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Redaktion
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S. Friesecke[1] · K. Träger[2] · G. A. Schittek[3] · Z. Molnar[4] · F. Bach[5] · K. Kogelmann[6] · R. Bogdanski[7] · A. Weyland[8] · A. Nierhaus[9] · F. Nestler[10] · D. Olboeter[11] · D. Tomescu[12] · D. Jacob[13] · H. Haake[14] · E. Grigoryev[15] · M. Nitsch[16] · A. Baumann[17] · M. Quintel[18] · M. Schott[19] · J. T. Kielstein[20] · A. Meier-Hellmann[21] · F. Born[22] · U. Schumacher[23] · M. Singer[24] · J. Kellum[25] · F. M. Brunkhorst[23,26,27]

[1] Klinik und Poliklinik für Innere Medizin B, Universitätsmedizin Greifswald, Greifswald, Germany; [2] Kardioanästhesiologie, Universitätsklinikum Ulm, Ulm, Germany; [3] Klinik für Anästhesiologie, Intensivtherapie und Palliativmedizin, Carl-Thiem-Klinikum Cottbus, Cottbus, Germany; [4] Department of Anesthesiology and Intensive Care, University of Szeged, Szeged, Hungary; [5] Klinik für Anästhesiologie, Intensiv-, Notfallmedizin, Transfusionsmedizin und Schmerztherapie, Evangelisches Krankenhaus Bielefeld, Bielefeld, Germany; [6] Klinik für Anästhesiologie und Intensivmedizin, Hans-Susemihl-Krankenhaus gGmbH, Emden, Germany; [7] Klinik für Anästhesiologie, AG Hämodynamik, Klinikum rechts der Isar TU München, München, Germany; [8] Universitätsklinik für Anästhesiologie/Intensiv-/Notfallmedizin/Schmerztherapie, Klinikum Oldenburg gGmbH, Carl von Ossietzky Universität, Oldenburg, Germany; [9] Klinik für Intensivmedizin, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [10] Anästhesie und Intensivmedizin, Kliniken Erlabrunn gGmbH, Breitenbrunn, Germany; [11] Anästhesie und Intensivmedizin, Krankenhaus Herzberg, Elbe-Elster-Klinikum GmbH, Herzberg, Germany; [12] Fundeni Clinical Institute, Bucharest, Romania; [13] Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Universitätsklinikum Magdeburg, Magdeburg, Germany; [14] Klinik für Kardiologie und Intensivmedizin, Kliniken Maria Hilf GmbH, Mönchengladbach, Germany; [15] Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation; [16] Klinik für Anästhesie, Intensiv-, Notfallmedizin und Schmerztherapie, Krankenhaus St. Elisabeth und St. Barbara Halle, Halle, Germany; [17] Klinik für Anästhesie, Intensiv-, Palliativ- und Schmerzmedizin, Berufsgenossensch. Uniklinik Bergmannsheil, Bochum, Germany; [18] Zentrum Anästhesiologie, Rettungs-und Intensivmedizin, Universitätsklinikum Göttingen, Göttingen, Germany; [19] Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Klinikum Region Hannover Nordstadt, Hannover, Germany; [20] Medizinische Klinik V, Klinikum Braunschweig, Braunschweig, Germany; [21] Anästhesie, Intensivmedizin und Schmerztherapie, HELIOS Klinikums Erfurt, Erfurt, Germany; [22] Herzchirurgische Klinik und Poliklinik, LMU München, München, Germany; [23] Center for Clinical Studies Jena (ZKS), Jena, Germany; [24] Intensive Care Medicine, University College London, London, UK; [25] Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA; [26] Center for Sepsis Control and Care (CSCC), Jena, Germany; [27] Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany

International registry on the use of the CytoSorb® adsorber in ICU patients

Study protocol and preliminary results

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00063-017-0342-5) includes (1) flowcharts and data content in the eCRF, (2) severity scores, (3) criteria defining sepsis and septic shock, and (4) abbreviations. The article and the appendix are available at http://www.springermedizin.de/mk-im. The appendix can be found at the end of the article under "Supplementary material".

Extracorporeal blood purification techniques have been used for treating critically ill patients for more than 15 years. This approach is based on current evidence that an excessive inflammatory host response which is accompanied by a continuous release of inflammatory mediators may contribute to multiple organ failure and finally death. Cytotoxic effects with substrate loss in several organs [1] and immune paralysis [2] resulting in an increased susceptibility to secondary infections characterize the consequences of an uncontrolled release of inflammatory mediators. This led to the view that eliminating inflammatory mediators, bacterial toxins, and tissue degradation proteins from the systemic circulation might restore immunoreactivity and positively affect outcomes. Several mechanisms of action are supposed to account for the efficacy [3–5] and many approaches of extracorporeal blood purification techniques (hemofiltration, hemadsorption, plasmapheresis, etc.) have been investigated [6]. By recording physiological parameters and surrogate markers, many studies have shown that these approaches are efficient and well tolerated. However, questions surrounding the appro-

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Table 1 Inclusion and exclusion criteria

Inclusion criteria
– Use of CytoSorb®
– Age ≥ 18 years
– Signed informed consent
Exclusion criteria
– None

priate application, timing, duration, and frequency remain to be elucidated. In addition, studies with a higher number of patients should assess efficacy by recording clinically relevant study endpoints (mortality, organ dysfunction).

Clinically established methods differ in several aspects, such as the spectrum of retainable pathogenic molecules (e. g., cytokines and/or endotoxins), loss and need for supplementation of physiological blood components (low molecular substances, albumin, antibiotics), use-related technical and staff effort, and product costs.

Several medical devices that are based on the principle of hemadsorption methods are in different phases of clinical development [7]. The active component of the approved Toraymyxin (Toray Industries, Japan) is polymyxin B, an antibiotic that is immobilized on polystyrene fibers. The active ingredient enables the extraction of endotoxins. Its use is associated with high costs. Another product, which adsorbs the endotoxin LPS (Alteco Medical, Sweden), has failed to show convincing results in clinical testing. The product OXiris (Gambro-Hospal, France) is being clinically tested. It contains a biopolymer that is able to eliminate endotoxins and cytokines. The MATISSE system (Fresenius, Germany) relies on the adsorption qualities of human albumin which is immobilized on polystyrene. However, clinical results remain unconvincing. The nonspecific adsorption of cytokines (but not endotoxins) on a synthetic resin module with subsequent hemofiltration is used in the product of the Italian manufacturer Bellco. Efficacy in septic patients is currently being tested.

The approved product CytoSorb® (CytoSorbents, USA) contains a biocompatible polystyrene and divinylbenzene copolymer as a sorbent. The agent eliminates inflammatory cytokines and metabolic products in a quick and reliable way, but cannot adsorb endotoxins. Its efficient and safe use in patients with septic shock was proven in a randomized clinical multicenter study (NCT 00359130).

Another study that recently started investigates the adsorber's use in elective cardiopulmonary surgical interventions. As the product is compatible with other methods of extracorporeal blood purification (renal replacement therapy, cardiopulmonary bypass), an above-average usage in clinical practice is very likely, and the medical community has signaled significant interest [8].

Table 2 Flow chart for study visits and data assessment in patients with sepsis

Activity	Baseline	Exam 1	Treatment	Exam 2	Follow-up
Inclusion criteria	x	–	–	–	–
Indication	x	–	–	–	–
Demographics and type of admission	x	–	–	–	–
Comorbidities for APACHE II/SAPS II	x	–	–	–	–
Sepsis criteria	x	–	–	–	–
Site and source of infection	x	–	–	–	–
Physiological parameters for APACHE II/SAPS II	–	x	–	–	–
Physiological parameters for the SOFA score	–	x	–	x	–
Relevant diagnostic tests	–	x	–	x	–
Treatments with CytoSorb® (duration, anticoagulation, blood pump speed, vasopressors, hydrocortisone)	–	–	x	–	–
Renal replacement therapy (type, filter)	–	x	x	x	–
Complications	–	–	–	x	–
Length of stay on ICU and in hospital	–	–	–	–	x
ICU and hospital survival status	–	–	–	–	x
Days with mechanical ventilation	–	–	–	–	x
Days with renal replacement therapy	–	–	–	–	x
Days on vasopressors	–	–	–	–	x
Assessment of treatment effect	–	–	–	–	x

Exam 1 = Time period of up to 24 h before CytoSorb® use; *Exam 2* = Time period of 24 h after end of CytoSorb® use; *Follow-up* = Discharge from hospital

Objectives and design

The aim of this registry is to record the use of CytoSorb® under real-life conditions in as many cases as possible. All CytoSorb® applications in different clinical settings and in all patients who are treated with this technology are expected to be documented. The objectives of the registry are collection of real-life data on a broad scale, centralized, structured and comprehensive documentation, and controlled data exchange. The information gathered will be used to augment the knowledge on the clinical efficacy of the technology, to optimize the quality of its therapeutic application, and to identify and promptly handle possible complications related to the use of CytoSorb®. The registry will record relevant information in the course of product use, e. g., diagnosis, comorbidities, course of the condition, treatment, concomitant medication, and clinical laboratory parameters. An active form of data collection where data is prospectively collected by qualified staff is particularly suited for this purpose [9]. Registry data might help close knowledge gaps and open practical issues. Due to the patient group's heterogeneity, the registry can identify subgroups, assess their risk–benefit profile and examine their safety profile. Registry data are essential for assessing a therapy's significance within the healthcare landscape [10]. Institutions that contribute data to the registry benefit in several ways:

Abstract · Zusammenfassung

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International registry on the use of the CytoSorb® adsorber in ICU patients. Study protocol and preliminary results

Abstract

Introduction. The aim of this clinical registry is to record the use of CytoSorb® adsorber device in critically ill patients under real-life conditions.

Methods. The registry records all relevant information in the course of product use, e. g., diagnosis, comorbidities, course of the condition, treatment, concomitant medication, clinical laboratory parameters, and outcome (ClinicalTrials.gov Identifier: NCT02312024). Primary endpoint is in-hospital mortality as compared to the mortality predicted by the APACHE II and SAPS II score, respectively.

Results. As of January 30, 2017, 130 centers from 22 countries were participating. Data available from the start of the registry on May 18, 2015 to November 24, 2016 (122 centers; 22 countries) were analyzed, of whom 20 centers from four countries provided data for a total of 198 patients (mean age 60.3 ± 15.1 years, 135 men [68.2%]). In all, 192 (97.0%) had 1 to 5 Cytosorb® adsorber applications. Sepsis was the most common indication for CytoSorb® treatment (135 patients). Mean APACHE II score in this group was 33.1 ± 8.4 [range 15–52] with a predicted risk of death of 78%, whereas the observed mortality was 65%. There were no significant decreases in the SOFA scores after treatment (17.2 ± 4.8 [3–24]). However interleukin-6 levels were markedly reduced after treatment (median 5000 pg/ml before and 289 pg/ml after treatment, respectively).

Conclusions. This third interim report demonstrates the feasibility of the registry with excellent data quality and completeness from 20 study centers. The results must be interpreted with caution, since the numbers are still small; however the disease severity is remarkably high and suggests that adsorber treatment might be used as an ultimate treatment in life-threatening situations. There were no device-associated side effects.

Keywords

Cytokines · Extracorporeal life support · Inflammation · Sepsis · Intensive care units

Internationales Register zur Nutzung des Adsorbers CytoSorb® bei Intensivpatienten. Studienprotokoll und erste Ergebnisse

Zusammenfassung

Einleitung. Zweck des vorgestellten klinischen Registers ist es, die Nutzung des Adsorbers CytoSorb® bei kritisch kranken Patienten unter Realbedingungen zu erfassen.

Methoden. Dokumentiert werden Diagnose, Komorbiditäten, Verlauf der Erkrankung, Behandlung, Begleitmedikation und Laborparameter (ClinicalTrials.gov-Identifier: NCT02312024). Primärer Endpunkt ist die Krankenhausmortalität im Vergleich zur Mortalität, die mit dem APACHE-II- bzw. SAPS-II-Score prognostiziert wurde.

Ergebnisse. Mit Stand vom 30. Januar 2017 nahmen 130 Zentren aus 22 Ländern am Register teil. Verfügbare Daten vom 18. Mai 2015 bis 24. November 2016 (122 Zentren; 22 Länder) wurden analysiert. Zwanzig dieser Zentren aus 4 Ländern lieferten Daten zu insgesamt 198 Patienten (Alter 60,3 ± 15,1 Jahre, 135 Männer [68,2 %]). Insgesamt 192 (97,0 %) hatten 1–5 Cytosorb®-Adsorber-Anwendungen. Sepsis war die häufigste Indikation zur CytoSorb®-Behandlung (135 Patienten). Der durchschnittliche APACHE-II-Score in dieser Gruppe betrug 33,1 ± 8,4 mit einem prognostizierten Sterberisiko von 78 %, während die beobachtete Mortalität bei 65 % lag. Es fanden sich keine signifikanten Verringerungen in den SOFA-Scores nach Behandlung (17,2 ± 4,8 [3–24]). Die Interleukin-6-Spiegel waren allerdings nach Behandlung deutlich reduziert (im Median 5000 pg/ml vor und 289 pg/ml nach Behandlung).

Schlussfolgerungen. Dieser dritte Zwischenbericht belegt die Machbarkeit des Registers mit einer exzellenten Datenqualität und -vollständigkeit aus 20 Studienzentren. Die Ergebnisse sind mit Zurückhaltung zu interpretieren, da die Patientenzahl immer noch gering ist; die Erkrankungsschwere ist allerdings bemerkenswert hoch, was vermuten lässt, dass der Adsorber als Ultima Ratio genutzt wird. Es gab keine device-assoziierten Nebenwirkungen.

Schlüsselwörter

Zytokine · Extrakorporale lebenserhaltende Maßnahmen · Entzündung · Sepsis · Intensivstationen

they will obtain continuous retrospective feedback of their own results, their data will be periodically compared with data from other participating sites, and they will have access to regularly published analyses of the results. On the basis of these data, they can optimize their use of CytoSorb® [11].

Study population

All medical institutions that use CytoSorb® are eligible for participation. At inception, data collection was planned for a period of 3 years. An extension of the registry duration beyond that period is possible. The expected sample is around 1000 patients/year. Inclusion criteria are depicted in **Table 1**. There are no exclusion criteria.

Patients with sepsis and septic shock

Patients with sepsis/septic shock are enrolled according to the afore mentioned criteria ("**Criteria defining sepsis and septic shock" in Supplementary material**).

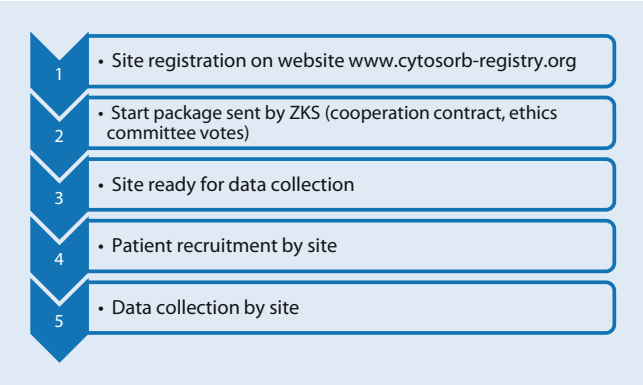

Fig. 1 ◀ Requirements before data collection by site

Patients undergoing cardiac surgery with CPB

This population includes patients who undergo cardiac surgery with the use of cardiopulmonary bypass (CPB). The most frequent cardiac interventions associated with CPB use include coronary artery bypass surgery, heart valves replacement surgery, and surgery of the major vessels.

Two possible variants for using the CytoSorb® device are envisaged, (1) preemptive use aiming to reduce circulating inflammatory cytokines immediately before and during surgery in risk patients; (2) postoperative use during the stay in ICU.

Other patients

Other patients are any other patients who are treated with the CytoSorb® device and who are not included in the sepsis/septic shock or cardiac surgery groups. The shortlist of indications includes, but is not restricted to: liver failure, acute pancreatitis, severe trauma, extensive burns, acute respiratory failure.

Data documentation

Data is recorded by assigned staff from the participating centers. If possible, data from each patient are recorded until being discharged from hospital. Data collection takes place at four time points during the hospital stay, as follows:

- Baseline, i. e. at inclusion
- Treatment phase with 2 exams—before and after CytoSorb® use
- Final assessment/follow-up at discharge from hospital

Data of patients subject to more than one CytoSorb® application for different indications are recorded separately; however, the fact they belong to the same individual is documented accordingly. The flow chart for study visits and data assessment in patients with sepsis, cardiac surgery, and other indications are depicted in **Table 2** and **"Flowcharts and data content in the eCRF" in Supplementary material,** respectively.

Data management

Data capture takes place via a web application on the servers of the Center for Clinical Studies at Jena University Hospital with OpenClinica®, a study management software. OpenClinica meets all regulatory requirements (GCP, 21CFRPart11). It has an integrated audit trail that records any kind of data changes automatically. This data recording cannot be modified by the users. In order to ensure a pseudonymized analysis of data, each patient data set is given a unique patient identification number when being entered into the study database. Data management is done by using the study management software OpenClinica®. Prior to its application, the study database is checked for errors (and corrected if necessary) by the database programmer and staff involved (e. g., biometricians, study investigator, study nurse). Only then is the database declared ready for use. Data is recorded in the study database via an encrypted data link (HTTPS) by use of data entry masks. While being entered, the data is already being checked for completeness and correctness. Missing or obviously erroneous values produce immediate error messages that require changes from the data inputting person. Correctness of data is verified by further range, validity, and consistency checks. The data collecting centers are contacted if data is not plausible or missing (query management) so that corrections/completions can be made. Any modification of the data—e. g. because of incorporation of query answers—is documented in the database by an audit trail. By applying a hierarchical, role-based access control, unauthorized access to patient data is impossible. Staff is informed about their obligation of nondisclosure of access codes. There is a daily backup of all data.

Each center has to complete a hospital/ICU questionnaire, and for each patient a questionnaire has to be filled in.

Recording adverse effects

The CytoSorb® registry is noninterventional observational data collection. Advice on treatment is not provided by the registry. Obligations to notify the authorities about adverse effects in clinical studies do not apply. There is no systematic recording of adverse effects in the registry. However, one objective of the registry is to record complications or effects that occurred while using CytoSorb®. Complications have to be recorded in the eCRF.

Implementation of the project

Potential participating centers are approached by the steering committee and via information that is delivered together with the CytoSorb® adsorber. In cases where a hospital is interested in participation, a questionnaire on the hospital's characteristics needs to be completed (**Fig. 1**). After receipt of this information, an account in the registry is created. A contract regulating rights and obligations is mandatory. Data collecting staff of participating centers is trained by the responsible CytoSorb Registry project manager at the Center for Clinical Studies in Jena. The physicians in charge of the registry are responsible for on-site dissemination of knowledge in their centers.

Table 3 Primary and secondary endpoints

Primary endpoint
Difference between mortality predicted by scoring systems (APACHE II/SAPS II, EuroSCORE II) and actual mortality within 30 days after intervention
Secondary endpoints
Organ dysfunction (SOFA score difference)
Concentration of biomarkers IL-6, CRP, PCT, myoglobin, free hemoglobin
Length of hospital and ICU stay (days)
Duration of mechanical ventilation (days)
Duration of renal replacement therapy (days)
Duration of vasopressor therapy (days)

ICU intensive care unit, *IL-6* Interleukin-6, *CRP* C-reactive protein, *PCT* Procalcitonin, *SOFA* Sequential Organ Dysfunction Score

Table 4 Baseline characteristics of patients according to indications for CytoSorb treatment

Parameter	Sepsis/septic shock		Cardiac surgery – preemptive		Cardiac surgery – postoperative		Other indications	
	Mean ± Std [Range]	*N* (135)	Mean ± Std [Range]	*N* (8)	Mean ± Std [Range]	*N* (17)	Mean ± Std [Range]	*N* (38)
Age [years]	61.5 ± 14.1 [22–92]	135	58.6 ± 13.6 [37–77]	8	67.2 ± 12.2 [44–84]	17	53.2 ± 17.8 [21–84]	38
APACHE II: score	33.1 ± 8.4 [15–52]	107	n.a.	–	22.1 ± 7.3 [2–33]	16	25.5 ± 8.9 [9–51]	26
APACHE II predicted mortality [%]	77.6% ± 20.7 [23–99]	107	n.a.	–	31.4 ± 18.2 [2–72]	16	54.1 ± 29.0 [8–98]	26
SAPS II: score	74.3 ± 16.8 [29–107]	74	n.a.	–	50.1 ± 13.2 [27–75]	14	61.9 ± 17.7 [30–97]	20
SAPS II predicted mortality [%]	81.0 ± 20.3 [10–99]	74	n.a.	–	46.3 ± 23.8 [8–89]	14	65.0 ± 28.0 [11–98]	20

SD standard deviation

Data analysis

The primary endpoint is observed in-hospital mortality, compared to the mortality predicted by the APACHE II and SAPS II scores, respectively [12, 13]. Survival rates are compared by use of a logistic regression model according to Knaus et al. [12]. Significance level is preset at $\alpha = 0.05$. If a difference is verifiable, a binominal test will be performed for the score groups 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, and ≥35. The significance level for the binominal tests will be adjusted by use of the Bonferroni–Holm correction in a mode that a total level of $\alpha = 0.05$ is preserved. Major secondary endpoint is the change of the SOFA scores (ΔSOFA). For this, the difference between SOFA scores of Exam 1 (within 24 h before CytoSorb® use) and Exam 2 (24 h after CytoSorb® use) are calculated. ΔSOFA is analyzed by using T-test. Further secondary endpoints are depicted in **Table 3**. In addition, an aggregated description of treatment-related complications (frequency per organ/system) and an assessment of the treatment success (descriptive, frequency analysis) are used for assessing the safety of CytoSorb® use. In patients with preemptive CytoSorb® application the survival analysis will be performed using the EURO score [14].

Calculation of sample size: the feasibility analysis indicated an expected number of 1000 patients per year. Based on these figures, and depending on the pivotal mortality probability p_1, the following odds ratios (OR) can be anticipated (two-sided, $\alpha = 0.05$, power 90 per cent): $p_1 = 0.5 \rightarrow$ OR 0.81; $p_1 = 0.7 \rightarrow$ OR 0.80; $p_1 = 0.8 \rightarrow$ OR 0.77 (GPower 3.1.6, z-tests for logistic regression).

Publication of results/registration of the data collection

The CytoSorb® registry is registered in the study registries ClinicalTrials.gov and the German Registry for Clinical Studies Freiburg (DRKS). Use of data from the CytoSorb® registry by participating centers and external parties is regulated by a data use agreement. Reports on the semiannual analyses and a retrospective access to their own data will be provided for all participating centers. Publication of results generated from registry data are subject to separate publication regulations and are coordinated by the steering committee.

Ethical principles and patient safety

The registry represents merely a collection of data on the use of CytoSorb® in accordance with the prescribing information. Therefore, there are no ethical objections concerning patients and patient safety. The decision of the attending physician is the sole factor which determines the assignment of a patient to treatment with CytoSorb®, and the physician's participation in the registry does not influence his decision. Patient information about the device is provided and signing of informed consent is an essential precondition for participation in the registry. In case patients are unable to consent because of critical illness, local practice for collecting data on these patients has to be applied. This study protocol has been submitted to the Institutional Review Board (IRB) of the Faculty of Medicine at Friedrich Schiller University, Jena that acts as the IRB in charge for Germany. All German ethic committees involved are informed about the participation of centers in their area of responsibility and the decision of the IRB in charge. In centers from outside Germany, approval of the local ethics commission in charge is obtained and all national regulations are adhered to.

Data protection

Data collection takes place in the participating centers. All collected medi-

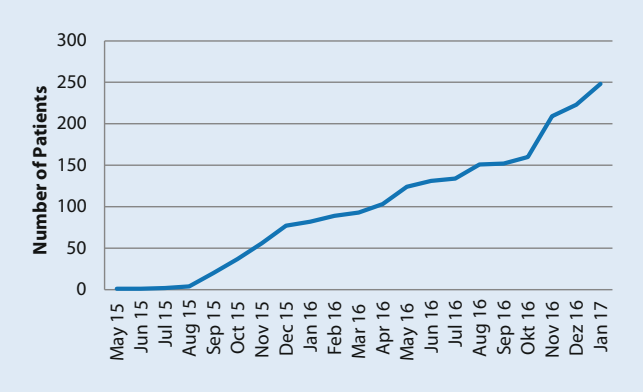

Fig. 2 ◀ Patient recruitment from May 18, 2015 to January 17, 2017 (248 patients)

cal data are entered by assigned staff of the centers into a computer-based online data entry system and immediately transferred to the documentation center at ZKS Jena. Informed consent on data collection and use is obtained prior to inclusion of the patient or at the earliest possible time. Due to the seriousness of the medical condition, it has to be assumed that most patients are unable to consent. Thus, oral or written informed consent prior to the data collection cannot be obtained. In this case, the data collecting institutions have to observe their locally established way of proceeding for including patients incapable of giving informed consent. The patient's consent is recorded in the patient file. Patients or their legal representatives have the right to withdraw their consent and to interrupt participation in the study at any time and without giving reasons. In this case, the patient's data will be deleted.

Data collection occurs upon early stage pseudonymization of the patients. Participating centers draw up local patient identification lists and allocate a unique multidigit number to each patient. Only pseudonymized patient-related medical data are transferred from the participating center to the documentation center; no information that allows identification of patients is revealed to the documentation center.

For answering queries that might arise while checking the data quality and plausibility, the data collecting center is able to trace back the pseudonym to the patient for a given period of time. The patient identification list remains at the data collecting center and can be accessed by a limited group of staff members (principal investigators).

The patient identification list has to be kept locked up for at least 10 years in the data collecting center. The local principal investigator is responsible for this. The sponsor has to authorize the destruction of the patient identification list.

Owners of the registry data are the steering committee members. The Center for Clinical Studies at Jena University Hospital is appointed as the documentation center, also in charge of data processing. Backup of data is done regularly. The data storage devices are stored in a locked, central room, accessible only by the system administrator. Only the following persons have access to the data: staff of the ZKS that are directly involved in the project (statisticians, data manager, IT coordinator). Analyses are carried out by statisticians of ZKS Jena.

Publication of the data takes place in an aggregated form only. Information about individual patients, ICUs or hospitals will not be published or shared.

All data collecting centers can request access to the data they contributed. Requests for data submitted by external interested parties are decided on by the steering committee. Again, disclosure of data takes place in an aggregated form only.

Data protection statement

Data entry is done in the data collecting centers. Data processing and analysis takes place at the Center for Clinical Studies at Jena University Hospital. Regulations of the data protection acts of all countries concerned are satisfied. Access to the study data is limited to registry staff. These persons are bound to secrecy. Data are protected from unauthorized access.

Sponsor and funding

For the success of a registry, close cooperation between users, product suppliers, and sponsors is crucial. Of particular importance is also the scientific editing of knowledge generated from the registry and the communication of results to all stakeholders. Jena University Hospital, represented by Prof. Dr. F. M. Brunkhorst, is the scientific institution that runs this registry. The steering committee supports the implementation of the registry. The CytoSorb® registry is funded by CytoSorbents Europe GmbH. The Center for Clinical Studies at Jena University Hospital is able to provide all necessary services in the field of data management and project management.

Results from the 3rd interim report

As of January 30, 2017, 130 centers from 22 countries were participating in the registry (**Figs. 2 and 3**). Data available from the start of the registry on May 18, 2015 to November 24, 2016 were analyzed. At this time point, 122 centers from 22 countries participated in the registry, of which 20 centers from four countries provided data from a total of 198 patients (**Fig. 4**). Baseline data was available in 191 patients, treatment phase data in 195 patients and follow-up-data in 193 patients.

Baseline characteristics

One hundred and thirty five (68.2%) patients were male. Mean age was 60.3 ± 15.1 (min–max 21–92) years. Patients with preemptive CytoSorb use in cardiac surgery and other indications were slightly younger (58.6 ± 13.6 and 53.2 ± 17.8, respectively) than patients with sepsis (61.5 ± 14.1), whereas patients with postoperative use in cardiac surgery were slightly older (67.2 ± 12.2). There were no relevant differences between the indication groups in body weight and body height. The majority of patients were ad-

Fig. 3 ◀ There were 130 participating study centers from 22 countries, as of January 17, 2017

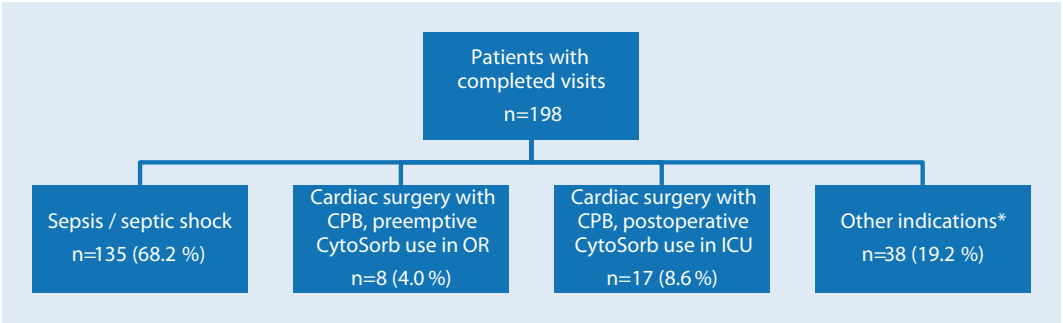

Fig. 4 ◀ Indications for CytoSorb treatment. *CPB* cardiopulmonary bypass; *OR* operation room; *ICU* intensive care unit. *other indications were: liver failure ($n = 11$), acute pancreatitis ($n = 4$), trauma ($n = 6$), ARDS with ECMO ($n = 12$), others ($n = 10$)

mitted for nonsurgical emergency reasons (91 [46.0%]), surgical emergency for 70 (35.4%) and elective surgical for 37 (18.7%) of the patients (**Table 4**).

Exposition to treatment

The majority of patients (192 patients, 97.0%) had one to 5 Cytosorb adsorber applications, up to 32 adsorbers have been used per patient.

Mean duration of treatment was 55.5 ± 83.2 h for the sepsis group ($N = 134$), 8.3 ± 13.8 h for patients with preemptive use in cardiac surgery ($N = 8$), 45.3 ± 23.3 h for patients with postoperative use in cardiac surgery ($N = 16$), and 60.8 ± 49.8 h for patients with other indications ($N = 37$). A single adsorber was used for 22.2 ± 15.3 h; the range of duration for a single adsorber was 15 min to 105 h.

Outcome

Sepsis group

Patients with sepsis were predominantly medical patients (71/135) and exhibited an extreme high risk of death when CytoSorb treatment was initiated (mean APACHE II score in 107/135 patients: 33.1 ± 8.4 [range 15–52]). This is substantial higher than in other sepsis trials, where mean APACHE II scores are usually between 20 and 25 (for instance in the MAXSEP and VISEP trials with 20.2 and 21.6 points and 28-day mortality rates of 22.9 and 25.4%, respectively). The predicted risk of death in the CytoSorb group would be around 78%, whereas the observed mortality was 65%.

This result in the sepsis group is supported by the high SAPS II scores (74.3 ± 16.8 [29–107]), with a predicted mortality of around 81%. The mean SOFA scores were also markedly elevated (17.3 ± 3.99 [6–24]). Substantially lower SOFA scores were observed in for instance the VISEP and MAXSEP trials (7.7 [7.3; 8.2] points). There were no significant decreases in the SOFA scores after treatment (17.2 ± 4.8 [3–24]). However, IL-6 levels were markedly reduced after treatment (median 5000 pg/ml before treatment and 289 pg/ml after treatment).

Treating physicians rated the condition as very much/much improved in 45%, as minimally improved in 18%, and as unchanged in 29%. Two patients (1.5%) were rated as much worse or very much worse.

Cardiac surgery with CPB, postoperative

Patients postoperatively treated following cardiac surgery with CPB had a mean APACHE II score of 22.1 ± 7.3 [2–33] (16/17 patients), with a predicted mortality of 31%, and an observed mortality

Table 5 Outcome parameters

Parameter	Sepsis/septic shock		Cardiac surgery – preemptive		Cardiac surgery – postoperative		Other indications	
		N (135)		*N* (8)		*N* (17)		*N* (38)
SOFA: score								
T1 Mean ± Std [Range]	17.3 ± 3.99 [6–24]	113	10.43 ± 5.47 [6–21]	7	16.88 ± 2.13 [12–21]	16	15.39 ± 4.74 [3–23]	31
T2 Mean ± Std [Range]	17.15 ± 4.75 [3–24]	82	12.71 ± 3.4 [9–19]	7	17.4 ± 1.99 [13–20]	15	14.94 ± 5.5 [4–23]	31
CRP [mg/L]								
T1 Mean ± Std [Range]	166 ± 140 [2–611]	121	72 ± 56 [8–180]	8	70 ± 129 [7–521]	16	136 ± 123 [3–495]	29
T2 Mean ± Std [Range]	161 ± 124 [2–626]	86	142 ± 94 [43–332]	7	115 ± 74 [23–290]	15	135 ± 96 [12–368]	28
PCT [ng/mL]								
T1 Mean ± Std [Range]	40.2 ± 69.3 [0–433]	124	0.1 ± 0.1 [0.0–0.2]	4	24.0 ± 17.1 [1.2–47.3]	12	24.7 ± 40.7 [0.1–179]	22
T2 Mean ± Std [Range]	25.1 ± 55.2 [0.4–443]	88	8.6 ± 16.0 [0.2–44.6]	7	22.1 ± 22.4 [1.7–67.3]	11	9.3 ± 15.5 [0.2–65]	22
IL6 [pg/mL][a]								
T1 Median [Range]	5000 [20–>10^7]	69	45	1	651 [88–5000]	14	531 [85–122,500]	16
T2 Median [Range]	289 [0–5000]	51	124 [41–2232]	7	56 [26–206]	12	97 [0.1–6263]	14
Length of ICU stay [days]								
Mean ± Std [Range]	34.9 ± 32.3 [2–165]	49***	6.2 ± 2.9 [3–11]	6***	13.9 ± 4.2 [7–21]	11***	30.2 ± 24 [4–116]	26***
Number (%) of deaths[b]	88 (65.2%)	135	1 (12.5%)	8	5 (29.4%)	17	12 (31.6%)	38

T1 = maximal values 24 h before CytoSorb treatment; T2 = maximal values 24 h after CytoSorb treatment, *Std* standard deviation

[a]IL6 values measured outside the predefined 1 h interval included

[b]Patients with unknown outcome at database closure have been counted as (still) alive

of 29%. Treating physicians rated the condition as very much/much improved in 53%, as minimally improved in 29%, and as no change in 12%.

Other indications

Patients treated in other indications had a mean APACHE II score of 25.5 ± 8.9 [9–51] (26/38 patients) with a predicted mortality of 54% and an observed mortality of 32%.

Treating physicians rated the condition as very much/much improved in 58%, as minimally improved in 13%, as no change in 10%, and as minimally worse in 3%.

Summary and Interpretation

This third interim report demonstrates the feasibility of the registry with excellent data quality and completeness from twenty study centers. The results must be interpreted with caution, since the numbers are still small; however disease severity is remarkably high and suggests that the adsorber treatment might be used as an ultimate treatment in life-threatening situations. The observed mortality is lower than predicted, but the numbers are too small to draw conclusions. There were no device-associated side effects. However, the duration of treatment with a single adsorber was relatively pronounced, and blood flow rate was low, factors which might be improved in order to increase the clinical efficacy of the device.

Corresponding address

Univ.-Prof. Dr. F. M. Brunkhorst
Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital
Erlanger Allee 101, 07747 Jena, Germany
Frank.Brunkhorst@med.uni-jena.de

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Compliance with ethical guidelines

Conflict of interest. F. Bach, R. Bogdanski, F. Born, E. Grigoryev, H. Haake, D. Jacob, J.T. Kielstein, A. Meier-Hellmann, F. Nestler, M. Nitsch, D. Olboeter, M. Schott, M. Singer and D. Tomescu declare that they have no competing interests. A. Baumann reports grants, personal fees and nonfinancial support from Cytosorbents GmbH, personal fees and nonfinancial support from Diamed GmbH, nonfinancial support and other from Orion Pharma, nonfinancial support and other from MSD Pharma, outside the submitted work. F.M. Brunkhorst reports grants and personal fees from CytoSorbents Europe. S. Friesecke reports grants, personal fees and nonfinancial support from cytosorbents Europe. J. Kellum reports grants and personal fees from Cytostorbenets, outside the submitted work. K. Kogelmann reports grants from Cytostorbenets, outside the submitted work. Z. Molnar reports personal fees from CytoSorbents Europe. A. Nierhaus reports personal fees from CytoSorbents Europe, Personal fees from Biotest AG, outside the submitted work. M. Quintel reports personal fees from Cytosorbent, outside the submitted work. G.A. Schittek reports personal fees from Cytosorbents Europe GmbH, outside the submitted work. U. Schumacher reports personal fees from BAYER, outside the submitted work (part time employee). K. Träger reports personal fees and other from Cytosorbents Europe. A. Weyland reports personal fees and other from CytoSorbents Europe GmbH, outside the submitted work.

This study protocol has been submitted to the Institutional Review Board of the Faculty of Medicine at Friedrich Schiller University, Jena that acts as the IRB in charge for Germany. All German ethic committees involved are informed about the participation of centers in their area of responsibility and the decision of the IRB in charge. In centers from outside Germany, approval of the local ethics commission in charge is obtained and all national regulations are adhered to.

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