± 136.5 [0.3-1200]	866	50.4 ± 67.2 [0.1-300]	161	71.0 ± 90.1 [0.4-521]	67	86.8 ± 104 [0-495]	219	142.8 ± 133.3 [0-1200]	1313
PCT at T1 (ng/mL) (Mean ± Std [Range])	34.9 ± 70.9 [0-995]	765	9.0 ± 39.1 [0-222]	32	19.1 ± 27.3 [0.1-139]	52	13.9 ± 30.4 [0.1-179]	161	29.9 ± 64.1 [0-995]	1010
IL-6 at T1 (pg/mL) (Median [Range])	4240 [0->10^7]	308	23 [2-5000]	71	446 [69-5000]	41	592 [0->10^8]	69	1034 [0->10^8]	489

Table 6. Demographics, treatment characteristics and baseline parameters.
ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation. Data are presented as mean ± standard deviation, mean [95% CI, confidence intervals], median [interquartile ranges] as appropriate. IL-6 shows lognormal distribution, transformation ln(value+1) was used for analysis, hence geometric mean of ratio with 95% confidence interval is given.

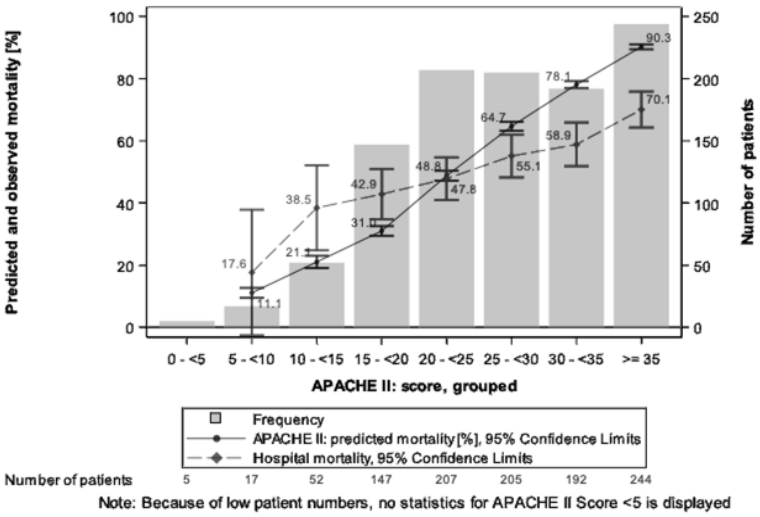

Figure 10. Actual and predicted mortality in the whole cohort.

Actual hospital mortality was 50.1%, while ICU mortality was 47.8%. The main result was the discrepancy between observed and anticipated mortality, which is detailed in Figure 10.

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. Table 2 provides a summary of organ support characteristics. Between T1 and T2, the overall SOFA ratings did not significantly change. The pulmonary and cardiovascular subscores, however, displayed significant variations by T2 (Table 7).

Parameter	Sepsis / septic shock		Cardiac surgery with CPB – preemptive		Cardiac surgery with CPB – postoperative		Other indication		Total	
	Value	N_{total}	Value	N_{total}	Value	N_{total}	Value	N_{total}	Value	N_{total}
Mortality at the end of CytoSorb therapy, n[%]	182 [19]	936	2 [0.1]	170	4 [6]	63	28 [11]	259	216 [15]	1434
ICU mortality, n[%]	524 [57]	928	17 [10]	170	17 [26]	66	121 [47]	256	679 [48]	1420
Hospital mortality, n[%]	548 [59]	923	18 [11]	168	17 [26]	66	129 [50]	253	712 [50]	1410
LOS ICU – survivors (days)	37.1 ± 34.0 [16-44]	400	8.1 ± 12.7 [3-8.5]	152	23.1 ± 24.5 [10-20]	49	25.4 ± 25.1 [10-34]	135	25.4 ± 25.1 [9-36]	736
LOS ICU – non-survivors (days)	19.7 ± 24.9 [4-25]	522	8.2 ± 11.5 [2-8]	17	15.5 ± 13.4 [8-23]	17	14.9 ± 15.5 [4-20]	119	18.4 ± 23.2 [4-23]	675
MV – survivors (days), median[IQR]	19 [7.5-32]	392	2 [1-3]	153	7 [5-17]	49	6 [1-19]	135	9 [2-26]	729
MV – non-survivors (days), median[IQR]	10 [3-20]	515	3 [2-7]	17	8 [4-14]	17	8 [3-16]	119	9 [3-18.5]	668
RRT – survivors (days), median[IQR]	9.5 [4-20]	392	0 [0-0]	149	7 [4-11]	49	7 [3-14]	135	6 [2-15]	725
RRT – non-survivors (days), median[IQR]	5 [2-13]	513	3 [1-5]	17	6 [4-10]	17	8 [3-12]	117	6 [2-13]	664
Days on vasopressors – survivors, median[IQR]	15 [6-29]	390	2 [1-3]	150	5 [4-14]	45	5 [1-12]	133	8 [3-20]	718
Days on vasopressors – non-survivors,median[IQR]	9 [3-18]	511	3 [2-7]	17	8 [5-15]	15	6 [3-12]	118	8 [3-17]	661
Change in SOFA score (T2-T1), mean[CI]	0.13 [-0.2, 0.4]	537 179†	0.6 [-0.03,1.3]*	111 1†	0.96 [0.03, 1.9]	56 4 †	0.05 [-0.4, 0.5]	172 28 †	0.23 [0, 0.5]*	876 212 †
Change in CVS subscore (T2-T1), mean[CI]	-0.54 [-0.6,-0.5]*	717	-0.05 [-0.4, 0.3]	146	-0.5 [-0.8, -0.17]*	62	-0.3 [-0.5, -0.09]*	221	-0.43 [-0.5,-0.3]*	1146
Change in pulmonary subscore (T2-T1), mean[CI]	-0.35 [-0.4,-0.3]*	662	0.18 [-0.05, 0.4]	142	-0.14 [-0.4, 0.2]	58	-0.07 [-0.2, 0.07]	206	-0.21 [-0.3,-0.2]*	1068
Delta CRP (T2-T1) (mg/L), mean[CI]	-46.4 [-57.5,-35.3]*	585	40.1 [26.9, 53.2]*	155	42 [14, 70]*	61	8.5 [-6.8, 23.8]	167	-17.5 [-25.5,-9.5]*	968
Delta PCT (T2-T1) (ng/mL), mean[CI]	-18.2 [-23.6,-12.8]*	488	-6.2 [-28.0,15.6]	22	-4.1 [-11.1, 3.0]	44	-8.8 [- 14.0, -3.5]	99	-15.4 [-19.6,-11.2]*	653
Delta IL-6 (T2/T1) (pg/mL), geometric mean[CI]	-2.6 [-3.0, -2.2]*	163	1.9 [1.3, 2.5]	61	-1.9 [-2.3, -1.4]*	31	-1.2 [-1.9, -0.4]*	32	-1.4 [-1.7, 1.1]	287

Table 7. Outcome parameters.
*ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation Data are presented as mean ± standard deviation, mean [95% CI, confidence intervals], median [interquartile ranges] as appropriate. † Number of patients who died under haemadsorption. IL-6 shows lognormal distribution, transformation ln(value+1) was used for analysis, hence geometric mean of ratio with 95% confidence interval is given. *p <0.05.*

Table 7 displays fundamental laboratory information. 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. Only in 67.5-45.5-20.2% of cases could these changes be analysed. From T1 to T2, CRP and PCT dramatically decreased across the entire sample. IL-6 also dropped, but not statistically significantly (Table 7). 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 (Table 8).

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 (Table 6). Within 35.5 [min: 0; max: 720] hours after the beginning of sepsis, treatment was initiated.

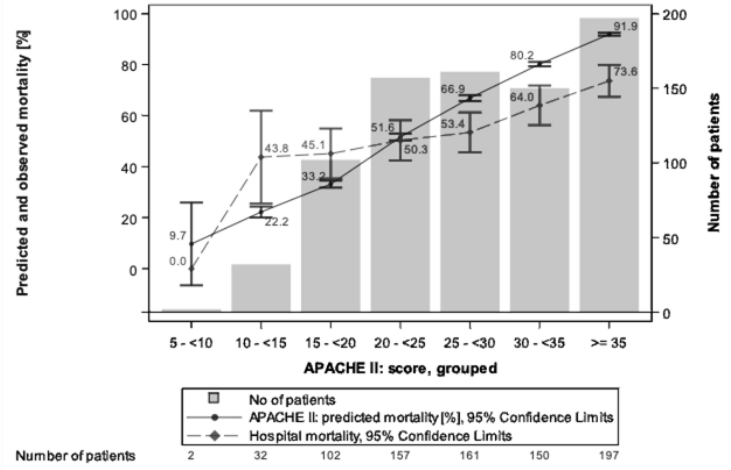

Figure 11. Actual and predicted mortality in the Sepsis cohort.

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 (Figure 10, overall, and Figure 11, sepsis cohort). Table 7 summarises the remaining results.

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% were already being given hydrocortisone at the time haemadsorption was started.

Similar to the entire group, both the pulmonary and cardiovascular subscores showed significant improvements (Table 7). The values of every inflammatory marker examined were higher than for the entire study population (Table 6). 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. Table 6 provides a summary of the remaining baseline characteristics for both categories.

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% (Table 6). Table 7 displays the remaining outcomes. Compared to the entire cohort, there were just a few small variations in these groups specifically. Even though both groups' cardiovascular SOFA subscores tended to improve, only the postoperative group's improvement was statistically significant (Table 7).

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 (Table 7).

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 (Table 8).

Change due to CytoSorb therapy	Sepsis/septic shock	Cardiac surgery with CPB - preemptive	Cardiac surgery with CPB - postoperative	Other indication	Total
Total number of patients	928	171	66	256	1421
Very much improved, n[%]	95 [10]	6 [4]	6 [9]	35 [14]	142 [10]
Much improved, n[%]	187 [20]	17 [10]	26 [39]	82 [32]	312 [22]
Minimally improved, n[%]	191 [21]	38 [22]	19 [29]	62 [24]	310 [22]
No change, n[%]	292 [32]	89 [52]	7 [11]	41 [16]	429 [30]
Minimally worse, n[%]	4 [0.4]	0 [0]	0 [0]	3 [1]	7 [0.5]
Much worse, n[%]	26 [3]	0 [0]	1 [2]	7 [3]	34 [2]
Very much worse, n[%]	13 [1]	0 [0]	2 [3]	0 [0]	15 [1]
No Assessment, n [%]	120 [13]	21 [12]	5 [8]	26 [10]	172 [12]

Table 8. Subjective assessment by physicians.

Other indications

Patients in the final cohort received CytoSorb therapy for a diverse range of pathologies (Table 9). Table 6 summarises their general demographics and baseline traits. This diverse subpopulation shares many of the same traits as the cohort as a whole.

Indication	N (%) of patients
Liver failure	109 (42.1 %)
Acute pancreatitis	32 (12.4 %)
Trauma	14 (5.4 %)
ARDS with ECMO	28 (10.8 %)
Other indication	91 (35.1 %)

Table 9. Indications other than sepsis and cardiac surgery.

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 (Table 7). 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 (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 (other data are only shown at baseline in Table 6). The G/L for the entire cohort (n=1130) was -74.2 [-84.7 to -63.7].

There were no known treatment-related problems in 1403 individuals (97.8%). 31 patients had 43 issues while receiving therapy.

The size of this study is the largest one ever published regarding haemadsorption therapy. The International CytoSorb Registry is a pioneering program designed to gather data under real-world conditions through extensive, centralised, structured, and thorough documenting of data in order to advance our understanding, boost clinical efficacy, and maximise its therapeutic applicability.

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. This is supported by the fact that the majority of patients were already taking hydrocortisone and on vasopressors, as well as by the high severity scores, the presence of multiple organ failure with more than four system failures in the vast majority of patients.

IV. Discussion

During the early stages of treatment-resistant septic shock, our proof-of-concept pilot trial discovered 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. The 24-hour haemadsorption treatment was shown to be safe in the current investigation since there were no intervention-related adverse effects, which is consistent with other reported case series and clinical trials [35,66,92,100]. 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. Although both groups had a 50% mortality rate, the intention was not to demonstrate how one particular therapy affected overall survival. Though patients in the CytoSorb group appeared to be in a worse condition, all of them were alive at the end of the whole 48-hour research period, whereas two patients in the Control arm deceased. The considerable decrease in the need for vasopressor support in the extracorporeal

cytokine elimination treatment group as compared to the Control group was one of the most marked outcomes of the current study. 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. The measured SVRI values agreed with this finding. These results at least give some physiological context that vasodilatation, most likely caused by the overwhelming effects of pro-inflammatory cytokines, was better controlled in the treated group, even though the difference between the groups did not reach statistical significance. This result is consistent with earlier data that was presented, both in case series and in more recent clinical investigations [67]. We need to note that contrary to previous reports, the most significant benefits were shown within the first 12 hours of treatment.

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. We decided on PCT and CRP because in our everyday practice we often measure them. 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 of 13 kDa, CytoSorb may directly adsorb PCT as the capsule's adsorption spectrum ranges from 5 to 60 kDa [101]. 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 T48, a pattern that has been shown in other investigations [102]. PCT is directly adsorbed by CytoSorb, and the adsorption is most efficient within the first 12 hours of treatment, according to a prior pilot study in which we assessed PCT simultaneously before and after the cartridge [103]. This explains why the PCT decline in the current study's CytoSorb group was more pronounced. This may also partially explain why, within the same 12-hour window following the start of extracorporeal cytokine adsorption treatment, the norepinephrine need decreased. These findings imply that switching the adsorber after 12 hours would be advantageous, although further research is required. The result, which further supports this was when upon termination of extracorporeal cytokine adsorption norepinephrine, PCT tended to rise, but non-significantly. These findings further imply that the PCT kinetics that we have previously established to forecast the suitability of an antibiotic treatment [104] 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 [105], but it also has the potential to be a hazardous mediator in sepsis [106]. According to the findings of this experiment, treating mice

beforehand with anti-PCT antigens before infecting them with E. coli significantly improved mortality, while all untreated animals perished [106]. In the current study, declining PCT concentration was linked to better clinical outcomes, including reduced need for vasopressors and enhanced oxygenation. This is consistent with our earlier observations that PCT kinetics distinguished patients who received the proper antibiotics from those who received the incorrect antibiotics considerably and within 12 to 24 hours, which was also reflected in superior clinical outcomes [102]. The results of a recently released clinical trial on extracorporeal cytokine adsorption therapy, in which the primary outcome was change in normalised IL-6 serum concentrations during the first and the seventh study day, but which found no significant difference compared to controls [104], are somewhat in conflict with this observation of significantly lower PCT concentrations, however, this trial had a different treatment strategy (for 6 hours every day), studied a different patient population, and omitted information on PCT concentrations and norepinephrine doses.

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 [107].

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 [108]. In our study, the serum BigET-1 level dropped in the CytoSorb group between T0 and T12, T24. 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.

The studies shown that the main advantage of haemadsorption therapy is reduced vasopressor need possibly via attenuation of vasodilation due to hyperinflammatory shock. Both healthy participants and critically ill patients have shown that vasopressors can reduce microvascular perfusion by causing vasoconstriction in the arterioles [109–111]. Digital ischaemia, tachyarrhythmias, bacterial growth promotion, and reduced host tolerance to microorganisms are some of the potentially major side consequences of high-dose vasopressor treatment.

The prolonged use of high-dose norepinephrine is linked to poor outcomes and is a reliable predictor of death, according to multiple retrospective investigations [112,113]. These findings

show that minimizing the requirement for vasopressor support in terms of both time and dosage could be advantageous for patients, despite the fact that one could argue that high-dose vasopressors are only indicators of disease severity in these individuals.

These results highlight the necessity of shock reversal with concurrent 'de-catecholaminisation', which should be carried out as soon as possible [114]. 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. Additionally, we have discovered evidence of a significant treatment impact of the therapy at 24 hours from baseline based on a pooled analysis of studies combining data on control cohorts.

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. We cannot rule out the possibility that this recurring observation is the consequence of a statistical phenomenon known as 'regression toward the mean', when a random variable has an extreme value on its first measurement but moves closer to the mean or average on its second measurement, or vice versa [115]. Actual mortality was observed to be lower than anticipated mortality in recent prospective and retrospective case series [35,97] and a retrospective propensity score matching study in sepsis/septic shock [116]. According to Friesecke et al.'s prospective case series, expected death was higher than 80% but observed mortality was only 55% [97]. Hospital mortality in another retrospective case series was 62% as opposed to the 92% projected. In a most recent retrospective analysis, mortality was projected to be 74.5% and was actually reported to be 47.8% [116]. 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. In a recent study, 'worst 24-hour APACHE II scores' and 'admission APACHE II scores' were contrasted in ICU patients [117]. The predicted mortality by the 'admission APACHE II' (12%) was lower than actual hospital mortality (16%), while the 'worse APACHE II' was closer (15%). As these were very low risk patients, it is unknown if this phenomenon would be enhanced in greater risk individuals. In contrast, it is crucial to remember that patients in the Registry had extremely high baseline mortality and that their APACHE II and SAPS II scores were higher than in any other sepsis trial [117].

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.

The whole study group as well as the Sepsis/Septic shock subgroup has an improved pulmonary subscore. Although there are very few data in this area, two recent case series revealed promising results. When haemadsorption was stopped, Kogelmann et al. discovered that PaO_2/FiO_2, peak inspiratory pressure, and positive end expiratory pressure were all significantly improved after just one 24-hour treatment and even more by the end of the whole course of therapy [118]. The outcomes of the aforementioned small case series are further supported by our data on several hundred patients.

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 [98,104]. 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 this 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. It is significant to emphasise that the patients in this group were gravely ill. According to a recent meta-analysis by Vincent et al. [1], hospital mortality was 38% and overall mortality was 46.5%. In comparison to comparable septic shock trials conducted to date, our cohort's APACHE II predicted death of 66% and actual mortality of 59% were both higher. This highlights the difficulty in choosing the correct patient population for further trials.

The fact that CPB triggers an inflammatory response that may lead to postoperative organ failure has been extensively recognised [119]. 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. Nonetheless, these trials all shared the inclusion of patients with pathologies and severity comparable to those seen in the Registry, with EuroSCORE scores of 5.4, 6.1, and 5.1, respectively [120–122]. 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 [58,67,123]. Our findings suggest that randomised trials should be conducted with a careful

selection of patients for elective cardiac surgery since they are most likely to benefit from haemadsorption. It is noteworthy that CytoSorb has been used for numerous additional indications, for example liver failure, pancreatitis, rhabdomyolysis, and drug overdose as presented in Table 4. These results may support further studies to learn more about the effectiveness of CytoSorb therapy in these areas.

In keeping with all previously published studies, regardless of the type of study or case report, the eleventh analysis of Registry data provides more evidence that CytoSorb therapy is safe. Unfortunately, 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. We are unaware of any other clinical registry in intensive care medicine that reports such a large number of patients as the International Registry. In addition, the Registry provides useful information for clinical practice and for those wanting to conduct clinical trials including haemadsorption.

V. Limitations

Our pilot study suffers from a number of shortcomings. To begin, 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. In addition, our results do not include any data on long term adverse events (also known as safety) and outcome. Because there were not enough studies with a comparable design that adhered to such stringent requirements in order to generate a patient population that was generally consistent, a power analysis was not carried out. Because of the wide variety of people who have septic shock, 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. It would have been desired to measure a variety of cytokines, particularly before and after the adsorber; however, this could not be accomplished due to the fact that there were both technical challenges and economical constraints.

In our review, we characterised the shift in the amount of norepinephrine dose that was required for the CytoSorb population by incorporating all different kinds of papers that had been

published. In point of fact, the data were derived from a diverse range of sources, and there was no attempt made to standardise with regard to patients (with the exception of observational studies and 25 individual case reports), pathophysiology, clinical conditions, or the duration of the observation period. In addition, we were unable to take into account the number of adsorbers that were used during the observational period that was taken into consideration, the length of time that each haemadsorption cartridge was in use, or whether or not treatment was continued after the most recent measurement of the vasopressor dose that was available. One more of our shortcomings is the fact that we only tested a single haemadsorption device. Even though there are other haemadsorbers available on the market (such as Jafron, which is manufactured by Jafron Biomedical Co. in Guangdong, China, and Biosky, which is manufactured by Biosun Medical Technology Co. in Foshan, China), as recently summarised by Krenn and Stelzer [93], published data are exceedingly few in general, and none are accessible in the current setting of haemodynamic stabilisation. We are unable to comment on shock reversal or other favourable impacts on outcome, including survival, due to a lack of evidence on metabolic alterations and other beneficial effects on outcome, respectively. These questions must be addressed and resolved in big prospective randomised research.

In spite of this, the findings of this study highlight the need for further investigation into the possible applications of the treatment in hastening the body's natural ability to recover from shock and enhancing the chances of survival for critically ill patients. In conclusion, the themes that have been presented in this article provide food for thought on the necessity to better examine the benefits that can be garnered from early control of the increasing cytokine storm in pre-hyperinflammatory situations.

The Registry also has a number of limitations. Although centres are urged to do so, there is no indication that every patient treated with CytoSorb is entered from sites that have registered with the Jena, Germany, coordinating centre. Consequently, selection bias cannot be ruled out entirely. The absence of control groups further restricts the validity of the results. In addition, there was a considerable quantity of missing data, particularly at T2, which weakens the secondary endpoints. We are unable, sadly, to provide answers to key issues such as the factors that led to the decision to delay initiating haemadsorption in some patients or the criteria that were used to select individuals for treatment. This undoubtedly reduces the extent to which our findings may be generalised. CytoSorbents has provided financial assistance to the project; however, this assistance has only been used to cover the administrative costs associated with the operation of the registry. It has not been used for personal payments to encourage recruiting or to provide financing for human resources. It is possible that a lack of manpower was one of

the primary reasons why ‘only’ 46 centres, the most of which were academic institutions, were able and ready to participate. A further weakness of the study is that the Registry was created using old consensus criteria [38] that did not contain lactate levels. This must be taken into account when assessing the changes in cardiovascular consequences. Yet, one of the greatest benefits of this Registry is that it is voluntary, that it reflects real-world conditions and behaviours, and that the data have been of continuously high quality since the last publication [124].

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 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. List of figures

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IX. References

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