CytoSorb Therapy: Evidence in septic and vasoplegic shock
1st Edition

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## CASE REPORTS

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Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study

Hawchar F, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z
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Summary
The aim of this proof of concept, prospective, randomized pilot trial was to investigate the effects of extracorporeal cytokine removal with CytoSorb applied as a standalone treatment in hemoperfusion mode in 20 patients with early (<24hrs) septic shock. Further inclusion criteria were: on mechanical ventilation; norepinephrine >10 μg/min; procalcitonin (PCT) >3 ng/mL; and without need for renal replacement therapy (RRT). Patients were randomized into a CytoSorb (n=10) for 24 hrs or control group (n=10). Clinical and laboratory data were recorded at baseline, 12, 24 and 48 hrs. Overall SOFA scores did not differ between the groups, however, in the CytoSorb group norepinephrine requirements and PCT as well as Big-endothelin-1 concentrations decreased significantly. All patients in the CytoSorb group survived to 48 hrs (2 patients in the control group died before the 48 hrs period). The authors note that the level of norepinephrine dose for the CytoSorb group was almost twice that of the controls at study entry. There were no CytoSorb therapy-related adverse events. This is the first trial to investigate the effects of early extracorporeal cytokine adsorption treatment in septic shock patients, used without RRT. CytoSorb was found to be safe, with significant effects on norepinephrine requirements, PCT and Big-endothelin-1 concentrations compared to controls.

Study design & patient collective
- Proof of concept, prospective, randomized pilot trial in 20 patients with early (<24hrs) septic shock treated with CytoSorb or control group (10 vs. 10)
- Inclusion criteria: Intubated, mechanically ventilated patients with suspected septic shock of medical origin; norepinephrine >10 μg/min; elevated lactate >2.0 mmol/L, and procalcitonin (PCT) >3 ng/mL concentrations; and without the need for RRT. Inclusion after at least 6 hours of resuscitation and antibiotic therapy, when there was no improvement as indicated by steady or increased norepinephrine requirements. Study treatment within the first 24 hrs after ICU admission or the onset of septic shock
- Patients fulfilling entry criteria were randomized into CytoSorb or control groups (10 vs. 10)
- Diagnoses in CytoSorb group: pneumonia (7), pancreatitis (1), toxic shock syndrome (1), urosepsis (1)
- Diagnoses in control group: pneumonia (6), meningococcal sepsis (2), cholangiosepsis (1), dermatomyositis (1)
- Patients in both groups received standard treatment according to the institutional adaptation of the Surviving Sepsis Guidelines
- All patients received advanced hemodynamic PiCCO monitoring

Treatment
- Patients in the CytoSorb group received a hemodialysis catheter inserted into a central vein (femoral, subclavian or internal jugular, as appropriate)
- CytoSorb was placed in a blood pump circuit using a renal replacement device (MultiFiltrate, Fresenius Medical Care, Bad Homburg, Germany)
- Blood flow rate: 250–400 mL/min
- Anticoagulation: heparin

Measurements
- Baseline characteristics
- Measurements were performed right after inclusion (control group) or after the start of CytoSorb therapy (T0), then 12, 24 and 48 hrs later (T12, T24, T48)
- Hemodynamic parameters: mean arterial pressure (MAP), heart rate (HR), cardiac index (CI) and pulse pressure variability (PPV), extravascular-lung water index (ELWI), systemic vascular resistance index (SVRI) and norepinephrine requirement
- Volume status: cumulative i.v. fluid and fluid balance
- Blood gas analysis: lactate, ScvO2, PaO2/FiO2
- Inflammation: C-reactive protein (CRP), procalcitonin (PCT), Big-endothelin-1 (BigET-1)
- Sequential Organ Failure Assessment (SOFA) scores
- ICU length of stay
- Safety, adverse events

Results
- No significant difference between CytoSorb and control groups regarding age, body mass index, days spent on the ICU and APACHE II scores
- Hemodynamics:
  - No significant differences between groups for MAP, HR, CI and PP
  - ELWI was higher in the CytoSorb group and showed decreasing tendencies in both groups
  - SVRI showed an increasing trend in the CytoSorb group during treatment while it decreased gradually in the control group until T24

CONCLUSIONS
- This is the first randomized controlled trial, in which extracorporeal cytokine adsorption treatment using CytoSorb was tested in hemoperfusion mode only
- CytoSorb was found to be safe with significant positive effects on norepinephrine requirements, PCT and Big-endothelin-1 concentrations compared to controls
- The lack of a significant difference in the SOFA scores may at least in part be explained by the existing treatments and a longer observation period
- The study further emphasizes the need for the early start of CytoSorb therapy, as the positive impact of CytoSorb treatment was achieved in patients who all had an early start of treatment within the first 24 hrs after the onset of septic shock
- This publication once again supports the high safety level of CytoSorb therapy in general, but also this time particularly as a stand-alone treatment, without the parallel presence of RRT
- Results may provide important support and guidance to future protocol designs and can help to define the appropriate study end points and sample size calculations of future clinical trials
The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial

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Summary
This was a randomized, controlled, open-label, multicenter trial, conducted from 2008 to 2011, that reported on the use of CytoSorb for 6 hrs daily for 7 days in 97 mechanically ventilated patients with severe sepsis or septic shock and acute lung injury or acute respiratory distress syndrome. The study was planned and powered to show safety and efficacy in terms of cytokine removal. The study was not able to detect differences in systemic plasma interleukin (IL)-6 levels on day 7 between the two groups (p = 0.15) although significant IL-6 elimination, averaging between 5 and 18% per blood pass throughout the entire treatment period on day 2 was recorded. There was also no statistically significant difference in the secondary outcomes multiple organ dysfunction score, ventilation time and time course of oxygenation. Of note, the proportion of patients receiving renal replacement therapy at the time of enrollment was much higher in the treatment group (31.9%) compared to the control group (16.3%), indicating a more severe disease state of patients in the treatment group.

Study design & patient collective
- Randomized, controlled, open-label, multi-center trial conducted in 10 German study sites from 2008 to 2011
- Included were mechanically ventilated patients with severe sepsis or septic shock in the setting of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) established within the previous 72 hrs
- Patients were randomly assigned to be treated either with standard care therapy and CytoSorb hemoperfusion for 6 hrs per day, up to seven consecutive days (treatment group) or to standard care therapy alone (control group)
- Manual randomization (time duration of 11 months effecting the randomization of n=32 patients) was switched to an electronic system following a randomization from the independent data monitoring and safety board

Treatment
- In the treatment group, the CytoSorb cartridge was either used alone in hemoperfusion mode or, if renal replacement therapy was clinically indicated, inserted proximally into a conventional continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF) circuit
- Target blood flow rates: 200–250 mL/min
- Anticoagulation: either regional citrate or systemic heparin anti-coagulation with a target partial thromboplastin time (PTT) of 60–80 seconds, or an activated clotting time (ACT) of 180–210 seconds
- Administration of antibiotics was recommended after CytoSorb treatment where possible
- Hemoperfusion was stopped earlier if patients were successfully weaned from mechanical ventilation

Measurements
- Primary endpoint: reduction in IL-6 serum concentrations to day 7, while on study day 2 five additional blood samples were drawn during hemoperfusion for IL-6 elimination kinetic analyses pre and post adsorber (T0, start of treatment; T15, 15 minutes after start of treatment; T60, 60 minutes after start of treatment; T180, 180 minutes after start of treatment; T360, 360 minutes after start of treatment)
- Secondary endpoints: ventilation time, 28-day all-cause mortality, oxygenation index, P/F-ratio and multiple organ dysfunction score (MODS), levels of chemokine ligand 2 (CCL2), CCL3, Interferon-γ (IFN-γ), IL-1β, IL-1α, IL-4, IL-8, IL-10, tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF), CD4+ T cell activation

Results
- In total 100 patients were enrolled and 97 patients were included in the analysis
- The majority of patients on enrollment had septic shock (96% control, 91.5% treatment) and ARDS (44% control, 70.2% treatment)
- There was significant IL-6 elimination, averaging between 5 and 18% per blood pass throughout the entire treatment period on day 2, however the study was not able to detect differences in systemic plasma IL-6 levels on Day 7 between the two groups (n = 75; p = 0.15)
- There was also no statistically significant difference in the secondary outcomes multiple organ dysfunction score, ventilation time and time course of oxygenation

Figure 1: CD4-cell-activation for control (grey boxes) and treatment group (white boxes) on different study days. Values > 1000 are evaluated as 1000, values <1 as 1.

Figure 2: IL-6 elimination (calculated as difference between arterial and venous IL-6 values) in the treatment group studied during the kinetic day (day 2) where IL-6 measurements were performed before the start of the study intervention (T0), 15 minutes (T15), 60 minutes (T60), 180 minutes (T180) and 360 minutes (T360) after the start of hemoperfusion.

CONCLUSIONS
- This is the first multicenter randomized controlled study investigating the effect of CytoSorb in a cohort of patients with primarily septic shock, ARDS, and multi-organ failure
- The primary aim of the study was to show the safety and efficacy of the CytoSorb cartridge and both aims of the study were reached. In this regard, CytoSorb appeared to be safe (no interruption of therapy necessary due to technical problems, no clotting, no significant impact on albumin, platelets and mortality) and its application led to a substantial removal of IL-6 by the adsorber in a severely ill patient population
- Of note, all the differences in outcome have to be interpreted in the light of the inhomogenous distribution of patients between the treatment and the control groups, with patients in the CytoSorb group being much sicker and already at a higher risk of death at time of inclusion into the study (with almost double the incidence of renal failure)
- Future studies should investigate safety of the device and be powered to evaluate clinical endpoints such as mortality
Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study

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Summary
Twenty consecutive patients with refractory septic shock (unresponsive to standard treatment) were included in this prospective study. CytoSorb treatment was started after 7.8 ± 3.7 hrs of shock therapy. Following the initiation of adsorption therapy, noradrenaline dose could be significantly reduced after 6 (p<0.03) and 12 hrs (p<0.001). Shock reversal was achieved in 13 (65%) patients; 28-day survival was 45% (predicted mortality rate is >80%). The use of CytoSorb adsorption therapy resulted in shock reversal in two thirds of these particularly difficult to treat patients.

Study design & patient collective
• Sepsis is the most common cause of death in medical intensive care units (ICU). If sepsis progresses to refractory shock, mortality may reach 90-100% despite optimum therapy
• In this study extracorporeal CytoSorb adsorption in addition to regular therapy was studied prospectively in 20 patients with refractory septic shock
• Noradrenaline was administered to achieve a mean arterial pressure (MAP) ≥65 mmHg.
• Dobutamin was given if the cardiac index (CI) was ≤3.0 l/min/m² and signs of shock persisted.
• Hydrocortisone was administered at the discretion of the attending physician
• Renal replacement therapy (Multifiltrate, Fresenius Medical Care, Germany) for acute renal failure was performed either as continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodialysis (CVVHD) at the discretion of the attending physician

Treatment
• CytoSorb was started after the diagnosis of refractory shock
• Flow rates were set to achieve a dialysis dose of 25 ml/kg/h
• Anticoagulation was performed with either heparin or citrate according to the local standard operating procedure
• The adsorber was connected in a pre-filter position
• The first exchange was performed within 24 h without interruption. Further adsorber exchanges were at the discretion of study physicians

Patient Follow-Up
• Shock reversal was achieved in 13 patients (65%) as seen by the decrease in noradrenaline requirements and an increase in lactate clearance
• Seven patients died from refractory shock. Four of the shock survivors died from other causes after shock reversal
• Despite the predicted mortality of the included patients being very high (>80%) according to the SOFA score, 9 patients (45%) survived to 28 days
• Time to shock reversal was 167 ± 84 hrs

Measurements
• Levels of noradrenaline 6 and 12 hrs after the start of CytoSorb
• Levels of lactate clearance
• Severity of Organ Function Assessment (SOFA) scores

Results
• CytoSorb treatment was started 7.8 ± 3.7 hrs after the start of shock therapy
• In 12 patients the noradrenaline dose could be reduced during the first 6 hrs of CytoSorb treatment. One patient died within the first 6 hrs. In 5 patients the decrease of noradrenaline demand began 6-12 hrs after the start of CytoSorb adsorption and in two patients the noradrenaline dose had to be increased
• Overall, the mean noradrenaline dose could be significantly reduced after 6 (-0.4 µg/kg/min; p<0.03) and 12 hrs (-0.6 µg/kg/min; p<0.001)
• Lactate clearance improved significantly. The initially high interleukin (IL)-6 concentrations could also be reduced. SOFA-scores on day 0, 1 and 2 remained unchanged
• Antibiotic doses were adapted so that at the start of CytoSorb, and at each adsorber replacement, one additional dose of the prescribed betalactam was administered. For patients on vancomycin, one extra gram was given at CytoSorb initiation. Subsequent doses were guided by drug levels
• A mean of 3.0±1.5 adsorbers per patient were used. Two patients were treated with only one adsorber because of early death

CONCLUSIONS
• This is the first prospective study showing the benefit of rescue therapy with CytoSorb in this extremely sick group of patients with severe septic shock unresponsive to standard treatment who generally have a mortality rate of up to 100%
• Until now there have been no evidence-based therapeutic options for these patients
• The use of CytoSorb adsorption therapy resulted in shock reversal in two thirds of these particularly difficult to treat patients
• Lactate clearance improved significantly
• Mortality in these patients was lower than predicted mortality rate (28-day survival was 45% compared to a predicted mortality from the SOFA score >80%)

Figure 1: Noradrenaline dose before and during treatment with CytoSorb. Values are shown as means with 95% CIs. Difference vs. “hrs 0” (CytoSorb start): *p<0.05, **p<0.01, ***p<0.001. Initial and start n=20, hrs 6, 12 and 18 n=19, hrs 24 n=18

Figure 2: Lactate clearance before and during treatment with CytoSorb. Values are shown as means with 95% CIs. Difference vs. “hrs -6 -0” (6 hrs before CytoSorb start): *p<0.05, **p<0.01, n.s. not significant
International registry on the use of the CytoSorb® adsorber in ICU patients: Study protocol and preliminary results

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2 Affiliations not listed for reasons of space
3 Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital.
Med Klin Intensivmed Notfmed 2017; epub

Summary
This is the third interim analysis from the CytoSorb clinical registry where the aim is to record the use of CytoSorb adsorbers in critically ill patients under real-life conditions. It records all relevant information in the course of product use, including diagnosis, comorbidities, course of the condition, treatment, concomitant medication, clinical laboratory parameters, and outcome. 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). 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, however IL-6 levels were markedly reduced after treatment, however IL-6 levels were markedly reduced after treatment (median 5000 pg/ml before and 289 pg/ml after treatment).

Patients treated for other indications had a mean age of 60.3 +/- 15.1 years. Patients with sepsis were predominantly males (68.2%) patients were male. Treating physicians rated the condition as very much/much improved in approximately 50% of cases and reported a very favorable safety profile with no device-associated side effects.

Measurement
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

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, C-reactive protein (CRP), procalcitonin (PCT), myoglobin, free hemoglobin
- Length of hospital and ICU stay (days)

Results from the 3rd interim report
- Baseline characteristics
  - 135 (80.2%) patients were male
  - Mean age was 60.3±15.1 years. Patients with preemptive CytoSorb use in cardiac surgery and other indications were slightly younger (58.6±13.6 and 53.2±7.8, 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 admitted for non-surgical emergency reasons (91 [46.0%]), surgical emergency for 70 (35.4%) and elective surgery for 37 (18.7%) of the patients.

- Exposure 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 hrs for the sepsis group (N=134), 8.3±13.8 hrs for patients with preemptive use in cardiac surgery (N=8), 45.3±23.3 hrs for patients with postoperative use in cardiac surgery (N=16), and 60.8±48.8 hrs for patients with other indications (N=37).
- A single adsorber was used on average for 22.2±15.3 hrs; the range of duration for a single adsorber was 15 min to 105 hrs
Continuation: International registry on the use of the CytoSorb® adsorber in ICU patients: Study protocol and preliminary results

Figure 1: Subjective, semiquantitative assessment of the treatment result after the application of CytoSorb

CONCLUSIONS

- 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.

Table 1: Baseline characteristics of patients according to indications for CytoSorb treatment as well as predicted and actual mortality

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<th>Parameter</th>
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<th>Cardiac surgery – postoperative</th>
<th>Other indications</th>
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<tr>
<td>Mean ± Std [Range]</td>
<td>N (135)</td>
<td>N (8)</td>
<td>N (17)</td>
<td>N (38)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.5 ± 14.1 [22–92]</td>
<td>58.6 ± 13.6 [37–77]</td>
<td>67.2 ± 12.2 [44–84]</td>
<td>53.2 ± 17.8 [21–84]</td>
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<td>APACHE II score</td>
<td>33.1 ± 8.4 [15–52]</td>
<td>n.a.</td>
<td>22.1 ± 7.3 [2–33]</td>
<td>25.5 ± 8.9 [9–51]</td>
</tr>
<tr>
<td>APACHE II predicted mortality [%]</td>
<td>77.6 ± 20.7 [23–99]</td>
<td>n.a.</td>
<td>31.4 ± 18.2 [0–72]</td>
<td>54.1 ± 29.0 [9–96]</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>74.3 ± 16.8 [29–107]</td>
<td>n.a.</td>
<td>50.1 ± 13.2 [27–75]</td>
<td>61.9 ± 17.7 [30–97]</td>
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<tr>
<td>SAPS II predicted mortality [%]</td>
<td>81.0 ± 20.3 [10–99]</td>
<td>n.a.</td>
<td>46.3 ± 23.8 [8–89]</td>
<td>65.0 ± 28.0 [11–98]</td>
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<td>Number (%) of deaths* (actual mortality)</td>
<td>88 (65.2%)</td>
<td>1 (12.5%)</td>
<td>5 (29.4%)</td>
<td>12 (51.6%)</td>
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*Patients with unknown outcome at database closure have been counted as (still) alive.
Use of hemoadsorption in sepsis-associated ECMO-dependent severe ARDS: A case series

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Journal of Intensive Care Society 2019; epub

CASE SERIES

Summary
This case series included seven consecutive patients admitted to the ICU with septic shock and acute respiratory distress syndrome (ARDS) who were treated with combined therapy of CytoSorb, continuous renal replacement therapy (CRRT) and veno-venous extracorporeal membrane oxygenator (VV-ECMO). On admission to ICU patients had an APACHE II score of 39 (predicted mortality rate of 90.8%). All patients received at least 3 CytoSorb treatments (average 24 hrs per adsorber) installed into the CRRT depending on their clinical response. The combined treatment for these patients was associated with a significant stabilization in hemodynamics and a clear reduction in hyperlactatemia. Patients also showed a significant improvement in lung function and ventilation invasiveness. Additionally, severity of illness and overall organ dysfunction showed a considerable decrease during the course of the combined treatment while observed mortality was only half that predicted by APACHE II. The authors conclude that CytoSorb might represent a potentially promising therapy option for patients with refractory ECMO-dependent ARDS in the context of septic shock. There were no CytoSorb device related adverse events or problems running the adsorber in conjunction with the two additional extracorporeal treatments.

Patient collective
- Seven consecutive patients with the diagnosis of septic shock due to pneumonia in combination with severe ARDS
- Inclusion criteria: known or suspected infection meeting the following criteria within a 24 hrs period: 3 or more signs of systemic inflammation and sepsis induced dysfunction of at least two organs or organ systems. Initial therapy followed the Surviving Sepsis Guidelines
- Criteria for severe ARDS had to be met following the Berlin definition. Initial ventilation was performed in a lung-protective manner including prone positioning for at least 16 hrs. If the initial ventilation settings failed to increase the Horovitz index above 150 mmHg after 24 h, VV-ECMO was indicated and installed
- One of the organ failures had to be acute kidney injury with the need for CRRT
- Criteria had to be fulfilled despite maximum standard therapy including adequate fluid resuscitation (following KDIGO guidelines), differentiated catecholamine therapy, antibiotics at least 1 hr after detection of septic shock and lung protective ventilation
- If there was no decrease of norepinephrine demand even after an additional corticoid treatment and if the patient met minimum AKI stage II (serum creatinine 2.0–2.9 times baseline, urine output <0.5 ml/kg/h for ≥12 hrs), CRRT in combination with CytoSorb therapy was initiated

Treatment
- Patients received a minimum of three treatments with CytoSorb with additional treatments according to the intensivist’s judgment. Adsorbers were changed every 24 hrs, or every 12 hrs if there was no or only a marginal effect (decrease of <30% in catecholamine-demand within the first 24 hrs of CytoSorb application)
- CytoSorb was not installed at any time into the VV-ECMO circuit and was run only in conjunction with a separate CRRT circuit and used in continuous venovenous hemodialysis (CVVHD) mode (Multifiltrate CiCa, AV1000 Fresenius Medical Care)
- Median number of CytoSorb treatments was 3 (range 3–7), median treatment time equaled 24 hrs per adsorber
- Blood flow rate: 100 - 150 ml/min
- Anticoagulation: citrate
- CytoSorb adsorber position: pre-hemofilter

Measurements
- SAPS-2 score, SOFA score, demand for norepinephrine to achieve a certain mean arterial pressure (NOR/MAP) (µg/h/mmHg²) before (pre) and after (post) as well as blood lactate levels (mg/dl) before (pre) and after (post) treatment.

Results
- Data from seven consecutive patients suffering from sepsis of medical etiology (mainly pneumonia) who were treated with the combined therapy of CytoSorb, CRRT, and ECMO fulfilling inclusion criteria were evaluated
- On admission to ICU, the median APACHE II score was 39, with a calculated predicted mortality of 90.8%. Decrease in SAPS II (12.2%) and SOFA-scores (14.3%) was observed when comparing pre and post treatment
- Clear stabilization in hemodynamics as demonstrated by a marked decrease in catecholamine need, which was reduced from a median of 41.6 pre-treatment to 8 mg/h/mmHg² post-treatment (81% reduction)
- 36% decrease in blood lactate levels when comparing median levels before (22 mg/dl) and after (14 mg/dl) treatment
- 30% reduction in PEEP comparing pre- and post-treatment levels (from a median of 17 to 12 cm H2O). Increase in Horovitz index (PaO2/FiO2) by 117% (pre 89 mmHg to post 194 mmHg). Pmax was reduced from a median of 32 to 22 mbar (32% reduction)
- Observed mortality (42.85%, 3 of 7 patients) was approximately half that predicted by APACHE II (90.8%)
- No CytoSorb device-related adverse events or problems running the adsorber in conjunction with the two additional extracorporeal treatments

CONCLUSIONS
- This is the first case series on the use of CytoSorb therapy in critically ill patients with septic shock, ARDS, and need for VV-ECMO as well as renal replacement therapy
- Combined treatment was associated with a significant stabilization of hemodynamics, a clear reduction in hyperlactatemia and a significant improvement in lung function and invasiveness of ventilation
- Severity of illness and overall organ dysfunction showed a considerable decrease during the course of the combined treatment, while observed mortality was only half that predicted by APACHE II
- Therefore, CytoSorb might represent a potentially promising therapy option for patients with refractory ECMO-dependent ARDS in the context of septic shock, which needs to be validated in well-designed future trials
CASE SERIES

Blood Purification With CytoSorb in Critically Ill Patients: Single-Center Preliminary Experience


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Artif Organs 2019; 43(2): 189 - 194

Summary

In this retrospective case series study in 40 critically ill cardiac surgery patients with multiple organ failure, the use of CytoSorb therapy inserted into either the extracorporeal membrane oxygenation (ECMO) circuit (19 pts), or as standalone hemoperfusion (21 pts) was evaluated for clinical outcomes. The series included patients in the Cardiac Surgery ICU with cardiogenic shock (28 pts), septic shock (2 pts), acute respiratory distress syndrome (ARDS - 9 pts), and liver failure (1 pt). Nineteen of the patients underwent ECMO, 11 had an intra-aortic balloon pump, 9 an Impella, and 6 had a ventricular assist device. Patients received at least one CytoSorb treatment (median number of adsorbers used 2). After CytoSorb treatment, total bilirubin, lactate, Creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) all decreased significantly as did the vasoactive-inotropic score. Thirty-day mortality was 55% and ICU mortality was 52.5% with an expected ICU mortality of 80% according to the sepsis-related organ failure assessment (SOFA) score. This case series shows that CytoSorb treatment is effective in reducing bilirubin, lactate, CPK and LDH in critically ill cardiac surgery patients most of whom had cardiogenic shock. No device related adverse events were observed.

Patient collective

• Retrospective case series in 40 consecutive critically ill cardiac surgery patients with multiple organ failure (MOF) who received CytoSorb treatment
• Treatment was started following clinical judgment by the treating physician who assessed severity of MOF and inflammatory status, sepsis-related organ failure assessment (SOFA) score. This case series shows that CytoSorb treatment is effective in reducing bilirubin, lactate, CPK and LDH in critically ill cardiac surgery patients most of whom had cardiogenic shock. No device related adverse events were observed.

Treatment

• CytoSorb therapy was inserted into either the extracorporeal membrane oxygenation (ECMO) circuit (19 pts), or as standalone hemoperfusion procedure (21 pts)

Measurements

• Vasoactive-inotropic score (after 48 hrs of treatment vs. baseline)
• Laboratory data (total bilirubin, lactate, creatine phosphokinase (CPK), lactate dehydrogenase (LDH)) were collected daily during ICU stay and peak values were compared to those measured at the end of CytoSorb treatment
• Hospital and ICU stay
• Safety, adverse events, technical feasibility

Results

• Significant reduction of the vasoactive-inotropic score after 48 hrs of treatment as compared to baseline (20 vs. 10)
• Values of total bilirubin, lactate, CPK and LDH were significantly reduced after CytoSorb treatment. There was no reduction in bilirubin values in patients with a total bilirubin ≤10 mg/dl while values of total, direct, and indirect bilirubin could be significantly reduced in patients with total bilirubin levels ≥10 mg/dl
• Hospital stay was 37±36 days and ICU stay 18±16 days
• Eight patients died during the CytoSorb treatment which equaled a 30-day mortality of 55% and an ICU mortality of 52.5% (compared to the expected mortality of 80%)
• No device-related adverse events were observed

Table 1: Laboratory values of 16 patients with total bilirubin ≥ 10 mg/dL

<table>
<thead>
<tr>
<th>Values</th>
<th>Baseline</th>
<th>End of treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>17.1 ± 5.0</td>
<td>10.8 ± 5.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>14.1 ± 4.7</td>
<td>8.9 ± 4.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Indirect bilirubin (mg/dL)</td>
<td>3.0 ± 1.8</td>
<td>1.8 ± 1.2</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Table 2: Peak and end treatment values - CPK, creatine phosphokinase; LDH, lactate dehydrogenase

<table>
<thead>
<tr>
<th>Values</th>
<th>Peak during treatment</th>
<th>End of treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>11.6 ± 9.2</td>
<td>6.8 ± 5.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>12.1 ± 8.7</td>
<td>2.9 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPK (U/L)</td>
<td>2416 (670–8615)</td>
<td>281 (44–2769)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1230 (860–3157)</td>
<td>787 (536–1148)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• This is the largest case series to date of very sick patients (SOFA score 15) with MOF receiving multiple extracorporeal supports including CytoSorb.
• Results emphasize that CytoSorb treatment is effective in reducing bilirubin, lactate, CPK and LDH, in critically ill cardiac surgery patients most of whom had cardiogenic shock.
• The value of CytoSorb hemoadsorption therapy is further strengthened by clinically relevant end points observed in this study, such as the reduction in vasoactive-inotropic score and the lower than expected mortality.
• However, there is a need for randomized controlled trials to provide more information on the potential benefits of blood purification with CytoSorb in critically ill patients.
Effect of hemoadsorption for cytokine removal in pneumococcal and meningococcal sepsis


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Case Reports in Critical Care 2018; 120561

Summary
In this case series five patients with pneumococcal (n=2) or meningococcal sepsis (n=3) were treated with a CytoSorb adsorber for cytokine removal. In these patients bacteria enter the blood stream, proliferate and provoke an immune and inflammatory reaction which may rapidly lead to fulminant septic shock. These bacteria may also cross the blood brain barrier causing bacterial meningitis. Due to the severity of the disease process including coagulation disorders, poor outcome, typically including necessity for extensive amputation of extremities, and a high mortality rate is not uncommon. All patients showed progressive stabilization in hemodynamics along with rapid and marked reduction of catecholamine dosages, stabilization in metabolic disorders and less than expected loss of extremities. None of the patients died within the first 28 days. In these patients, use of CytoSorb for cytokine removal seemed to be a valid and safe therapy in the management of meningococcal and pneumococcal diseases and may contribute to patient stabilization and prevention of severe sequelae.

Patient collective
- Presentation of five patients with pneumococcal (n=2) or meningococcal sepsis (n=3)
- All patients were empirically treated with broad-spectrum antibiotics and steroids without change in dosage
- CytoSorb treatment was initiated early between 8 and 24 hrs after initial diagnosis
- Therapy was continued until catecholamine demand drastically decreased or was stopped and until an important reduction in lactate levels was observed

Treatment
- Hemoadsorption treatments were performed for 24 hrs, except for two cases in which the system had to be re-set up after 12 hrs due to severe coagulative disorders of the patients

- All the CytoSorb treatments were performed in combination with continuous renal replacement therapy (CRRT)
- Blood flow rate: 100-180 ml/min
- Dialysis dose: 30 and 35 ml/kg/h
- Anticoagulation: citrate

Measurements
- Hemodynamics and catecholamine requirement (epinephrine, norepinephrine)
- Inflammatory mediators (Procalcitonin PCT, Interleukin (IL)-6)
- Metabolic disorders (lactate)
- Loss of extremities
- 28-day survival
- Safety, adverse events

Results
- All patients showed progressive stabilization in hemodynamics along with rapid and marked reduction of catecholamine dosages
- Impressive reduction of PCT and of IL-6 (IL-6 was only measured in one patient)
- Stabilization in metabolic disorders as seen by a consistent decrease in lactate levels
- All patients also showed a stabilization in coagulation parameters, showing attenuation of the embolic septic status
- Less than expected loss of extremities
- None of the patients died within the first 28 days
- The combined treatment of CRRT and CytoSorb was well tolerated in all patients

CONCLUSIONS
- This is the first report on the successful use of hemoadsorption for cytokine removal therapy in a set of patients with meningococcal and pneumococcal sepsis
- Use of CytoSorb seemed to be a valid and safe therapy in the management of meningococcal and pneumococcal sepsis and may contribute to patient stabilization and prevention of severe sequelae.
- Importantly, despite the commonly occurring coagulation disorders often leading to extensive amputations, the authors noticed only minor loss of extremities in three patients (some phalanges and one toe) and even no need for amputation at all in one patient
- After these promising initial data, solid proof of efficiency is needed for CytoSorb implementation in a larger cohort
Hemoadsorption by CytoSorb in septic patients – a case series

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Summary
In this case series the authors evaluated the impact of CytoSorb, used as adjunctive therapy, on hemodynamics and clinically relevant outcome parameters in 26 critically ill patients with septic shock and need for renal replacement therapy. Treatment of these septic shock patients was associated with hemodynamic stabilization and a reduction in blood lactate levels. Actual mortality was lower than that predicted by the APACHE II score. This effect was more pronounced in patients where therapy was started within 24 hrs after the diagnosis of sepsis. Medical patients seemed to benefit more than post surgical patients in terms of survival. Treatment with the CytoSorb was safe and well tolerated with no device related adverse events during or after the treatment sessions.

Case presentation
• Patients were eligible for inclusion if they had known or suspected infection and if they met the following criteria within a 24 hrs period: 3 or more signs of systemic inflammation and sepsis induced dysfunction of at least two organs or organ systems
• Initial therapy followed the Surviving Sepsis Guidelines. One of the organ failures had to be acute kidney injury (AKI) with the need for renal replacement therapy
• These criteria had to be fulfilled despite maximum standard therapy including adequate fluid resuscitation (following KDIGO guidelines), differentiated catecholamine therapy including administration of norepinephrine to achieve a mean arterial pressure (MAP) ≥60 mmHg, antibiotics at least 1 hr after detection of septic shock and lung protective ventilation
• If there was no decrease of norepinephrine demand even after an additional corticoid treatment and if the patient met minimum AKI stage II (serum creatinine 2.0–2.9 times baseline, urine output <0.5ml/kg/h for ≥12 hrs) continuous renal replacement therapy (CRRT) in combination with CytoSorb therapy was initiated

Treatment
• Patients received a minimum of one treatment with CytoSorb. Adsorbers were changed every 24 hrs or every 12 hrs if there was no or only a marginal effect within a certain amount of time (defined as <20% decrease of catecholamine demand within 24 hrs)

• Treatment was continued until need for catecholamine demand ceased, or there was a reversal in shock (defined as a decline in catecholamine demand to 10% of the initial dose prior to treatment start)
• CytoSorb was used in CVVHD mode (Multifiltrate CiCa, AV1000 Fresenius Medical Care)
• Blood flow rate: 100 - 150 ml/min
• Anticoagulation: citrate
• CytoSorb adsorber position: pre-hemofilter

Measurements
• SAPS-2 score, SOFA score, APACHE II score, demand for norepinephrine to achieve a certain MAP, lactate levels before and after each CytoSorb treatment
• Catecholamine-free days (in relation to ICU days)
• Three time periods were defined (time delay from sepsis diagnosis to start of therapy up to 24 hrs, between 24 – 48 hrs or more than 48 hrs)

Results
• 26 consecutive patients fulfilled the inclusion criteria (post-surgical: 13, pneumonic: 13). Patients had a median APACHE II score of 35 with a predicted mortality rate of 89.9%. Importantly, the actual 28-day, ICU and hospital mortality were 61.54%, 73.08% and 80.77%, respectively
• Median number of CytoSorb treatments was 3 (range 1 – 5)
• Vasopressor dose could be reduced during treatment by 67%. The percentage of catecholamine-free days in ICU survivors was 68.29%, non-survivors only spent 7.5% of their ICU stay catecholamine-free
• Blood lactate decreased by 26.4% when pre and post treatment levels were compared
• Both vasopressor and lactate levels showed a sustained reduction even beyond 72 hrs after the last CytoSorb treatment
• SAPS II decreased by 18.1% and SOFA Score decreased by 4.1% when comparing pre and post CytoSorb treatment scores (number of treatments between 1-5)

Measurements

• Shock reversal was observed in 10 patients (38.5%). All patients who survived to day 28 showed a decrease in catecholamine demand to between 0–29.2% of the pre-adsorber levels, irrespective of the initial level of catecholamine. Hospital survival was also higher in this group. Non-survivors showed no reduction in vasopressor demand, even if their initial catecholamine demand was lower

Patient Follow-Up
• Non-survivors had a greater delay in the start of therapy (>48 hrs), were older, and showed a poorer response to therapy in terms of reduction of catecholamine demand. Median start of CytoSorb therapy in hospital non-survivors was much later than in survivors (36 h vs. 24 h). All ICU survivors in the early treated patients left the hospital alive, while none of the patients treated with a delay >48 hrs did
• Hospital mortality in post-surgical patients who started therapy early was 75% (predicted mortality 93.25%) while medical pneumonia patients with early therapy had a hospital mortality of 60% (predicted mortality 87%)

CONCLUSIONS
• This is the first case series reporting the use of CytoSorb therapy in severely ill patients with septic shock from two different origins.
• Treatment of these patients with a combination of CytoSorb and CVVHD was associated with a clear stabilization in hemodynamics and concomitant decrease in vasopressor doses.
• Actual mortality was lower than the mortality predicted by APACHE II. Patients had a median APACHE II score of 35 with a predicted mortality rate of 89.9%. Importantly, the actual 28-day, ICU and hospital mortality were 61.54%, 73.08% and 80.77%, respectively.
• These favorable effects seem to be more pronounced in patients where therapy started within 24 hrs after the septic shock. Therefore, an early start in therapy (preferably within less than 24 hrs after the onset of septic shock) seems to potentially have advantages in terms of survival.
• Treatment using the CytoSorb device was safe and well-tolerated with no device related adverse events during or after the treatment sessions.
First successful hemoadsorption using CytoSorb® in a septic pediatric patient in Kazakhstan: A case report

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Int J Antifur Drugs 2015: epub

Summary
This is the first CytoSorb treatment in Kazakhstan where CytoSorb was used in an 8-month-old patient with a body weight of 5600g. The patient was admitted with acquired severe laryngeal stenosis, chronic tracheal cannulation and protein energy malnutrition after being born at 34 weeks and previously requiring subsequent readmissions for pneumonia and cytomegalovirus infection. The patient underwent balloon dilatation of the larynx however then developed pneumonia, respiratory failure and bacterial and fungal infections. After an eight-day stay in the pediatric intensive care unit, and due to no improvement of the ongoing multi organ failure, continuous venovenous hemodialysis (CVVHD) was started along with CRRT. CytoSorb resulted in a reduction of inflammation markers interleukin (IL)-6, S100, procalcitonin (PCT), and C-reactive protein (CRP). Simultaneously, the level of transaminases, creatine kinase, and troponin were normalized. By the end of the treatment the patient’s hemodynamics were stable, there was no further need for vaspressors, the acid-base balance was maintained, and the patient was weaned from mechanical ventilation and spontaneous breathing. The patient was subsequently discharged to the ward and then home. The authors conclude that CytoSorb treatment was safe and well-tolerated in this very small pediatric patient, easy to use with CVVHD, and has proven its practical value as an adjuvant therapy for sepsis in such populations.

Case Presentation
• A 8-month-old patient with a body weight of 5600 grams was admitted with the diagnosis of acquired severe laryngeal stenosis, chronic tracheal cannulation, and protein energy malnutrition
• Medical history revealed that the patient was born prematurely at 34 weeks of gestation with a weight of 2200g, and that he had required in-hospital treatment for pneumonia and cytomegalovirus infection in regional hospitals four times in the last 6 months
• On day 2 after admission, balloon dilatation was performed under direct suspension laryngoscopy followed by prescription of cefazolin (75 mg/kg per day) according to the clinical protocol
• The following day the patient’s condition worsened with fever and dyspnea
• Medical examination revealed bilateral pneumonia, respiratory failure and fungal-bacterial sepsis (Burkholderia cepacia + Staphylococcus aureus)

MRSA + Candida albicans) resulting in the initiation of antibacterial and antifungal therapy (ceftriaxone 100 mg/kg per day, azithromycin 10 mg/kg per day, and fluconazole intravenously 5 mg/kg). Later, antibiotics were changed to ciprofloxacin (50 mg/kg per day) and vancomycin (45 mg/kg per day) due to continued worsening of the patient’s condition
• After transfer to the pediatric intensive care unit (PICU) he received prolonged mechanical ventilation (APV SIMV mode, RR 40 per minute, VT 38 mL, PEEP 6.0 mmHg, FiO2 40%) with subsequent stabilization over the following days
• However, despite intensive care management with a combination of potent antibacterial and antifungal agents, sepsis progressed with increasingly unstable hemodynamics (blood pressure values 42–23 mmHg) necessitating escalating inotropic support with dopamine up to 7.5 μg/kg/min
• The patient’s condition became extremely severe with multiple organ failure syndrome and acute kidney injury. Eight days after transfer to the PICU, blood examination showed the following: leucocytosis up to 103.0 × 103/l, increased C-reactive protein (CRP) to 6.0 mmHg, S100, procalcitonin (PCT), and C-reactive protein (CRP) necessitating escalating inotropic support with dopamine up to 7.5 μg/kg/min

Treatment
• One treatment with CytoSorb for 36 hrs
• CytoSorb was used in combination with CRRT (Multifiltrate, Fresenius Medical Care) run in CVVHD mode
• Blood flow rate: 56 ml/min, replacement fluid (as predilution only) 250 ml/h
• Ultrafiltration rate: 30 ml/h
• Anticoagulation: prolonged heparinization
• Copeptin: 6–30 IU/kg/h
• CytoSorb adsorber position: the system was installed in series before the KitPaed filter
• Special priming procedure: normal saline was used for priming of the circuit and system testing, prior to connecting the device to the patient normal saline was replaced by red blood cell suspension

Measurements
• Hemodynamic situation
• Inflammatory parameters
• Transaminases, creatine kinase (CK), troponin
• Renal function
• Lung function
• Acid–base balance
• Effect on electrolyte balance

Results
• Clear stabilization of the hemodynamic condition (blood pressure 109/52 mmHg at 36 hrs) accompanied by discontinuation of vasopressor support at the end of the treatment
• Application of CytoSorb therapy resulted in a rapid reduction of inflammatory mediators such as IL-6, S100, PCT, and CRP reaching only slightly raised levels after 36 hrs
• Simultaneously, the level of transaminases, creatine kinase (CK), and troponin normalized

CONCLUSIONS
• Combined application of CVVHD and CytoSorb was associated with rapid hemodynamic and metabolic stabilization with concomitant reduction in vasopressor therapy, a reduction of inflammatory mediators and an improvement in renal and lung function
• CytoSorb treatment was shown to be effective and has proven its practical value as a promising adjuvant therapy for sepsis and related conditions in this population
• CytoSorb was safe, well-tolerated and easy to use with CVVHD in this very small pediatric patient with no adverse side effects during or after the combined extracorporeal support

Figure 1: CytoSorb system installed in the middle of the “drainage” line before the KitPaed filter. (1) Air trap. (2) KitPaed filter (S—0.2 μm) . (3) Ultrafiltration line. (4) Air trap. (5) Replacement solution. CytoSorb was installed before filter (2). Replacement fluid was administrated as predilution, after air trap (1), before the installed CytoSorb.
Successfully treated necrotizing fasciitis using ECLS combined with hemoadsorption device and continuous renal replacement therapy

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2Intensive Care Unit, University Hospital of Angers, Angers, France

Summary
In this case study a 41-year-old patient presented with necrotizing fasciitis and multiorgan failure. Extracorporeal life support (ECLS – veno-arterial - VA) was implemented to compensate for his heart failure (ejection fraction 15%) along with high doses of catecholamines. Due to acute renal failure continuous renal replacement therapy (CRRT) was also started. Despite these treatments the patient continued to deteriorate, so a CytoSorb adsorber was added to the CRRT circuit, in parallel to the ECLS. Two consecutive treatments were run for 24 hours each. After the two sessions catecholamines could be decreased dramatically, and hemodynamic stabilization was observed, along with normalization of lactic acidosis and other blood parameters. This case describes the successful use of CytoSorb with CRRT and ECLS used in combination to overcome a critical phase of septic shock in a young adult patient with necrotizing fasciitis.

Case Presentation
- A previously healthy 41-year-old patient was admitted to the Emergency Department of a secondary hospital
- One week before, he had already complained of digestive symptoms such as nausea and diarrhea, and 1 day prior to admission, the patient had pain in his lower left limb and a swelling that rapidly worsened
- On admission, both clinical and radiological explorations pointed towards an acute infection of the left lower limb, and infection with Streptococci or an intertrigo was proven later. This condition evolved into necrotizing fasciitis (Fournier’s gangrene)
- Antibiotic therapy was initiated with amoxicillin 3x2 g/day, clindamycin 4x600 mg/day, and gentamicin 8 mg/kg/day
- Due to hemodynamic instability, the patient was then transferred to the intensive care unit
- Vital signs reflected hemodynamic failure with an arterial pressure of 75/50 mmHg and tachycardia (130 per minute). The patient clinically presented signs of peripheral hypoperfusion. Arterial blood gas analysis showed a pH of 7.39, PO2 of 106 mmHg, PCO2 of 25.7 mmHg, hyperlactatemia of 4.8 mmol/L, and bicarbonates of 15.2 mmol/L
- He further exhibited acute renal dysfunction with creatinine levels of 109 μmol/L, sodium of 131 mmol/L, and potassium of 4.4 mmol/L
- Lymphocytopenia was also present with 200/mm3 and hematologic analysis showed a prothrombin time of 55% (or 17.4 s) and fibrinogen of 6.13 g/L
- Elevated levels of creatinine kinase (9587 U/L) suggested ongoing rhabdomyolysis
- Over time, the patient developed multiple organ failure (cardiovascular, pulmonary, and renal) with hemodynamic failure and rhabdomyolysis being the most prominent features
- Bedside ultrasound revealed severe global left ventricular dilatation and systolic failure with an ejection fraction of 30% on day 1 and 15% on day 2
- Increased doses of noradrenaline were required (from 0.7 μg/kg/min increasing to 7 μg/kg/min within 3 days) and dobutamine infusion was started
- Despite these treatments, systolic function still decreased and the decision for ECLS installation was made on day 3
- The patient had still not improved despite ECLS therapy with catecholamines doses remaining high (norepinephrine: 5.8 μg/kg/min, dobutamine: 10 μg/kg/min)
- Due to progressing renal failure and further clinical deterioration, CRRT was started and the medical team decided to additionally install a CytoSorb adsorber into the CRRT circuit placed in parallel to the ECLS circuit. 48 hrs after the initial start of ECLS therapy

Treatment
- Two consecutive treatments with CytoSorb were performed for a total treatment duration of 48 hrs (days 5–7)
- CytoSorb was used in conjuction with CRRT run in continuous veno-venous hemofiltration (CVVHDF) mode
- CVVHDF was placed on the venous line of the ECLS circuit after the centrifugal pump for blood inflow and before the oxygenator for blood outflow
- CytoSorb adsorber position: pre-hemofilter
- Setup was technically easy and no side effects were reported with the addition of the adsorption column

Results
- After two sessions of combined CytoSorb/CRRT/ ECLS treatment, doses of norepinephrine (from 5.8 to 0.3 μg/kg/min and later to 0.15 μg/kg/min) and dobutamine (from 10 to 5 μg/kg/min) could be reduced significantly and were eventually tapered off on day 13
- Lactate levels decreased from 2.4 to 1.6 mmol/L during both CytoSorb treatment sessions
- Leucocytes decreased from 31.7 to 21.7 Gpt/L while platelet blood count tended to increase
- Decrease of CRP from 464 mg/L on day 4-decreasing to 58 mg/L on day 8
- Creatinine levels decreased to 162 μmol/L after therapy. The patient was anuric during the acute phase

Measurements
- Hemodynamics and need for catecholamines
- Lactate
- Leucocytes and thrombocytes
- C-reactive protein (CRP)
- Creatinine and diuresis
- Safety, adverse events, feasibility

Patient Follow Up
- Wasting of his lower left limb due to streptococcal infection, requiring several skin resections, vacuum-assisted closure therapy and hyperbaric oxygen therapy to facilitate wound healing
- Multifactorial peripheral hypoperfusion secondary to both ECLS procedure and high doses of noradrenaline finally led to necrosis of the distal right lower limb necessitating amputation extended to half-tibia
- Multiple infectious episodes were all successfully treated with antibiotic therapy
- A first attempt of ECLS withdrawal was made on day 8, which was finally successful on day 10
- After discontinuation of CytoSorb, ECLS, and CRRT the patient required further dialysis treatment for another 25 days
- The acute phase persisted for 12 days, and the patient spent a total of 52 days on the ICU
- Today, the patient is well and uses a wheelchair

CONCLUSIONS
- This case describes the successful use of CytoSorb with CRRT and ECLS used in combination to overcome a critical phase of septic shock in a young adult patient with necrotizing fasciitis
- The combination of extracorporeal procedures resulted in hemodynamic improvement of the patient, a decrease in vasopressor and dobutamine demand and a decrease in lactate levels as well as consistent improvement in his blood parameters
- Data therefore suggest that CytoSorb might represent an efficient rescue treatment in adult patients in the context of necrotizing fasciitis and septic shock
Use of Hemadsorption in a Case of Pediatric Toxic Shock Syndrome

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Case Rep Crit Care 2017; 3818407

Summary
This case report describes the successful treatment of toxic shock syndrome (a potentially fatal disease mediated by gram-positive bacterial toxins) in a 5 year old pediatric Downs syndrome patient who presented with an inflamed area surrounding an insect bite, signs of systemic inflammation, and multiple organ failure. As attempts at resuscitation (including fluids, catecholamines and antibiotics), and immune modulatory therapies (including hydrocortisone, plasma exchange therapy and immunoglobulin therapy) were unsuccessful, renal replacement therapy supplemented with the CytoSorb adsorber was started. This was associated with a rapid and significant stabilization in the hemodynamic situation, and a decrease in inflammatory mediators within hours after the initiation of therapy. The application of CytoSorb therapy was simple and safe. The use of CytoSorb proved potentially beneficial by removing bacterial toxins and inflammatory mediators in this case and could therefore play a role in the clinical management of toxic shock syndrome.

Case Presentation
- Five-year-old girl with Down’s syndrome presented with an inflamed area on her right leg surrounding a 2 day old insect bite. Antibiotics had been started by her GP the day before, however, the infection had continued to spread towards the groin region.
- On admission to the Emergency Dept blood examination revealed leukocytosis, neutrophilia, mild anemia, normal platelets and elevated C-reactive protein (CRP, 260.98mg/L).
- Over the next two days her condition deteriorated so rapidly she was transferred to the intensive care unit with severe uncompensated metabolic acidosis (pH 6.77). Septic shock was diagnosed and resuscitation measures started (fluid boluses, oxygen therapy, additional antibiotics, and dopamine, dobutamine and noradrenaline due to a poor cardiovascular response).
- Hydrocortisone was also given along with an antimyotic agent and immunoglobulin therapy due to suspected immunodeficiency. The patient had to be intubated and ventilated and was also given plasma exchange therapy.
- Her skin lesions continued to spread with the development of purpura and petechiae and toxic shock syndrome was confirmed. When the patient became anuric around hrs 56 continuous venovenous hemodialysis (CVVHD) was started. Thrombocytopenia, anemia, and hyponatremia were supported by administration of blood products.
- A CytoSorb adsorber was added to this circuit around hour 91.

Treatment
• CVVHD in combination with CytoSorb
• Anticoagulation with citrate
• Treatment was continued for 72 hrs

Measurements
• Cardiovascular status
• Ventilator settings
• Pro-inflammatory and immunomodulatory cytokines

Results
• Treatment was associated with rapid cardiovascular stability (lower vasopressor doses), improvement in FIO2, airway pressures and respiratory rate
• In addition, levels of important laboratory parameters decreased (see Table 1) as did plasma concentrations of proinflammatory and immunomodulatory cytokines (Figure 1).
• The attenuation of the inflammatory response correlated with the clinical improvement. The need for platelets decreased dramatically 48 hrs after CytoSorb was started and her skin lesions began to fade.

Patient Follow Up
- On day 20 she developed a staphylococcal infection however, this was appropriately managed and she was discharged from ICU on day 25.

Table 1: Laboratory parameters during the course of multiple immune-modulatory therapies including CVVHD+CyoSorb.

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CRP - C-reactive protein, PCT - procalcitonin, WBC - white blood cell, BUN - blood urea nitrogen, ALT - alanine aminotransferase, AST - aspartate aminotransferase, LDH - lactate dehydrogenase, IVIG - intravenous immune globulin, CVVHD - continuous venovenous hemodialysis. | Normal values of laboratory results provided by the examiner institution: Lactate: 0-2.2mmol/L, CRP <0.2mg/L, PCT <0.5µg/L, WBC: 4.5-11.5G/L, platelets: 100-300G/L, BUN: 1.8-4.4mmol/L, creatinine: 0.5-2.0mmol/L, ALT <40UI, AST<40UI, and LDH<254UI.

Figure 1: Course of pro-inflammatory and immunomodulatory cytokines before, during and after combined CVVHD+ CytoSorb treatment.

CONCLUSIONS
• After several other immunomodulatory therapies had failed, CytoSorb treatment of this pediatric patient with toxic shock syndrome was associated with rapid and significant stabilization of the patient’s condition (hemodynamic, respiratory, inflammatory) within hours of therapy starting.
• The need for platelets decreased dramatically and the diffuse rash, purpura and petechiae vanished.
• The treatment was well-tolerated.
• CytoSorb could therefore play a future role in the clinical management of toxic shock syndrome.
Effect of extracorporeal cytokine removal on vascular barrier function in a septic shock patient

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Summary
A 32-year-old female presented with septic shock and accompanying acute kidney injury to ICU. In spite of a broad anti-infective regimen, adequate fluid resuscitation, and high doses of catecholamines, she remained in refractory hypotensive shock. The extraordinary severity of septic shock suggested an immense overwhelming host response assumingly accompanied by a notable cytokine storm. Thus, a CytoSorb adsorber was added into the dialysis circuit. To analyze the endothelial phenotype in vitro before and after extracorporeal cytokine removal, the authors tested the patient’s serum on human umbilical vein endothelial cells (HUVECs) and the effect on the endothelial integrity was assessed. The authors found severe alterations in cell-cell contacts, the cytoskeletal architecture, and profound functional permeability changes (in other words clinical vascular leakage syndrome) when blood from the patient taken prior to the CytoSorb adsorber was added to the HUVECs. However, the endothelial barrier was protected from these profound adverse effects when blood serum was collected after the CytoSorb adsorber (cytokine removal) and added to the HUVECs. In conclusion the benefit of extracorporeal cytokine removal with serum from the same patient after CytoSorb treatment were comparable with cells from a healthy control (in other words, the integrity of cell junctions were better preserved after CytoSorb treatment). The patient remained in refractory hypotension despite a broad anti-infective regimen, adequate fluid resuscitation, and high doses of inotropes and catecholamines.

Case presentation
- 32-year-old female patient with a 4-day history of fever, malaise, and cough was found unconscious and hypoxic by the emergency team
- The patient was successfully resuscitated and after initial treatment at a local hospital transferred to the authors institution for extracorporeal membrane oxygenation (ECMO) due to influenza pneumonia, which caused respiratory failure and severe Acute Respiratory Distress Syndrome (ARDS)
- She also had an abscess of her left breast that grew Escherichia coli bacteria
- Due to sepsis (peak C-reactive protein (CRP) 222 mg/L; peak procalcitonin (PCT) 81.2 μg/L) and accompanying acute kidney injury (AKI), the patient required additional organ support by continuous veno-venous hemodialysis (CVVHD)
- Sequential Organ Failure Assessment (SOFA) score was 18

Results
- Improved hemodynamic stability within the process of cytokine removal - after 24 hrs of treatment, mean arterial pressure (MAP) could be maintained above 65 mmHg with markedly reduced need for vasopressors, even allowing the removal of excessive fluids by ultrafiltration
- Noradrenaline doses could be reduced from 0.40 to 0.09 μg/kg/min after the 24 hrs treatment (reduction to 0.11 μg/kg/min possible within the first 12 hrs)
- During the course of the single treatment creatinine could be lowered from 242 to 70 μmol/L and lactate from 3.1 to 0.9 mmol/L
- Significant removal of all cytokines and chemokines (except IL-13)
- Pre- and post- CytoSorb treatment drug levels of antibiotics yielded a marked reduction for meropenem and piperacillin as well as a slight reduction for clindamycin
- Treatment of endothelial cells challenged with serum from the septic patient pre CytoSorb treatment exhibited structural alterations with an increase in permeability, the cellular correlate for the clinical “vascular leakage syndrome”, while cells stimulated with serum from the same patient after CytoSorb treatment were comparable with cells from a healthy control (in other words, the integrity of cell junctions were better preserved after CytoSorb treatment).

Patient follow-up
- Unfortunately, clinical and radiologic signs of severe hypoxic brain injury forced the authors to switch the therapeutic strategy to palliative care and the patient died the next day

CONCLUSIONS
- Extracorporeal cytokine removal using CytoSorb led to a stabilization of septic shock within hours
- Due to the observed decrease in levels of antibiotics, the authors recommend therapeutic drug monitoring during CytoSorb use in septic patients, as with the use of any other extracorporeal removal strategies
- This is the first publication showing that a protective effect of CytoSorb on capillary integrity, and as a result, on microcirculation, can be assumed with a high probability
- There is no doubt that this report from a single patient is hypothesis generating in nature, so that a future systematic study is highly desirable
Rescue of cytokine storm due to HLH by hemoadsorption in a CTLA4-deficient patient

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4Center for Chronic Immunodeficiency, Medical Center – University of Freiburg, Germany
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Journal of Clinical Immunology 2017; 37(3): 272 – 6

Summary
In this letter to the editor the authors describe the use of a CytoSorb in a patient with secondary hemophagocytic lymphohistiocytosis (HLH) caused by CTLA-4 deficiency. The 50 yr old patient was admitted to ICU with systemic inflammatory response syndrome (SIRS) and multi-organ failure. Despite aggressive intervention his clinical condition rapidly worsened so a CytoSorb adsorber was added into the circuit of the hemodiafiltration. In total 4 adsorbers were used, with columns being changed every 24 hrs. Cytokine adsorption resulted in an immediate decrease in inflammatory parameters and the clinical condition improved in parallel. This suggests the CytoSorb was the decisive therapeutic intervention in this case. The patient was discharged to the regular ward nine days after CytoSorb initiation.

Case presentation
- The 50 year old male patient was admitted to ICU with systemic inflammatory response syndrome (SIRS) and multiorgan failure after persistant fever. He had been receiving treatment for CTLA-4 for several months.
- On admission his C-reactive protein (CRP) was 173 mg/l, procalcitonin (PCT) 14 ng/ml, and interleukin (IL)-6 5168 pg/ml. No pathogens were identified in blood, urine or bronchial secretions.
- Whole body CT ruled out an infectious focus so HLH was confirmed. The probable trigger was Epstein Barr Virus (EBV) viremia.
- Patient developed oligo-anuric acute renal failure (maximum creatinine 2.34 mg/dl) requiring continuous veno-venous hemodiafiltration. Patient was coagulopathic (INR 1.62, PTT 72 sec) and had liver failure. Cholestatic hepatopathy worsened (maximum bilirubin 35.2 mg/dl). Patient was intubated and ventilated due to reduced consciousness due to encephalopathy and hypoxic/hypercapnic respiratory failure.
- Because of the rapidly worsening clinical situation with progressive multi-organ failure, the CytoSorb was added to the circuit of the hemodiafiltration.

Treatment
- Extracorporeal therapy was continued for four days with replacement of the CytoSorb adsorber every 24 hrs.

Measurements
- Inflammatory parameters (CRP, PCT, sIL 2-R, IL6), bilirubin and lactate.

Results
- The addition of CytoSorb resulted in an immediate decrease in inflammatory parameters, bilirubin and lactate (figure 1).
- Patient was discharged to the ward nine days after the initiation of CytoSorb.

Patient follow-up
- Histological analysis of a lymph node removed after the acute phase provided retrospective evidence of an EBV associated Hodgkin lymphoma as the likely reason for secondary HLH.
- Recent 12 month check up confirmed complete remission and complete donor chimerism.

Figure 1: Profile of inflammatory and HLH parameters: C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), soluble interleukin-2 receptor (sIL-2R), bilirubin and lactate. The dotted line indicates the initiation of the hemoadsorption.

Conclusions
- This is the first case of a successful application of extracorporeal hemoadsorption in a patient with CTLA-4 deficiency and SIRS due to secondary HLH triggered by EBV associated Hodgkin lymphoma.
- There was a rapid reduction of all measured proinflammatory cytokines and of severe hyperbilirubinemia.
- The instant reponse within hours after the onset of cytokine removal suggests that CytoSorb was the decisive therapeutic intervention.
Combination of ECMO and cytokine adsorption therapy for severe sepsis with cardiogenic shock and ARDS due to Panton-Valentine leukocidin-positive Staphylococcus aureus pneumonia and H1N1

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Department of Anaesthetic and Critical Care, Harefield Hospital, Royal Brompton & Harefield NHS Foundation Trust, England


Summary

Sepsis-induced cardiogenic shock in combination with severe acute respiratory failure represents a life-threatening combination that is often refractory to the conventional methods of treatment. Here the authors describe the case of a 33-year-old patient who developed acute cardiovascular collapse and Acute Respiratory Distress Syndrome (ARDS) secondary to superinfection of Panton-Valentine leukocidin-positive Staphylococcus aureus and H1N1 pneumonia who underwent successful combination therapy for severe sepsis-related cardiomyopathy and respiratory failure using extracorporeal membrane oxygenation (ECMO) and CytoSorb therapy. Use of the CytoSorb appeared to result in rapid resolution of neutropenia and reversal of toxic shock and rapid weaning of the high dose vasopressor infusions.

Case presentation

- 33-year-old previously fit female (5-month post-partum) presented to the local Emergency Department following a 4-day history of flu-like symptoms with breathlessness, delirium, chest and abdominal pains
- On the initial assessment, she was pyrexial, tachypneic, tachycardic, and hypotensive with cool peripheries
- Examination and investigations revealed clinical evidence of severe acute respiratory failure with extensive air space shadowing throughout with hypoxemia and metabolic acidosis (pH 7.1, lactate 5 mmol/L, base deficit -11 mmol/L)
- Cardiac assessment by transthoracic echocardiography revealed severe left ventricular failure with a left ventricular ejection fraction (LVEF) of 5–15%
- Furthermore, she was severely neutropenic (white blood cell count 0.6x10^9/l, neutrophils 0.3 x10^9/l)
- She rapidly deteriorated requiring intubation and mechanical ventilation and treatment was initiated for community acquired pneumonia
- In addition, she required significant amounts of vasopressor and inotropic support to achieve an adequate mean arterial pressure, highlighting the central cardiovascular involvement in her critical state
- In view of clinical deterioration and cardiovascular and respiratory instability, she was transferred to the hospital of the authors for ongoing care and consideration of extracorporeal life support
- On arrival, she had severe respiratory failure with a Murray score of 3.7 (PaO₂/FiO₂ ratio 11.1 kPa, PEEP 12, compliance 32 ml/cmH₂O, four-quadrant infiltration on chest radiograph)
- She was hypotensive with a MAP of 50 mmHg, despite high-dose infusions of noradrenaline (1–1.5 µg/kg/min) and vasopressin 0.04 U/h in addition to dobutamine 7.5 µg/kg/min
- Transthoracic echocardiography revealed a severely impaired, non-dilated left ventricle and normally functioning, non-dilated right ventricle
- There was metabolic acidosis (base deficit -6 mmol/L, lactate 4 mmol/L) and oliguria
- Care was initially supportive comprising mechanical ventilation, titration of high-dose inotropic and vasopressor agents, fluids, and continuous veno-venous hemodialfiltration
- She was treated empirically for severe sepsis and community acquired pneumonia and influenza. Subsequent analysis of sputum from direct bronchoscopy showed a heavy growth of Staphylococcus aureus (SS), which was positive for expression of Panton-Valentine leukocidin (PVL). Viral PCR was also positive for H1N1 Influenza A. Clindamycin was added and intravenous immunoglobulin G (IVIg) therapy was commenced.
- In view of the severity of the combined respiratory and cardiac failure and evidence of worsening organ function, peripheral veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) was instituted within 5 hrs of arrival and in view of the severe sepsis and high amount of vasopressors, CytoSorb was added to the hemofilter circuit

Treatment

CytoSorb was added to the CVVH circuit (Prismaflex, Gambro, Sweden) and run parallel to the VA-ECMO circuit (Thoratec Centrimag pump at 4 L/min with inspired oxygen through the Medos hilite 700LT oxygenator set at 100%)
Can cytokine adsorber treatment affect antibiotic concentrations? – A case report

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J Antimicrob Chemother 2015; 70(7): 2169 – 71

Summary
This case study reports on a male patient with septic shock and multiple organ failure who was admitted to the ICU. The patient’s condition was characterized by an excessive inflammatory response. Initial laparotomy revealed an ischemic bowel with peritonitis requiring jejunal and colon segmental resection and ileo-transverse colostomy. Immediate antibiotic treatment with meropenem was started and linezolid was added 5 hours after admission. Due to the persisting excessive cytokine storm, adjuvant therapy with a CytoSorb adsorber was initiated with a total of 4 treatments over the following days. Subsequently, the patient’s condition substantially improved. The use of CytoSorb in this patient with severe septic shock proved to be effective (decrease of interleukin (IL)-6) and safe (antibiotic levels well above the lower limit of the therapeutic range).

Measurements
- Analysis of antibiotic serum concentrations (i.e. Linezolid and Meropenem) to detect potential elimination by CytoSorb
- IL-6 elimination

Results
- Substantial reduction of IL-6 over the course of the 4 CytoSorb treatments from 563,000 pg/ml on day 1 to 19,400 pg/ml on day 4
- High intra-patient variability for Linezolid and Meropenem levels was observed, which might be caused by adsorption effects by CytoSorb but also by the effects of critical illness
- By using a higher loading dose for Linezolid and Meropenem in this patient, all the antibiotic concentrations measured were sufficient and did not approach the lower limit of therapeutic level

Case presentation
- Male patient with septic shock and multiple organ failure was admitted to ICU at the University Hospital of Munich
- Initial laparotomy showed an ischemic bowel with peritonitis
- Immediate jejunal and colon segmental resection with an ileo-transverse colostomy was performed
- The further course of the treatment was characterized by severe sepsis with multiple organ failure and an excessive inflammatory response
- Antibiotic treatment with Linezolid (4 x 600 mg on day 1 continuing with 2 x 600 mg) and Meropenem (4 g/d) was started
- As the patient showed a persisting excessive cytokine storm, a CytoSorb adsorber was applied
- At this time, the patient was treated with Linezolid and Meropenem intravenously by short duration infusions (15-60 min) and daily CytoSorb use

Treatment
- 4 sessions with CytoSorb were performed over a period of 96 hours
  - day 1: 7 h
  - day 2: 10 h
  - day 3: 8 h
  - day 4: 5 h

Post-treatment period and follow-up
- After four weeks and seven re-laparotomies the patient died from multiple organ failure

CONCLUSIONS
- First time in vivo pharmacokinetic monitoring of Linezolid and Meropenem during treatment with CytoSorb
- Use of CytoSorb in this patient with severe septic shock proved to be effective (decrease of IL-6) and safe (antibiotic levels well above the lower limit of therapeutic range)
- Using a high loading dose for Linezolid and Meropenem, antibiotic concentrations were always within the therapeutic range
- However, the results indicate that Linezolid and Meropenem serum concentrations might be reduced by the use of CytoSorb
- In the absence of therapeutic drug monitoring, high loading doses and shorter intervals between antibiotic administrations could be used to achieve adequate antibiotic levels
- Further studies are necessary to understand the impact of CytoSorb on concentrations of different antimicrobials
CytoSorb Therapy – REGAIN CONTROL