

Literature on CytoSorb®-Therapy and Related Topics

Rating:

- very helpful and worth reading
- helpful and worth reading
- helpful and worth reading to a limited extent

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New Publications

1. Clinical Data

1.2 Case Series

1.2.1 Sepsis

NEW: Feasibility and safety of combined cytokine adsorption and continuous veno-venous hemodialysis with regional citrate anticoagulation in patients with septic shock

Dimski T, Brandenburger T, Slowinski T, Kindgen-Milles D.

Int J Artif Organs 2019; epub

1.3 Case Reports

1.3.5 Other Indications

NEW: Cardiogenic shock in a hemodialyzed patient on flecainide: treatment with intravenous fat emulsion, extracorporeal cardiac life support and CytoSorb hemoadsorption

De Schryver N, Hantson N, Haufroid V, Dechamps M

Case Reports in Cardiology 2019; epub

3. Background and Review

NEW: Recommendations for the management of hemophagocytic lymphohistiocytosis in adults

La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, Kumar A, van Laar JAM, Lachmann G, Nichols KE, Ramanan AV, Wang Y, Wang Z, Janka G, Henter JI.

Blood 2019; 133(23): 2465 – 77

1. Clinical data

1.1. Studies

1.1.1. Sepsis

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

Journal of Critical Care 2019; 49:172-178

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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 20 patients with early (<24hrs) septic shock. Inclusion criteria also included: on mechanical ventilation; norepinephrine >10 µg/min; procalcitonin (PCT) >3 ng/mL; and without the need for renal replacement therapy (RRT). Patients were randomized into CytoSorb (n=10) for 24 hours or Control groups (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 concentrations decreased significantly (p=0.016 and p=0.004 respectively). Big-endothelin-1 concentrations were also significantly lower in the CytoSorb group (p = 0.003). All patients in the CytoSorb group survived to 48 hrs (2 patients in the control arm died before the 48 hr 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 when compared to controls.

<https://www.ncbi.nlm.nih.gov/pubmed/30448517>

The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial

Schaedler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jorres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK

PLoS One 2017; 12(10): e0187015

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Summary;

This first clinical study ever conducted with CytoSorb (2008 – 2011) was a randomized, controlled, open-label, multicenter trial that reported on the use of CytoSorb for 6 hours daily for 7 days in 97 mechanically ventilated patients with severe sepsis or septic shock and acute respiratory distress syndrome (ALI / ARDS). The study was not able to detect differences in systemic plasma IL-6 levels between the two groups (n = 75; p = 0.15) although significant IL-6 elimination, averaging between 5 and 18% per blood pass throughout the entire treatment period was recorded. There was also no statistically significant difference in the secondary outcomes multiple organ dysfunction score, ventilation time and time course of oxygenation. The proportion of patients receiving renal replacement therapy at the time of enrollment was higher in the treatment group (31.9%) compared to the control group (16.3%).

After adjustment for patient morbidity and baseline imbalances, no association of hemoperfusion with mortality was found ($p = 0.19$).

<https://www.ncbi.nlm.nih.gov/pubmed/29084247>

Extracorporeal Cytokine Elimination as Rescue Therapy in Refractory Septic Shock - a Prospective Single-Center Study

Friesecke S, Stecher SS, Gross S, Felix SB, Nierhaus A
Journal Artif Organs 2017; 20(3): 252-9

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Summary;

Mortality from refractory septic shock may reach 90-100% despite optimum therapy. In this study cytokine adsorption using CytoSorb in addition to regular therapy was studied prospectively in 20 patients with refractory shock (defined as increasing vasopressor dose required to maintain mean arterial blood pressure above 65 mmHg or increasing lactate levels despite protocol-guided shock therapy for six hours). CytoSorb® treatment was started after 7.8 ± 3.7 hours of shock therapy. Following the initiation of CytoSorb, noradrenaline dose could be significantly reduced after 6 ($p=0.03$) and 12 hours ($p=0.001$). Lactate clearance improved significantly. Shock reversal was achieved in 13 (65%) patients; 28-day survival was 45% (predicted mortality from the SOFA score was $>80\%$). The use of CytoSorb adsorption therapy resulted in shock reversal in two thirds of these particularly difficult to treat patients.

<https://www.ncbi.nlm.nih.gov/pubmed/28589286>

1.1.2. Cardiac surgery

Hemoadsorption to Reduce Plasma Free Hemoglobin during Cardiac Surgery: Results of REFRESH I Pilot Study

Gleason TG, Argenziano M, Bavaria JE, Kane LC, Coselli JS, Engelman RM, Tanaka KA, Awad A, Sekela ME, Zwischenberger JB.

Semin Thorac Cardiovasc Surg 2019; epub

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Summary

This prospective, multi-center REFRESH I (REduction in FREe Hemoglobin) randomized controlled trial (RCT) evaluated the safety and feasibility of CytoSorb hemoadsorption therapy to reduce plasma free hemoglobin (pfHb) and activated complements (C3a and C5a) during prolonged (expected duration > 3 hrs) cardiopulmonary bypass (CPB). Initially 46 patients underwent surgery (23 in each group), and 38 patients went on to have their pfHb and activated complements evaluated (18 in the CytoSorb efficacy group, 20 in control group). In the CytoSorb group, two parallel 300 ml cartridges were set up in a side circuit during CPB and the control group received standard care. CytoSorb was ran for, on average, 2.5 hours. Results showed that the type and number of serious adverse events (44 vs 43 CONTROL) were similar, as was 30-day mortality. A transient reduction in platelets during CPB was observed in both groups, especially the treatment group, but returned to pre-treatment levels after CPB without bleeding.

Peak pfHb was positively correlated with the length of time on CPB ($p=0.01$) but the high variability of pfHb, due to the broad surgical procedure mix, prevented detection of changes in pfHb in the CytoSorb population. However,

the valve replacement surgery subgroup (8 CytoSorb vs 10 control) had the highest peak pfHb levels, and use of CytoSorb resulted in significant pfHb reductions vs the control group (p 0.05) in CPB \geq 3h. In the 18 CytoSorb patients who had their activated compliments measured, C3a and C5a were significantly reduced by treatment throughout surgery. The authors conclude that intraoperative hemoadsorption with CytoSorb was safe and feasible in this 8 centre, randomized, controlled pilot study during complex cardiac surgery and resulted in significant reductions in pfHb during valve replacement surgery and reductions in C3a and C5a in the overall CytoSorb group.

<https://www.ncbi.nlm.nih.gov/pubmed/31085219>

Cytokine clearance with CytoSorb during cardiac surgery: A pilot randomized controlled trial

Poli EC, Alberio L, Bauer-Doerries A, Marcucci C, Roumy A, Kirsch M, De Stefano E, Liaudet L, Schneider AG.

Critical Care 2019; 108

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Summary

In this single center, pilot, randomized controlled trial, 30 patients undergoing elective cardiac surgery and deemed at risk of complications were included and randomly allocated to either standard of care (n=15) or CytoSorb (n=15) during cardiopulmonary bypass (CPB). The primary outcome was the difference between the two groups in various cytokines levels measured at various time points. In a subgroup of patients (10 in the CytoSorb group, 11 in control group), cross-adsorber as well as serial measurements of coagulation factors activity were also measured. CytoSorb use during CPB was not associated with any increased incidence of adverse events, nor did the procedure result in any significant alterations in conventional hematological parameters or coagulation factors levels. However, in this patient population with predominantly low inflammatory response the use of CytoSorb was not associated with a significant impact on pro- or anti-inflammatory cytokine levels, nor with a change in relevant clinical outcomes. However, the procedure appeared safe and feasible.

<https://ccforum.biomedcentral.com/track/pdf/10.1186/s13054-019-2399-4>

Haemadsorption improves intraoperative haemodynamics and metabolic changes during aortic surgery with hypothermic circulatory arrest

Saller T, Hagl C, Woitsch S, Li Y, Niedermayer S, Born F, Luehr M, Kammerer T, Pichlmaier M, Scheiermann P, Peterss S

Eur J Cardiothorac Surg 2019; epub

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Summary

In this single center study 336 patients who had undergone aortic surgery involving hypothermic circulatory arrest (HCA) were retrospectively analyzed. 168 patients with CytoSorb hemoadsorption (HA) were matched to 168 patients receiving standard therapy without HA (control) by propensity score matching and then compared. When used, CytoSorb was inserted into cardiopulmonary bypass circuit and continuously perfused at a rate of 500 ml/min. During aortic surgery, HA significantly reduced the requirement for

vasopressors, including norepinephrine and vasopressin, and patients had a more stable acid-base balance and lower lactate levels throughout the procedure. CytoSorb use also significantly decreased the need for transfusion of packed red blood cells, fresh frozen plasma and fibrinogen. In the HA group, a slight increase of the requirement of prothrombin complex concentrate was observed. There were not enough data on pro-inflammatory cytokine markers and hence, statistical tests could not be performed. The differences in 30 day mortality (HA: 7 patients, 4.8%; Control: 13 patients, 8.8%) and the length of hospital stay were not statistically significant. The authors conclude that the use of CytoSorb in the setting of acute pathologies such as acute aortic surgery benefits the patients intraoperative course by improving hemodynamic stability as well as acid-base balance and reducing the need for transfusions.

<https://www.ncbi.nlm.nih.gov/pubmed/30891592>

Cytosorb adsorption during emergency cardiac operations in patients at high risk of bleeding

Hassan K, Kannmacher J, Wohlmuth P, Budde U, Schmoeckel M, Geidel S
Annals of Thoracic Surgery 2019; 108(1); 45 - 51

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Summary

This study included 55 consecutive patients undergoing emergency open-heart operations who were at high risk of bleeding due to prior treatment with coagulation-active substances (Ticagrelor – 43 pts, or Rivaroxaban - 12 pts). In 39 of 55 cases, Cytosorb adsorption was installed into the heart-lung-machine (CA-group). Bleeding complications during and after surgery were analyzed in detail and compared to 16 patients without adsorption (WA-group), 11 of whom were on ticagrelor and 5 on rivaroxaban. In the CA-group no re-thoracotomies had to be performed. Drainage volumes over 24-hours were only 350 mls after Ticagrelor administration and 390 mls after Rivaroxaban therapy. In the majority of patients, transfusions of blood products were not needed. Compared to this, in the WA-group, multiple bleeding complications occurred and were associated with a longer total operation time, higher drainage volumes, more red blood cell and platelet transfusions, a higher re-thoracotomy rate, a prolonged retention in the intensive care unit and a longer hospital stay (all differences statistically significant between groups). The authors attribute these favorable results directly to the effect of CytoSorb adsorbing Ticagrelor or Rivaroxaban during the surgery which, they note, is the only way currently available in this patient population to increase patient safety, and reduce bleeding complications. They also believe that the use of Cytosorb helps to reduce the costs of such operations as its use was associated with an operation time reduced by almost one hour and the decreased use of blood components. Furthermore, there could be cost savings made by faster discharge of patients from the ICU. They note the safe intraoperative use of Cytosorb and recommend its use in patients with Ticagrelor or Rivaroxaban who require emergency cardiac surgery.

<https://www.ncbi.nlm.nih.gov/pubmed/30684482>

Hemadsorption during cardiopulmonary bypass reduces interleukin 8 and tumor necrosis factor α serum levels in cardiac surgery: a randomized controlled trial.

Garau I, März A, Sehner S, Reuter DA, Reichenspurner H, Zöllner C, Kubitz JC. *Minerva Anesthesiol.* 2018; epub

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Summary

In this prospective, randomized single centre study, serum cytokine levels of interleukin 8 (IL-8), interleukin 6 (IL-6) and tumor-necrosis-factor α (TNF α) were assessed in elective on-pump (cardiopulmonary bypass – CPB) cardiac surgery patients with CytoSorb hemoadsorption (study-group - SG, n=20) and without (control-group - CG, n=20). Cytokine levels were assessed prior to and at the end of CPB (mean duration of bypass 141 mins in SG and 139 mins in CG), and 6 and 24 hours after the end of CPB, together with a hemodynamic assessment. The CytoSorb SG had significantly lower IL-8 serum levels at the end of CPB ($p=0.008$) and TNF α levels were also below those in the CG at both the end of and 6h after CPB ($p=0.034$). After 24 hours, TNF α levels were at baseline in both groups. No significant differences were found for IL-6. There was a significant impact of CytoSorb treatment on the hemodynamic situation as evidenced by a higher cardiac index in the SG after weaning from CPB. This prospective randomized study shows a significant reduction in the pro-inflammatory cytokines IL-8 and TNF α as well as an improvement of the cardiac index, when CytoSorb is used in on-pump cardiac surgery whilst also demonstrating safety in its application.

<https://www.ncbi.nlm.nih.gov/pubmed/30481999>

Hemoadsorption does not Affect Hemolysis During Cardiopulmonary Bypass.

Bernardi MH, Rinoesl H, Ristl R, Weber U, Wiedemann D, Hiesmayr MJ.

ASAIO J 2018; epub

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Summary

Cardiopulmonary bypass (CPB) induces hemolysis, which manifests as plasma free hemoglobin (pfHb), which increases the risk of post-operative complications including decreased blood flow and organ damage. Haptoglobin scavenges hemoglobin, but has limited capacity. This is a post hoc analysis from the previously published study (Bernardi MH et al. Effect of hemoadsorption during cardiopulmonary bypass surgery - a blinded, randomized, controlled pilot study using a novel adsorbent. *Crit Care* 2016; 20(1): 96) and investigated whether the use of CytoSorb affected hemolysis during CPB. A total of 35 patients undergoing elective CPB surgery with expected CPB duration of more than 120 min were included in the analysis where CytoSorb was used (17 in the intervention group and 18 in the control group). Postoperative pfHb levels were not significantly different between the groups, however, there were statistically significant differences between the treatment and control groups in the median levels of haptoglobin (58.4 vs. 17.9 mg/dL, respectively; $P < 0.01$) and lactate dehydrogenase (353.0 vs. 432.0 U/L, respectively; $P < 0.05$) on postoperative day 1. Although the study did not find a statistically significant effect on hemolysis in patients treated with hemoadsorption, statistically significant lower haptoglobin levels and higher secondary hemolysis markers on postoperative day 1 in patients not treated

with the device may be an indication of some moderate positive effect of CytoSorb.

<https://www.ncbi.nlm.nih.gov/pubmed/30325849>

Impact of intraoperative cytokine adsorption on outcome of patients undergoing orthotopic heart transplantation – an observational study

Nemeth E, Kovacs E, Racz K, Soltesz A, Szigeti S, Kiss N, Csikos G, Koritsanszky KB, Berzsenyi V, Trembickij G, Fabry S, Prohaszka Z, Merkely B, Gal J.
Clinical Transplantation 2018; 32(4):e13211

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Summary

The aim of this study was to assess the influence of intraoperative cytokine adsorption using CytoSorb on the perioperative vasoplegia, inflammatory response and outcome during orthotopic heart transplantation (OHT). Patients were separated into the cytokine adsorption (CA) treated group or historic controls. In the 16 matched pairs, the median noradrenaline requirement was significantly less in the CA-treated patients than in the controls on the first and second postoperative days ($P=0.039$ and $P=0.047$). The inflammatory responses (assessed by PCT and CRP) were similar in the two groups. There was a trend towards shorter length of mechanical ventilation and intensive care unit (ICU) stay in the CA-treated group compared to the controls. No difference in adverse events was observed, however, the frequency of renal replacement therapy was significantly less in the CA-treated than in controls ($P=0.031$). In summary, intraoperative CytoSorb during OHT proved to be safe and was associated with reduced vasopressor demand and less frequent renal replacement therapy with a favorable tendency in length of mechanical ventilation and ICU stay.

<https://www.ncbi.nlm.nih.gov/pubmed/29377282>

Use of cytokine filters in cardiopulmonary bypass machines (Einsatz eines Zytokinfilters in die Herz-Lungen-Maschine)

Deppe AC, Weber C, Choi YH, Wahlers T
Z Herz- Thorax-Gefäßchir 2016;30(4):254-259

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Abstract and article in German, abstract only in English.

Summary:

Cardiac surgery using a cardiopulmonary bypass (CPB) machine induces a systemic inflammatory reaction due to activation of multiple inflammatory cascades which may result in systemic inflammatory response syndrome (SIRS). Activation of various inflammatory mediators, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) can lead to postoperative complications, organ dysfunction, morbidity and mortality. The effect of adsorption of cytokines using CytoSorb with a CPB machine is evaluated in this prospective, observational pilot study to determine the clinical impact on the serum levels of IL-6, IL-8 and TNF-alpha. This pilot study includes 300 patients planned for elective surgical myocardial revascularization, split into 3 groups; 100 patients with on-pump myocardial revascularization with CytoSorb; on-pump myocardial revascularization without CytoSorb and off-pump myocardial revascularization. Primary outcome measures are IL-6, IL-8, TNF-alpha, complement C3/C4, leucocyte counts and C-reactive protein. Secondary outcome measures are

length of intensive care unit and total hospital stay, duration of ventilation, duration of catecholamine therapy, kidney injury as well as major adverse cardiac and cerebrovascular events. Interim analysis after 60 % of patients had been included revealed a well- balanced group allocation of patients. In the CytoSorb group IL-6 values are decreased, whereas TNF-alpha values are comparable between the three groups. There was reduced sternal wound infections and lower usage of antibiotics in the CytoSorb group. The use of the CytoSorb® filter during CPB is safe compared with standard procedure and without technical difficulties. CytoSorb reduces cytokine load and seems to attenuate the inflammatory response.

<http://link.springer.com/article/10.1007/s00398-016-0075-4>

Effect of hemoadsorption during cardiopulmonary bypass surgery - a blinded, randomized, controlled pilot study using a novel adsorbent

Bernardi MH, Rinoesl H, Dragosits K, Ristl R, Hoffelner F, Opfermann P, Lamm C, Preißing F, Wiedemann D, Hiesmayr MJ, Spittler A

Crit Care 2016;20(1):96

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Summary:

Objective of this blinded, randomized, controlled single-center trial in 46 adult patients undergoing elective coronary artery bypass graft [CABG], valve surgery, or combined procedure with an expected CPB duration of more than 120 min, was to test CytoSorb installed in the cardiopulmonary bypass (CPB) circuit (intraoperative usage) with changes in pro- and anti-inflammatory cytokines levels, inflammation markers, and differences in patients' perioperative course. The authors did not find any reduction in the pro-inflammatory response between patients and therefore no changes in their perioperative course. Of note, only the least sick cohort of patients undergoing relatively low-risk cardiac surgery were included in this study. Therefore the observed inflammatory response was only moderate even in the control group. The use and installation of the CytoSorb adsorber in a CPB circuit was technically feasible, and no adverse device-related side effects occurred. The results showed that albumin and platelet levels are not significantly affected by CytoSorb. There was a possible protective effect of the observed elevated IL-10 levels postoperatively, which have been associated with lower mortality in previous studies. After safety and feasibility have been demonstrated, patient groups with the best clinical benefit from CytoSorb need to be identified.

<http://www.ncbi.nlm.nih.gov/pubmed/27059056>

RECCAS - REMoval of Cytokines during CARDiac Surgery: study protocol for a randomised controlled trial

Baumann A, Buchwald D, Annecke T, Hellmich M, Zahn PK, Hohn A

Trials 2016;17(1):137

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Summary:

On-pump cardiac surgery triggers a significant postoperative systemic inflammatory response, sometimes resulting in multiple-organ dysfunction associated with poor clinical outcome. CytoSorb may attenuate this inflammatory response. The aim of this single-centre randomised, two-arm, patient-blinded RECCAS trial is to assess the efficacy of intraoperative

CytoSorb use during cardiopulmonary bypass (CPB) to reduce the pro-inflammatory cytokine (i.e. IL-6) burden during and after on-pump cardiac surgery, as well as to evaluate the effects on postoperative organ dysfunction and outcomes in high risk patients. Differences in secondary outcome variables between the study groups may give rise to further studies and may lead to a better understanding of the mechanisms of CytoSorb treatment.

www.ncbi.nlm.nih.gov/pubmed/26971164

1.1.3. Other indications

Pancreatitis CytoSorbents (CytoSorb) inflammatory cytokine removal: A Prospective Study (PACIFIC)

Huber W, Algül H, Lahmer T, Mayr U, Lehmann M, Schmid RM, Faltlhauser A. *Medicine* 2019; 98(4): e13044

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Summary

Severe Acute Pancreatitis (SAP) has a mortality rate of around 42% with outcome closely related to the development of systemic inflammation and consecutive organ failures. In this article the authors describe the protocol for a study that intends to evaluate the effectiveness of two consecutive 24hr treatments with CytoSorb on hemodynamics in patients with early SAP. The primary endpoint is changes in the vasopressor dependency index (VDI) - derived from mean arterial pressure (MAP) and catecholamine dosage - compared to matched controls from recent studies within the same setting and same centres. Several other parameters will also be measured including cytokine levels. Ultimately it is hoped that the study will show that CytoSorb could be a therapeutic option in the early treatment of SAP by providing a pathophysiological rationale.

<https://www.ncbi.nlm.nih.gov/pubmed/30681551>

International registry on the use of the CytoSorb(R) adsorber in ICU patients : Study protocol and preliminary results.

Friesecke S, Trager K, Schitter GA, Molnar Z, Bach F, Kogelmann K, Bogdanski R, Weyland A, Nierhaus A, Nestler F, Olboeter D, Tomescu D, Jacob D, Haake H, Grigorjev E, Nitsch M, Baumann A, Quintet M, Schott M, Kielstein JT, Meier-Hellmann A, Born F, Schumacher U, Singer M, Kellum J, Brunkhorst FM.

Med Klin Intensivmed Notfallmed 2017; epub

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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 interleukin-6 levels were markedly reduced after treatment (median 5000 pg/ml before and 289 pg/ml after treatment, respectively). This third interim report demonstrates the feasibility of the registry with excellent data quality and completeness from 20 study centers. Patient numbers are still small; however disease severity is remarkably high and suggest that adsorber treatment might be used as a potentially beneficial treatment in life-threatening situations. Treating physicians rated the condition of the patients as much or very much improved in approximately 50% of cases and reported a very favorable safety profile with no device-associated side effects.

<https://www.ncbi.nlm.nih.gov/pubmed/28871441>

Feasibility study of cytokine removal by hemoadsorption in brain-dead humans

Kellum JA, Venkataraman R, Powner D, Elder M, Hergenroeder G, Carter M
Crit Care Med 2008;36(1):268-72

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Summary:

Through numerous mechanisms, brain death is associated with a massive release of proinflammatory cytokines, detectable both in blood and transplantable organs. This increased inflammatory response has been associated with poor allograft function before and after transplantation. Therefore, this *in vivo* study examines the feasibility of hemoadsorption (using CytoSorb) to remove cytokines in 8 brain-dead humans.

<http://www.ncbi.nlm.nih.gov/pubmed/18090355>

1.2. Case series

1.2.1. Sepsis

NEW: Feasibility and safety of combined cytokine adsorption and continuous veno-venous hemodialysis with regional citrate anticoagulation in patients with septic shock

Dimski T, Brandenburger T, Slowinski T, Kindgen-Milles D.
Int J Artif Organs 2019; epub

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Summary

In this article the feasibility, efficacy, and safety of CytoSorb with regional citrate-anticoagulated continuous veno-venous hemodialysis (CVVHD) in 11 patients with septic shock and stage 3 acute kidney injury was recorded. Twelve cycles of CytoSorb were included with parameters of citrate anticoagulation, circuit lifetime, laboratory parameters, hemodynamics, and vasopressor demand recorded. Ten out of 12 adsorber/CVVHD circuits reached the target of 24 hrs runtime (one system clotted and one was stopped as the patient needed emergency surgery). Nine of the remaining continuous renal replacement circuits reached their 72 hr lifetime. Using the standard citrate protocol, serum ionized calcium and pH remained in the normal range, urea and creatinine were significantly reduced, and norepinephrine dose significantly decreased from 0.47 to 0.16 µg/kg/min ($p = 0.016$) after 24 h. This study shows that combined CytoSorb/CVVHD is safe and effective for controlling pH, reducing urea and creatinine, and improving hemodynamics by

significantly reducing norepinephrine doses in patients with septic shock. It can be applied safely with standard settings of regional citrate anticoagulation rendering sufficiently long filter lifetimes for the CytoSorb adsorber and the CVVHD circuit.

<https://www.ncbi.nlm.nih.gov/pubmed/31379256>

Use of hemoadsorption in sepsis-associated ECMO-dependent severe ARDS: A case series

Kogelmann K, Scheller M, Drüner M, Jarczak D

Journal of Intensive Care Society 2019; epub

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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 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 as 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.

<https://journals.sagepub.com/doi/full/10.1177/1751143718818992>

Effect of hemoadsorption for cytokine removal in pneumococcal and meningococcal sepsis

Leonardis F, De Angelis V, Frisardi F, Pietrafitta C, Riva I, Martino Valetti T, Broletti V, Marchesi G, Menato L, Nani R, Marson F, Fabbris M, Cabrini L, Colombo S, Zangrillo A, Coniglio C, Stalteri L, Giuliani G, Dalmastrì V, Gordini G, La Manna G. *Case Reports in Critical care* 2018; 1205613

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Summary

In this case series five patients with pneumo (n=2) or meningo-coccal sepsis (n=3) were treated with a CytoSorb adsorber for cytokine removal. In these patients bacteria enters 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.

<https://www.hindawi.com/journals/cricc/2018/1205613/>

Hemoadsorption by CytoSorb in septic patients – a case series

Kogelmann K, Jarczak D, Scheller, M, Drüner M

Crit Care 2017;21:74

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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 septic shock patients with a need for renal replacement therapy. Treatment 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 hours 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.

<https://www.ncbi.nlm.nih.gov/pubmed/28343448>

Case series of patients with severe sepsis and septic shock treated with a new extracorporeal sorbent

Laddomada T, Doronzio A, Balicco B

Crit Care 2016;20(Suppl 2):P193

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Summary:

In this case series of 8 patients with severe sepsis and septic shock treated with CytoSorb, the influence of CytoSorb on clinical outcomes such as mean arterial pressure (MAP), vasopressor need and inflammatory markers, e.g. procalcitonin (PCT) was analyzed. There was an overall improvement in MAP with a rapid reduction in vasopressor dosages. Moreover, CytoSorb treatment in combination with CRRT was associated with a marked decrease in PCT levels and an improvement in renal function. In non-survivors, MAP was hard to stabilize and decreased, and there was an aggravation in the patients overall condition. The authors conclude that the timely use of CytoSorb in combination with standard therapy may have benefits in improving hemodynamics and help with more rapid stabilization.

<http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1208-6>

Early report: The use of Cytosorb haemabsorption column as an adjunct in managing severe sepsis: initial experiences, review and recommendations

Morris C, Gray L, Giovannelli M

Journal of Intensive Care Society 2015;16(3):257-64

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Summary:

In this article the authors describe the use of CytoSorb hemoabsorption device in 2 patients with overwhelming sepsis following community acquired pneumonia. In addition, the authors consider the experience and evidence supporting the use of CytoSorb in clinical practice. They state that while Cytosorb haemoabsorption is mechanistically distinct from other extracorporeal therapies in sepsis and appears effective in reducing inflammatory cytokines during sepsis, much of the basic science and clinical benefits remain unclear. Suggestions for future research and how Cytosorb could be incorporated into practice are provided.

<http://inc.sagepub.com/content/early/2015/03/10/1751143715574855.full.pdf>

Clinical experience of using a novel extracorporeal cytokine adsorption column for treatment of septic shock with multiorgan failure

Sathe P, Sakhavalkar P, Kumar S, Choudhary S

Crit Care 2015;19 (Suppl 1):P130

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Summary:

In aim of this retrospective case series in 19 ICU patients treated with standard care plus CytoSorb as an adjuvant therapy was to analyze clinical safety. In a subgroup of patients where CytoSorb was used, selection of timing for initiation, number of CytoSorb devices required per patient, and selective markers to identify its initiation was studied. All of the patients had high predicted mortality (APACHE II >17, SOFA >11). Four patients survived with use of CytoSorb therapy. Importantly, three of them were treated early (<24 hours of admission). APACHE scores decreased >5 points in five patients after a single application of CytoSorb therapy. Of those patients who died, the majority (n = 11) were given CytoSorb treatment only once and seven were treated late (>24 hours). The authors state that a better outcome could be expected if therapy was initiated earlier (<24 hours). However, future studies are needed to clarify the role of CytoSorb in patients with MOF/septic shock.

<http://ccforum.com/content/19/S1/P130>

1.2.2. Cardiac surgery

Comparison of intra-operative versus intra- plus postoperative hemoabsorption therapy in cardiac surgery patients with endocarditis

Kühne L-U, Binczyk R, Rieß FC.

Int J Artif Organs 2019; 42(4): 194 - 200

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Summary

In this study the use of CytoSorb therapy in 20 endocarditis patients was investigated in two groups: intraoperative use only (10 pts - group 1) versus intra- plus post-operative use (10 pts – group 2). The decision whether to continue CytoSorb therapy postoperatively was made on clinical grounds, including the indication for renal replacement therapy, hence the patients in group 2 had more pronounced disease severity (higher EuroSCORE, higher reoperation rates, longer cardiopulmonary bypass times, worse inflammatory status and higher incidence of acute renal failure). Patients in both groups had a marked decrease in the requirement for vasoactive drugs and in their

inflammatory parameters in the postoperative course. Despite being sicker and having a higher rate of postoperative complications as well as a longer ICU stay, patients in group 2 showed equal ICU and 90-day survival compared to group 1 patients who were only treated intraoperatively. This data suggests that the postoperative continuation of CytoSorb might be beneficial for patients with endocarditis who develop perioperative renal failure and hemodynamic instability.

<https://www.ncbi.nlm.nih.gov/pubmed/30803290>

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

Calabro MG, Febres D, Recca G, Lembo R, Fominskiy E, Scandroglio AM, Zangrillo A, Pappalardo F

Artif Organs 2019; 43 (2): 189 - 94

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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 with cardiogenic shock (28), septic shock (2), acute respiratory distress syndrome (9), and liver failure (1). Of the 19 patients who underwent ECMO, 11 had an intra-aortic balloon pump, 9 with Impella, and 6 had a ventricular assist device. Patients received at least one CytoSorb treatment (median number of filters 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 patients mainly due to cardiogenic shock. No device related adverse events were observed.

<https://www.ncbi.nlm.nih.gov/pubmed/30156308>

Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - A case series

Traeger K, Skrabal C, Fischer G, Datzmann T, Schroeder J, Fritzler D, Hartmann J, Liebold A, Reinelt H

Int Art Organs J 2017;40(5):240-9

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Summary:

In this retrospective case series, the authors describe 39 cardiac surgery patients with proven acute infective endocarditis undergoing valve replacement during cardiopulmonary bypass surgery in combination with intraoperative CytoSorb hemoadsorption. In comparison an historical group of 28 similar patients treated without the use of intraoperative CytoSorb were evaluated. CytoSorb treatment was associated with a reduction in postoperative cytokines (IL6, IL8) and clinical metabolic parameters (lactate and base excess). Moreover, in comparison to the non-CytoSorb group, the CytoSorb patients showed hemodynamic stability (higher mean arterial

pressure) during and after the operation with the need for vasopressors (norepinephrine and epinephrine) being lower within hours after completion of the procedure. The authors conclude that these improvements in patient outcome could be attributed to the use of the CytoSorb adsorber treatment and that its use is a potentially promising therapeutic option for this group of critically-ill patients leading to cytokine reduction, improved hemodynamic stability and organ function.

<https://www.ncbi.nlm.nih.gov/pubmed/28525670>

Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series

Traeger K, Fritzler D, Fischer G, Schröder J, Skrabal C, Liebold A, Reinelt H
Int J Artif Organs 2016;39(3):141-6

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Summary:

Objective of this case series in 16 adult patients undergoing standard or emergency cardiothoracic surgery procedures with prolonged CPB time, developing post-CPB SIRS over the course of the first post-operative 24 hours was to test the effect of CytoSorb on changes of inflammatory cytokines levels, metabolic parameters hemodynamic variables, and patient outcome. Treatment of these patients with CytoSorb in conjunction with CVVHD was associated with decreases in the proinflammatory cytokines, IL-6 and IL-8, as well as a clear stabilization of hemodynamic, metabolic and organ function parameters. All patients with an APACHE score of up to 30 survived. This is the first case series reporting the use of CytoSorb therapy in patients with post-CPB SIRS. Due to a modulation of the cytokine response, CytoSorb may offer a potentially promising new treatment option for severe post-CPB SIRS that presents with hemodynamic instability and requires high doses of vasopressors.

<http://www.ncbi.nlm.nih.gov/pubmed/27140295>

Systemic Inflammatory Response Syndrome in der Herzchirurgie: Neue Therapiemöglichkeiten durch den Einsatz eines Cytokin-Adsorbers während EKZ?

Born F, Pichlmaier M, Peterß S, Khaladj N, Hagl C
Kardiotechnik 2014;2:42-46

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Summary:

In this retrospective observational study in 40 patients undergoing a major cardio-surgical procedure with the use of Cardio-Pulmonary-Bypass (CPB) (n=20 with CPB, n=20 with CPB and an additional CytoSorb-adsorber in the circulation) the authors tested whether intraoperative treatment with CytoSorb has a positive effect on the development of post-operative SIRS. Results showed that CytoSorb contributes to a significant reduction in post-operative SIRS in these patients and emphasizes the reliability and safety of CytoSorb in the setting of cardiac surgery.

<http://www.dgfk.de/content/kardiotechnikoriginalausgaben/214/Born.pdf>

1.2.3. Other indications

Cytokine Adsorption in Critically Ill Patients Requiring ECMO Support.

Lothar A, Benk C, Staudacher DL, Supady A, Bode

C, Wengenmayer T, Duerschmied D

Front Cardiovasc Med. 2019;6:71

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Summary

Systemic inflammation is a key characteristic of sepsis but also in non-infectious conditions such as post-cardiac arrest syndrome. Cytokine adsorption and extracorporeal membrane oxygenation are emerging therapies applied in these critically ill patients, but experience is limited. In this study the authors evaluated cytokine adsorption in critically ill patients requiring support with either veno-venous (vv) or veno-arterial (va) extracorporeal membrane oxygenation (ECMO) support. Data from the first six cases of a prospective single-center registry of patients was analysed (4 with sepsis, 2 post cardiac arrest). The CytoSorb was incorporated directly into the ECMO circuit without interruption of continuous ECMO support. No relevant side effects attributable to the use of CytoSorb were observed. Thirty-day mortality was 83% (predicted mortality 87%), indicating that the decision for adding cytokine adsorption may have been considered as an ultima ratio decision in severe cases with poor prognosis. Data suggest that incorporation of cytokine adsorption into the management of critically ill patients requiring continued ECMO support is feasible and easy to handle. Additional data regarding whether cytokine removal improves clinical outcome in ECMO-treated patients is now being gathered.

<https://www.ncbi.nlm.nih.gov/pubmed/31275944>

Application of hemoadsorption in neonatal and pediatric hyperinflammatory states: a case series.

Milella L, Ficarella M, Calabrese G, Sisto M, Grieco N, Moliterni P, Raimondo P, Cito F, Bellino V, Ranieri M, Giordano M.

American Journal of Pediatrics 2019; 5(2): 34 - 42

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Summary

This was a single center retrospective case series in ten patients (age range 1– 312 months, weight 3.5 – 52 kgs) from a neonatal and pediatric general intensive care unit. The use of CytoSorb in combination with standard therapy, continuous renal replacement therapy (CRRT) and plasmapheresis was observed for the treatment of multiple organ failures of various etiologies including sepsis and cardiac failure. The effect was reported on the inflammatory status, hemodynamics (reduction in catecholamine doses), clinically relevant outcome parameters, feasibility and safety of CytoSorb application. The authors observed a marked decrease in inflammatory mediators (IL-6, IL-10, procalcitonin, C reactive protein, presepsin), a reduction in catecholamine (norepinephrine, epinephrine) and milrinone dosages and an improvement in organ functions, which was particularly pronounced in patients who survived. Early onset of treatment (within 24-48 hours after diagnosis of sepsis) seemed to be beneficial for eventual survival. In this neonatal and pediatric

population, CytoSorb was easy to implement and worked well in combination with simultaneous extracorporeal CRRT / plasmapheresis therapy.

<http://www.sciencepublishinggroup.com/journal/paperinfo?journalid=380&doi=10.11648/j.ajp.20190502.11>

Clinical Effects of hemoadsorption with CytoSorb in patients with severe acute pancreatitis: a case series

Tomescu D, Popescu M, Corina D, Dima S.

Intl J Artif Organs 2019; 42(4): 190 - 3

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Summary

This prospective case series included 12 patients with severe acute pancreatitis who were treated with continuous venovenous hemodiafiltration (CVVHDF) and CytoSorb. Clinical data including organ failure and level of vasopressor support were collected pre- and post CVVHDF and CytoSorb treatment. All patients except one required three consecutive sessions. C Reactive Protein and procalcitonin (PCT) decreased from 242 – 180 mg/L ($p=0.04$) and 2.21 – 1.1 ng/ml ($p=0.02$) respectively. The mean vasopressor support was 0.1 mg/h at the start of treatment but was able to be discontinued in all cases post treatment ($p=0.01$). The number of organ dysfunctions decreased from four to three post treatment. No deaths were recorded during CytoSorb therapy and the 24 hours thereafter, whereas 28 day survival was 66.7%. The therapy was well tolerated and no adverse outcomes were noted during the therapy or up to 24 hrs after the last session. In this first published case series of patients with severe acute pancreatitis, treatment with CytoSorb and CVVHDF improved hemodynamics, decreased vasopressor support, and appeared to re-balance the inflammatory response, as shown by the decrease in inflammatory markers.

<https://journals.sagepub.com/doi/full/10.1177/0391398818823762>

Novel use of Cytosorb haemadsorption to provide biochemical control in liver impairment

Dhokia VD, Madhavan D, Austin A, Morris CG

Journal of Intensive Care Society 2019;20(2): 174 - 181

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Summary

In this case series the use of CytoSorb is described in the management of two patients with drug induced cholestasis and a third with alcoholic hepatitis and subsequent acute on chronic liver failure. CytoSorb was used in these patients to remove bilirubin and bile acids by supporting impaired excretory hepatic function. The first two patients were admitted to the intensive care unit specifically for a trial of CytoSorb therapy for alleviating their symptoms (including general malaise, anorexia and severe pruritus) and as a bridge to recovery of endogenous liver function. In all three cases, meaningful reductions in bilirubin (typically around 50% with 24 h CytoSorb therapy) and even more impressive reductions in bile acids were observed and, in conscious patients, were associated with an improvement in symptoms. The authors conclude that for patients with liver impairment where recovery might be expected or where transplantation is not clinically appropriate, and especially where an existing CRRT extracorporeal circuit is in use (? In AKI),

clinicians may wish to consider CytoSorb as a convenient and effective means of reducing jaundice and clearing bile acids, although further studies are needed. The authors note that these cases suggest that CytoSorb should also be evaluated as an adjunct to support liver excretory functions in other arenas, such as acute liver failure or drug overdose.

<https://www.ncbi.nlm.nih.gov/pubmed/31037112>

1.3. Case reports

1.3.1. Sepsis

Successful application of CytoSorb® hemadsorption in an immunocompromised teenager with collapsing glomerulopathy, acute respiratory distress syndrome, and sepsis.

Keles E, Fidan K, Yenicesu I, Kalkan G

Int J Artif Organs 2019; epub

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Summary

In this case report, a 17-year-old male was admitted to the hospital with severe diarrhoea and was then found to have elevated creatinine levels and proteinuria consistent with collapsing glomerulopathy, a severe form of kidney injury. He was treated with multiple immunosuppressive agents including corticosteroids, mycophenolate mofetil, and rituximab as well as several courses of hemodialysis and plasmapheresis. *Stenotrophomonas maltophilia* bacteria was then found in his blood and catheter cultures. He was un-responsive to treatment (antibiotics, intravenous immunoglobulin, and supportive management including albumin, platelet and erythrocyte concentrations, and fresh frozen plasma), and severe sepsis and multi-organ dysfunction developed. CytoSorb was then added to the hemodialysis for three consecutive days. The use of CytoSorb resulted in an immediate attenuation of the inflammatory response which correlated with a clinical improvement. Specifically the authors reported an immediate recovery in renal parameters, respiratory status, and oxygen demand. The need for erythrocyte, platelet, and albumin transfusions decreased dramatically 24hrs after CytoSorb therapy. Despite a high mortality risk (Pediatric Index of Mortality score (PIM II) of 100), the patient was able to be transferred from the intensive care unit to the general ward after the three sessions of CytoSorb. In this immune-compromised patient with sepsis and collapsing glomerulopathy with multiorgan failure CytoSorb was successfully used as a rescue therapy. The authors state that the use of CytoSorb in this case was without any device related adverse events and there were no problems installing the adsorber.

<https://www.ncbi.nlm.nih.gov/pubmed/31277560>

Clindamycin clearance during CytoSorb hemoadsorption case report and pharmacokinetic study

Poli E, Simoni C, Andre P, Buclin T, Longchamp D, Perez M-H, Ferry T, Schneider A
Int J of Artif Organs 2019; 42(5):258 - 62

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Summary

This is a case report of a severely sick 14-year-old boy with Panton-Valentine leucocidin producing methicillin-resistant *Staphylococcus aureus* infection (PVL-MRSA) and also Influenza B pneumonia requiring veno-arterial extra-corporeal membrane oxygenator (VA-ECMO) for refractory shock. In the absence of any response to conventional therapy, Cytosorb was inserted directly into the VA-ECMO circuit resulting in, according to the authors, a spectacularly rapid and sustained decrease in vasopressor requirements (noradrenaline, vasopressin and dopamine). In total four adsorbers were used for 81 hours, and eventually, despite the severity of his initial condition the patient was discharged home on day 156. Since the antibiotic clindamycin which is a key component of PVL-MRSA treatment might be removed by Cytosorb hemoadsorption, the authors developed a pharmacokinetic model incorporating variable plasma clearance based on serial plasma concentrations measurements which were performed before, during and after Cytosorb use. According to this model, use of Cytosorb did not seem to result in significant clindamycin removal so therefore its use with CytoSorb appears safe and feasible requiring no adaptation of dosage necessary.

<https://www.ncbi.nlm.nih.gov/pubmed/30819024>

First successful hemoadsorption using CytoSorb(R) in a septic pediatric patient in Kazakhstan: A case report.

Saparov A, Sazonov V, Tobylbaeva Z, Isakov S, Bekpan A, Autalipov D, Muratbekova B, Manaybekova Z, Anikin V.

Int J Artif Organs 2019;42(6):315-317

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Summary

This is the first CytoSorb treatment in Kazakhstan where CytoSorb was used in an 8-month-old patient with a body weight of 5600 g. 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 veno-venous hemodialysis (CVVHD) was started along with CytoSorb which was run for 36 hours. CytoSorb resulted in a reduction of inflammation markers IL-6, S100, procalcitonin, and C-reactive protein. 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 vasopressors, the acid-base balance was maintained, and the patient was weaned from mechanical ventilation onto 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. While it must be noted that CytoSorb use in the pediatric population is currently 'off label', this is the smallest case reported so far in the peer review literature (5600g).

<https://www.ncbi.nlm.nih.gov/pubmed/30614343>

Successful use of combined blood purification techniques in splenectomised patient with septic shock in streptococcus pneumoniae infection - a case report.

Sinkovic A, Kit B, Markota A.

BMC Infect Dis 2018; 18(1): 433

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Summary

Septic cardiomyopathy, caused by the cytokine storm, is a severe cardiac impairment in sepsis and is completely reversible if the patient survives. This is a case of a 52 yr old woman with a history of chemotherapy for lymphoma, splenectomy and autologous bone marrow transplantation, who suffered acute severe pneumococcal sepsis, septic shock and septic cardiomyopathy, resistant to pharmacological therapy including fluids and vasopressors. After 36 hrs of maximum standard therapies, it was decided to add extended hemodynamic monitoring, and continuous veno-venous hemofiltration plus CytoSorb therapy because of the persistently resistant shock, to try to improve the hemodynamic situation and modulate the inflammatory response. After 24 hours of therapy the hemodynamic situation stabilized (including left ventricular systolic function), her IL-6 level dropped from 114 pg/ml to 14.2pg/ml and vasopressors could be ceased. This case shows that early removal of inflammatory cytokines enabled the reversal of circulatory failure and significant improvement of the septic cardiomyopathy resulting in improved hemodynamic status, lactacidosis and clinical outcome in this patient.

<https://www.ncbi.nlm.nih.gov/pubmed/30157806>

Hemoadsorption in a Case of Severe Septic Shock and Necrotizing Fasciitis Caused by Nontraumatic Renal Rupture due to Pyelonephritis with Obstructive Uropathy

Kousoulas L, Wittel U, Fichtner-Feigl S, Utzolino S.

Case Rep Crit Care 2018: 5248901

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Summary

In this case a 25-year-old female presented with a four week history of acute worsening abdominal pain. She was found to have peritonitis, leukocytosis, severe lactic acidosis and pronounced anaemia, with imaging consistent with nontraumatic renal rupture with retroperitoneal abscess, perforation of the colon, and severe necrotizing fasciitis of the right lower limb. She underwent a right nephrectomy, a right hemicolectomy, surgical debridement of the retroperitoneum, and upper thigh amputation. Due to severe septic shock and rhabdomyolysis with acute renal failure combined treatment of hemoadsorption using Cytosorb (three cycles) and continuous venovenous hemodialysis (CVVHD) was started. Treatment was associated with rapid hemodynamic stabilization and decrease in IL-6 as well as myoglobin levels. Subsequently the patient recovered and was discharged home with no signs of infection and with normal renal function. The authors conclude that early treatment of the patient with Cytosorb led to the rapid hemodynamic and metabolic stabilization and preservation of the renal function, suggesting that hemoadsorption might be a rescue therapy in patients with severe septic shock and traumatic rhabdomyolysis.

<https://www.ncbi.nlm.nih.gov/pubmed/29854478>

A case of viper snake bite presenting with gangrene and sepsis associated multi-organ failure, successfully treated with CytoSorb as an adjunct therapy – a clinical experience

Paul R, Jha BK, Shetty VK.

J. Evid. Based Med. Healthc 2018; 5 (6): 559 – 61

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Summary

This is a case of a 32-year old male patient bitten by a viper who developed cellulitis, acute renal failure, and disseminated intravascular coagulation (DIC), septicemia and acute respiratory distress syndrome (ARDS). Because of necrotizing fasciitis and gangrene he had to have his lower limb amputated and was admitted to Intensive Care post op in septic shock (APACHE II 29 and SOFA 15). On the third post op day, in view of the multi-organ failure, he was treated with Cytosorb, along with standard care as per the International Sepsis Guidelines. After two Cytosorb treatments each for 24-hours, renal, hemodynamic and respiratory parameters improved remarkably and returned to normal over 5 days. The authors state that Cytosorb along with standard care can be a safe and advantageous extracorporeal therapy option to treat snake bite patients with multi organ failure to help them recover.

[https://jebmh.com/assets/data_pdf/Rajib_Paul - FINAL.pdf](https://jebmh.com/assets/data_pdf/Rajib_Paul_-_FINAL.pdf)

Use of CytoSorb in Traumatic Amputation of the Forearm and Severe Septic Shock

Stelzer H, Grieb A, Mustafa K, Berger R.

Case Reports in Critical Care 2017; Article ID 8747616

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Summary

This case study reports on a 49-year-old male patient admitted to hospital following traumatic amputation of his right forearm that was cut off at the elbow joint while working on a land fill site. After initial treatment for shock, he received immediate replantation and was transferred to the ICU. Due to the anticipated risk of a complex systemic infection, continuous renal replacement therapy in combination with CytoSorb was initiated. The patient received 6 CytoSorb treatments for 12 hrs each. During the course of the combined treatment, a rapid improvement in hemodynamics was noticed (noradrenaline dose could be halved during the first treatment), as well as a significant reduction in IL-6 (from >5000 to 43 pg/ml) and lactate levels (from 4 mmol/l to within the normal range). Despite recurring sepsis and the necessity for amputation, the patient clinically stabilized and underwent complete recovery 18 days after admission. Early treatment with a combination of CVVHDF and CytoSorb was accompanied by an attenuation of the systemic inflammatory reaction, which subsided without major or permanent organ damage, despite the impressive pathogen spectrum and the pronounced local damage.

<https://www.ncbi.nlm.nih.gov/pubmed/29423323>

Use of Hemadsorption in a Case of Pediatric Toxic Shock Syndrome

Berkes A, Szikszay E, Kappelmayer J, Kerenyi A, Szabo T, Ujhelyi L, Bari K, Balla G, Balla J

Case Rep Crit Care 2017: 3818407

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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 female 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 which 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 for removing bacterial toxins and inflammatory mediators and could therefore play a role in the clinical management of toxic shock syndrome.

<https://www.ncbi.nlm.nih.gov/pubmed/28791185>

Effect of extracorporeal cytokine removal on vascular barrier function in a septic shock patient

David S, Thamm K, Schmidt BM, Falk CS, Kielstein JT

J Intensive Care 2017;5:12

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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 inotropics and 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 to 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 CytoSorb in septic shock patients might-at least in part-be promoted via protection of vascular barrier function.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=28127473>

Hemadsorption with Adult CytoSorb(R) in a Low Weight Pediatric Case

Cirstoveanu CG, Barascu I, Mc Kenzie Stancu S

Case Rep Crit Care 2017:6987167

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Summary

This case study describes a nine-month old male infant admitted to the Neonatal Intensive Care Unit due to sepsis post cardiac surgery (Fallot tetralogy), and multi-system organ failure (MSOF), including liver and renal failure which was successfully treated by a combination of continuous hemodiafiltration (HDF) and hemoadsorption with CytoSorb®. CytoSorb was added to the set up on day 9 due to increasing bilirubin levels. Over the 49 hour period of hemoadsorption plus CytoSorb, total bilirubin decreased from 54 to 14 mg/dl, the patient's general status improved considerably, accompanied by a rapid decrease in liver enzymes (aminotransferases). Hemodynamic status also improved and requirement for inotropes decreased rapidly during the two days of CytoSorb treatment. The patient was discharged home after 34 days of hospitalization, in good general health. This is the first published case of the successful use of CytoSorb treatment in such a young patient (9 months old, 9 kilos in weight).

<https://www.ncbi.nlm.nih.gov/pubmed/?term=28127437>

Cytokine Adsorption in Septic Shock and Multiorgan Failure Following Major Obstetric Hemorrhage

Withanage RK, Nilmini Wijesuriya N

Journal of Case Reports 2017;7(1):124-126

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Summary

In this case report a 38-year-old previously healthy patient developed septic shock with multi-organ failure following recurrent cardiac arrests due to massive obstetric hemorrhage. She had secondary hepatic impairment and acute kidney injury. Her medical care involved several surgical interventions and admission to intensive care. Continuous Renal Replacement Therapy was started on day 3 in ICU and CytoSorb was added to the hemofilter. Her liver enzymes (AST and ALT) and bilirubin started to decrease quite dramatically 12 hrs after the start of CytoSorb, her white blood cell count and CRP also decreased, and her vasopressor and inotropic support could also start to be tailored off. This case shows how a patient with major obstetric hemorrhage leading to recurrent cardiac arrests complicated by ischemic hepatocellular and kidney injury with secondary sepsis was managed successfully with the cytokine adsorber.

<http://www.casereports.in/articles/7/1/Cytokine-Adsorption-in-Septic-Shock-and-Multiorgan-Failure-Following-Major-Obstetric-Hemorrhage-abstract.html>

Hybrid blood purification strategy in pediatric septic shock

Bottari G, Taccone FS, Moscatelli A

Crit Care 2016;20(1):366

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Summary:

In this letter to the editor, the case of a 12 year old girl with a history of acute lymphatic leukemia and recent chemotherapy admitted with fever and fatigue is described (cause of which later found to be klebsiella pneumonia from a central line infection). She was give fluid resuscitation, empiric antibiotics and admitted to ICU. Because of ongoing hypotension, epinephrine and norepinephrine were initiated, however she remained severely hypotensive. Continuous renal replacement therapy was started with a high cut off filter (Septex) along with a CytoSorb adsorber. After 48 hours a significant

reduction in the vasopressors was observed, lactate decreased as did procalcitonin. The 'hybrid' extracorporeal blood purification - EBP (combination of CytoSorb and Septex) was continued for 72 hours in total and the patient discharged after 10 days. No adverse events related to the procedure were observed. The authors state that the combination of 'hybrid' EBP might have a synergistic effect in the setting of pediatric septic shock. <https://www.ncbi.nlm.nih.gov/pubmed/27832804>

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

Lees NJ, Rosenberg A, Hurtado-Doce AI, Jones J, Marczin N, Zeriouh M, Weymann A, Sabashnikov A, Simon AR, Popov AF
J Artif Organs 2016;19(4):399 - 402

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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 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 and Cytosorb therapy. Use of the Cytosorb appeared to result in rapid resolution of neutropenia, reversal of toxic shock and rapid weaning off of the high dose vasopressors. <http://link.springer.com/article/10.1007%2Fs10047-016-0915-8>

First case of toxic shock treated with haemoadsorption by CytoSorb in the Netherlands

van der Linde GW, Grootendorst A
Neth J Crit Care 2016;24(2):27-29

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Summary:

This case study reports on a 17-year-old male who reported a local rural hospital with complaints of pretibial pain in his right leg, after he accidentally cut his leg while in the fields a few days earlier. He was diagnosed with having a phlegmon with an abscess followed by surgical debridement with wound nettoyage with no clinical signs of subcutaneous emphysema or necrotising fasciitis. Postoperatively the patient's condition deteriorated and after admission to ICU he developed erythema, spreading from the right lower leg to the right upper leg, abdominal wall and the left leg, consistent with toxic shock syndrome and subsequent development of septic shock due to invasive S. aureus infection with respiratory failure, hemodynamic instability treated with vasopressors, hydrocortisone, antibiotic therapy. Due disease severity, CRRT was initiated with a CytoSorb adsorber with the only goal to remove cytokines (despite absence of acute kidney injury and no need for renal replacement therapy). Within six hours the erythema progression stopped and after 12 hours the need for vasopressors diminished. The erythema diminished after a few hours and had disappeared after 24 hours. After

cessation of CytoSorb physicians concluded that the patient was no longer septic and diuretics were started because of fluid overload. Respiration improved, the ventilator support was weaned and the patient was extubated on day 5 after admission, within 72 hours of cessation of CRRT. In the authors opinion, the patient would have survived without CytoSorb, but they felt that his stay in the ICU might have been shortened by the CytoSorb adsorber http://njcc.nl/sites/default/files/pdf/case-report4_0.pdf

Cytokine Reduction in the Setting of an ARDS-Associated Inflammatory Response with Multiple Organ Failure

Traeger K, Schuetz C, Fischer G, Schroeder J, Skrabal C, Liebold A, Reinelt H
Case Reports in Critical Care 2016; Vol 2016: 9852073

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Summary:

This case study reports on a 45-year-old male admitted with a small bowel obstruction due to torsion who was immediately scheduled for surgical intervention. At anesthetic induction, the patient aspirated and subsequently developed severe systemic inflammatory response syndrome with acute respiratory distress syndrome, and multiple organ failure requiring the use of ECMO, CRRT, antibiotics, and low dose steroids. Due to the rapid deterioration in his clinical status and a concurrent surge in inflammatory biomarkers, CytoSorb was added to the CRRT circuit. The combined treatment resulted in a rapid and significant reduction in the levels of circulating inflammatory mediators. This decrease was paralleled by marked clinical stabilization of the patient including a significant improvement in hemodynamic stability and a reduced need for norepinephrine and improved respiratory function, and indirect measures of capillary leak syndrome. The authors attribute the clinical improvement to the rapid control of the hyperinflammatory response and the reduction in the inflammatory mediators using a combination of CytoSorb and other therapies. CytoSorb treatment was safe and well tolerated, with no device-related adverse effects observed. <http://www.hindawi.com/journals/cricc/2016/9852073/>

CytoSorb, a novel therapeutic approach for patients with septic shock: a case report

Hinz B, Jauch O, Noky T, Friesecke S, Abel P, Kaiser R
Int J Artif Organs 2015;38(8):461-4

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Summary:

This case study reports on 72-year-old male patient with periodically recurring infectious episodes admitted with suspected urosepsis. Over the following hours his hemodynamic situation deteriorated markedly, with respiratory-metabolic acidosis, elevated inflammatory markers, severely disturbed coagulation, increased retention parameters, liver dysfunction, and confirmation of bacteria and leucocytes in his urine. After admission to the ICU in septic shock the patient received renal support with additional hemoadsorption using CytoSorb. Three CytoSorb sessions were run over the following days resulting in reductions in procalcitonin, C-reactive protein and bilirubin and a markedly reduced need for vasopressors and corresponding hemodynamic improvement (i.e., cardiac index, extravascular lung water). Due

to a recurring inflammatory “second hit” episode, another CytoSorb session was run, resulting in the marked decrease in leukocytosis and liver (dys)function parameters. The rapid hemodynamic stabilization with reduction in vasopressor needs and reduction of the capillary leak as well as the quick reduction in infection markers were the main conclusions drawn from the use of CytoSorb in this patient. Additionally, treatment appeared to be safe and was well tolerated. Further studies are necessary to elucidate to what extent these favorable consequences are attributable to the adsorber itself.

<http://www.ncbi.nlm.nih.gov/pubmed/26349530>

CytoSorb-friend or foe!!

Pattnaik SK, Panda B.

Indian J Crit Care Med 2015;19(5):296

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Summary:

In this letter to the editor the authors refer to the case report by Basu et al. (PMID 25538418), share their experiences with a similar patient treated with CytoSorb and discuss some of the intriguing points of their treatment. A 79-year-old male patient with severe septic shock (urosepsis) and multi-organ failure and an APACHE II score of 32, was started on CytoSorb therapy plus sustained low effusion dialysis along with standard surviving sepsis guidelines treatment. Within 3 days, hemodynamic parameters, ventilator requirements and urine output improved. APACHE II score improved after day 3 of therapy, and IL-6 levels reduced after the last session. Since the patient started to deteriorate clinically from day 5 despite on-going supportive care, the authors bring up a possible immunosuppressive effect and express their concern as to whether CytoSorb therapy could be the cause of this. They note that randomized controlled trials are necessary to check the risk-benefit ratio of hemadsorption therapy in severely septic patients.

<http://www.ncbi.nlm.nih.gov/pubmed/25983446>

Can cytokine adsorber treatment affect antibiotic concentrations? A case report

Zoller M, Döbbeler G, Maier B, Vogeser M, Frey L, Zander J

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

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Summary:

This case study reports on a patient with an excessive inflammatory response, septic shock and multi organ failure. Initial laparotomy revealed an ischemic bowel with peritonitis requiring immediate jejunum and colon segmental resection and ileotransverse colostomy. Intravenous antibiotic treatment was started with meropenem and linezolid. Due to the persistent excessive cytokine storm, four CytoSorb adsorbers were used over 96 hours. Therapy for septic shock included surgery, antibiotic treatment and CytoSorb which resulted in a substantial improvement in the patient’s condition, including renal and liver function, and cardiorespiratory status. However, after 4 weeks and seven further repeat laparotomies, the patient died from multiple organ failure. The use of CytoSorb in this patient proved to be effective and safe. Of note, intra-patient variability of antibiotic levels was high with substantially lower peak levels for both antibiotics when CytoSorb was in use, pointing towards

potential adsorption however, no negative impacts on the effectiveness of antibiotic therapy was detected. The authors suggest therapeutic drug monitoring wherever possible or, if not available, high loading doses or shorter intervals of administration be used to achieve adequate antibiotic levels with further studies needed.

<http://www.ncbi.nlm.nih.gov/pubmed/25786479>

First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: A case report

Bruenger F, Kizner L, Weile J, Morshuis M, Gummert JF
Int J Artif Organs 2015;38(2):113-6

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Summary:

This case study reports on a 39-year-old patient with fulminant Acute Respiratory Distress Syndrome and cardiogenic septic shock. After implantation of a veno-arterial ECMO for circulatory support the patient developed acute renal failure making initiation of CVVH necessary. Due to a complete cardiac arrest in both ventricles, a left ventricular assist device (LVAD) in combination with right ECMO (rECMO) was implanted despite manifest septic conditions. In the post-operative course his condition deteriorated drastically and a CytoSorb adsorber was installed in to the CVVH circuit resulting in a decrease in IL-6, procalcitonin, and C-reactive protein concomitant with significantly reduced vasopressor support. No adverse device-related side effects were documented during or after the treatment sessions. This is the first clinical case report of a highly septic patient treated with the combined use of LVAD, rECMO, CVVH, and CytoSorb. The combination was practical, technically feasible, and beneficial for the patient and might represent a reasonable approach for improving survival in patients with multiple organ dysfunction necessitating several organ supportive techniques.

<http://www.ncbi.nlm.nih.gov/pubmed/25656010>

Use of a novel hemoadsorption device for cytokine removal as adjuvant therapy in a patient with septic shock with multi-organ dysfunction: A case study

Basu R, Pathak S, Goyal J, Chaudhry R, Goel RB, Barwal A
Indian J Crit Care Med 2014;18:822-4

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Summary:

This case study reports on a 36-year-old female diagnosed with urosepsis and multi-organ dysfunction (Acute Respiratory Distress Syndrome, Acute Kidney Injury, and arterial hypotension). SOFA score was 15, MODS score 10 and APACHE II score 30. CytoSorb was added along with CRRT. The patient received three consecutive treatments with CytoSorb over the following three days. After initiation of therapy the patient improved hemodynamically. During the further course urine output increased with improvement in ventilator parameters. SOFA score at the end of treatment was 4, MODS score was 5 and APACHE II score was 7. There were no adverse events and laboratory parameters before and after CytoSorb therapy were within normal range.

CytoSorb therapy in septic shock patients with multi-organ failure might be an option as a rescue therapy.

<http://www.ncbi.nlm.nih.gov/pubmed/25538418>

Effects of a novel cytokine haemoadsorption system on inflammatory response in septic shock after cephalic pancreatectomy – a case report

Tomescu D, Dima SO, Tănăsescu S, Tănase CP, Năstase A, Popescu M
Romanian Journal of Anaesthesia and Intensive Care 2014;21(2):134-138

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Summary:

This case study reports on a 50 year old man with postoperative septic shock after undergoing cephalic pancreatectomy for a pancreatic cystic tumor. In total, two consecutive CVVH sessions with CytoSorb were performed over a period of 64 hours (24 hours each). The clinical effects associated with CytoSorb correlated with a rebalance in cytokine levels and translated into a more stable hemodynamic profile with a stable cardiac output and normalization of systemic vascular resistance index and decreased vasopressor requirements. The technology was simple to use, well tolerated with no adverse events, and could be easily added into conventional CVVH machines.

<http://www.jurnalul-anestezie.ro/2014/2/11.pdf>

Septic shock secondary to β -hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy

Hetz H, Berger R, Recknagel P, Steltzer H
Int J Artif Organs 2014;37(5):422-6

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Summary:

This case study reports on a 60-year-old female who was admitted to hospital due to a radial fracture. After surgical wound care by osteosynthesis the patient developed surgical wound infection progressing to necrotizing fasciitis with additional proven infection from β -hemolytic streptococcus. The patient went into septic shock exhibiting a full picture of a MODS. Therefore, the patient was treated with CytoSorb therapy over a period of four days, resulting in a significant reduction of IL-6 and an overall improvement of the patient's condition. In this case, CytoSorb seems to be an interesting and safe extracorporeal therapy to stabilize and bridge septic patients to surgery or recovery.

<http://www.ncbi.nlm.nih.gov/pubmed/24811308>

Pattern of cytokine removal using an adsorption column CytoSorb during severe *Candida albicans* induced septic shock

Bracht H, Schneider EM, Weiß M, Hohmann H, Georgieff M, Barth E
Infection 2013;41(Suppl 1:S1–S90); Abstract No. 133

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Summary:

This **case study** reports on a 46 old female with hypodynamic septic shock and documented candidemia infection. CRRT was started in combination with CytoSorb therapy. Within 24 h of hemoadsorption, vasopressor and inotropic support could be withdrawn. Several inflammatory mediators (e.g. IL-6, 8, 10)

could be reduced significantly. Interestingly, the authors also found an almost perfect immunological reconstitution of a variety of immune parameters including HLA-DR.

Improvement of hemodynamic and inflammatory parameters by combined hemoadsorption and hemodiafiltration in septic shock: a case report

Mitzner SR, Gloger M, Henschel J, Koball S

Blood Purif 2013;35(4):314-5

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Summary:

This case study reports on an 80 year old male diagnosed with pneumogenic septic shock. The patient was in clinical need for renal replacement therapy and was therefore started on citrate-anticoagulated CVVHD in combination with a CytoSorb adsorber for 24 hours. Over time IL-6 and other markers of inflammation as well as need for vasopressors could be drastically reduced while treatment was safe and well tolerated.

<http://www.karger.com/Article/Abstract/351206>

1.3.2. Cardiac surgery

CytoSorb hemoadsorption and mechanical circulatory support in a newborn with refractory shock after congenital heart surgery

Perez MH, Maitre G, Longchamp D, Amiet V, Natterer J, Ferry T, Schneider A, Plaza Wuthrich S and Di Bernardo S.

Int J Artif Organs 2019; epub

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Summary

This is the case of a 4kg newborn boy with cardiogenic and vasoplegic shock secondary to cardiopulmonary bypass for atrioseptostomy, and prostaglandin treatment in the context of hypoplastic left heart syndrome performed around 24 hours post-partum. Post-operatively he required ongoing high levels of vasopressor and inotropic support so mechanical circulatory support (MCS) was added to restore adequate tissue perfusion. However, refractory vasoplegic shock continued requiring ongoing high doses of vasopressors, the patient remained anuric, and, as he also did not respond to steroids, the decision was taken to install CytoSorb into the MCS circuit. After an initial short hypotensive episode, blood pressure stabilized, diuresis restarted and increased, lactate normalized and vasopressor support was able to be gradually weaned over the following hours. The same adsorber was used for 72h due to the low weight of the patient. During these 72hrs, antibiotics levels (piperacillin and vancomycin) were monitored when possible. The dosage of prostaglandins was also increased due to their possible removal by CytoSorb. Once the CytoSorb was removed there was a rebound in the vancomycin levels due to a lack of timely dose reduction, hence the authors recommend therapeutic drug monitoring also immediately after CytoSorb. Of note, despite the initial severity of the condition, multiple organ failure did not develop. This is the first case in such a young patient (around 2 days old), and only 4kg in weight. The authors state that the association of the CytoSorb with mechanical circulatory support finally allowed a rapid and significant stabilization of the hemodynamic situation accompanied by weaning of catecholamine treatment

and resumption of diuresis within a few hours after initiation of CytoSorb therapy. This case shows that CytoSorb is a feasible and easy therapy that can have a positive effect in the management of an uncontrolled inflammatory process even in a newborn.

<https://www.ncbi.nlm.nih.gov/pubmed/30968739>

Bilirubin Removal Using CytoSorb Filter in a Cardiac Surgical Patient.

Singh A, Mehta Y, Trehan N.

J Cardiothorac Vasc Anesth 2019; 33: 881 – 3

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Summary

In this case report a 63 year old woman was admitted to the Cardiac Intensive Care following mitral and tricuspid valve repair. Her postoperative course was complicated by prolonged ventilatory support, tracheostomy, very high vasopressor support (norepinephrine 3.5 µg/kg/min), sepsis and multiorgan failure involving the liver, kidneys, and brain. Continuous venovenous hemodiafiltration (CVVHDF) with CytoSorb was initiated and continued for 3 days in total, resulting in significant decreases in interleukin-6 (from 245.5 to 53.9 pg/mL) and bilirubin (from 24.5 to 10.8 mg/dL), with reductions in vasopressor requirement (norepinephrine 0.5 µg/kg/min) and improvement in urine output (0.5 mL/kg/h). The authors describe the role of CytoSorb as an effective means for the irreversible removal of cytokines and toxic molecules, concluding that it may act as a promising therapeutic option for critically ill patients with multiorgan failure after cardiac surgery and may help in cytokine reduction with improved organ function.

<https://www.ncbi.nlm.nih.gov/pubmed/30292390>

Continuous cytokine haemoadsorption incorporated into a venoarterial ECMO circuit for the management of postcardiotomy cardiogenic and septic shock – a case report

Nemeth E, Szigeti S, Varga T, Doroczi L, Barati Z, Merkely B, Gal J.

Perfusion 2018; 33(7): 593-6

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Summary:

In this case a 46-year-old male patient underwent emergency cardiac surgery because of infective endocarditis (IE). The development of postcardiotomy cardiogenic shock associated with cardiac surgery required the implantation of venoarterial (VA)-ECMO. Three days later the patient developed secondary septic shock, and, due to rapidly increasing vasopressor requirements, CytoSorb was installed into the VA-ECMO circuit. A significant and rapid improvement in the patients hemodynamic and metabolic parameters was observed and after 24 hrs of treatment, the CytoSorb treatment could be stopped and VA ECMO ceased after 7 days. Advanced intensive care led to an improvement in the patient's condition however the patient died from a new onset of fulminant septic shock two months after his initial cardiac surgery. This case demonstrates that VA-ECMO is suitable for direct installation of the CytoSorb cartridge. The authors report that this novel application of CytoSorb is safe, feasible and effective and can contribute to the optimal management

of patients suffering from simultaneous postcardiotomy cardiogenic shock and septic shock.

<https://www.ncbi.nlm.nih.gov/pubmed/29779449>

ECMO and cytokine removal for bridging to surgery in a patient with ischemic ventricular septal defect - a case report

Marek S, Gamper G, Reining G, Bergmann P, Mayr H, Kliegel A
Int J Artif Organs 2017; 40(9): 526-9

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Summary:

Post-infarction ventricular septal defect (VSD) remains a serious and often lethal complication of percutaneous coronary intervention. This is a case report the use of veno-arterial extracorporeal membrane oxygenation (VA ECMO) and extracorporeal blood purification therapy (CytoSorb) in a 64-year-old patient with ischemic VSD leading to protracted cardiogenic shock and hemodynamic instability requiring large doses of catecholamines after a myocardial infarction. After a few hours with ECMO and CytoSorb the patient began to stabilize hemodynamically. The catecholamines could be significantly reduced within the first 36 hours of treatment. After 4 days of treatment with ECMO and CytoSorb the patient was stable enough to be taken to surgery, where repair of the VSD and bypass grafting was successfully performed.

<https://www.ncbi.nlm.nih.gov/pubmed/28574104>

1.3.3. Liver

Hemoadsorption in isolated conjugated hyperbilirubinemia after extracorporeal membrane oxygenation support. Cholestasis of sepsis: A case report and review of the literature on differential causes of jaundice in ICU patient.

Piowarzyk P, Kutnik P, Potrec-Studzinska B, Sysiak-Slawecka J, Pypulak E, Borys M, Czuczwar M
Int J Artif Organs 2019;42(5): 263 - 8

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Summary

In this case report a patient with septic shock and severe acute respiratory distress syndrome was retrieved to the authors hospital for veno venous Extracorporeal Membrane Oxygenation (VV ECMO). Three days after initiation of ECMO, the patient developed jaundice, with an increase in liver enzymes including bilirubin, Gamma-glutamyltransferase and Alkaline phosphatase, but without elevation of alanine aminotransferase and INR. Although ECMO was stopped, bilirubin serum levels continued to increase, reaching the peak of 18.41 mg/dL of total and 15.67 mg/dL of direct bilirubin. Abdominal computed tomography excluded viral hepatitis and sepsis-related cholestasis was diagnosed. Despite cessation of sedation, the patient remained unconscious. Hemoadsorption therapy with CytoSorb was initiated with renal replacement therapy due to prolonged high levels of conjugated bilirubin. After 2 x 24 hrs of treatment, total bilirubin levels decreased to 2.4 mg/dL, the patient regained spontaneous eyes opening and could be transferred back to the regional hospital. Hyperbilirubinemia did not return in the 3 month follow up period indicating that CytoSorb may have supported a sustained rebalance between the inflammatory process, cytokine production and bilirubin turnover. In this patient, CytoSorb was a useful therapeutic option in sepsis induced prolonged

cholestasis.

<https://www.ncbi.nlm.nih.gov/pubmed/30919732>

Use of hemoadsorption in a case of severe hepatic failure and hyperbilirubinemia

Faltlhauser A, Kullmann F

Blood Purif 2017;44:98–99

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Summary:

In this case study a 59 yr old patient with active hepatitis B, elevated liver enzymes and increased total bilirubin was given CVVHD with CytoSorb for 7 days for acute kidney injury and to rebalance the excessive hyperbilirubinemia. Hepatic encephalopathy, bilirubin and liver enzymes all reduced daily with ammonia levels returning to normal. This is the first clinical case describing the use of CytoSorb hemoadsorption during hyperbilirubinemic hepatic dysfunction due to active hepatitis B infection.

<https://www.ncbi.nlm.nih.gov/pubmed/28355595>

Application of Hemoadsorption in a Case of Liver Cirrhosis and Alcohol-Related Steatohepatitis with Preexisting Hepatitis C Infection

Buttner S, Patyna S, Koch B, Finkelmeier F, Geiger H, Sarrazin C, Farnik H

Blood Purif 2017; 44(1): 30-31

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Summary:

This is the first case study that confirms the successful direct removal of liver toxins, including ammonia and bile acids by CytoSorb. In this report a 36-year-old patient with chronic viral hepatitis C and chronic alcohol abuse was admitted to ICU with decompensated ethanol toxic liver cirrhosis. Despite an initial attempt to stabilize the patient using an albumin infusion and multiple paracenteses the patient developed hepatorenal syndrome and subsequent dialysis dependency. An evaluation as to whether the patient could be listed for a liver transplantation was rejected. As a „last resort“, CytoSorb treatment was initiated with the rationale to remove inflammation-triggering factors and liver toxins (bile acids, bilirubin, ammonia) in the context of his systemic inflammatory condition as well as his acute-on-chronic liver failure. In total two treatments with CytoSorb were carried out for 6 hours each with a treatment pause of 5 days between adsorbers due to lack of evidence of use in this kind of patient. Pre and post adsorber measurements during the second treatment confirmed efficient removal of ammonia, bilirubin and bile acids. After initially recovering well, the patient subsequently developed nosocomial pneumonia, then fulminant pneumogenic sepsis and died three weeks later. In this case report treatment with combination of CRRT and CytoSorb worked extremely well and effectively as a liver support. As a consequence, hepatic encephalopathy improved significantly due to efficient removal of liver toxins including ammonia.

<https://www.ncbi.nlm.nih.gov/pubmed/28237980>

First report of cytokine removal using CytoSorb® in severe noninfectious inflammatory syndrome after liver transplantation

Tomescu DR, Dima SO, Ungureanu D, Popescu M, Tulbure D, Popescu I

Int J Artif Organs 2016;39(3):136-40

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Summary:

In this report a 46-year-old man with primary graft non-function after liver transplantation who underwent emergency re-transplantation with an ABO-incompatible graft is described. A severe inflammatory response syndrome (SIRS) was noted in the perioperative period of re-transplantation. The patient was successfully treated with CytoSorb in combination with CVVH throughout the intraoperative and early postoperative period. During and after each treatment a significant and rapid decrease of pro- and anti-inflammatory cytokines was observed (IL-6, IL-10, MCP-1). Reduction in cytokines was associated with normalization of cardiac output, systemic vascular resistance, and improved liver function. The authors believe this is the first case in which hemoadsorption in combination with CVVH has been used to manage SIRS in a patient with primary graft non-function undergoing emergency re-transplantation.

<http://www.ncbi.nlm.nih.gov/pubmed/27079418>

First description of SPAD combined with cytokine adsorption in fulminant liver failure and hemophagocytic syndrome due to generalized HSV-1 infection

Frimmel S, Schipper J, Henschel J, Yu TT, Mitzner SR, Koball S.

Liver Transpl 2014;20(12):1523-4

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Summary:

This case study reports on a 50-year-old immunocompetent woman who was admitted to hospital for acute hepatitis with acute liver failure. After transfer to ICU the patient rapidly developed multi organ failure and was listed for highly urgent liver transplantation. Since existing liver support techniques (MARS treatment) for bridging while waiting for liver transplantation had no effect, Single Pass Albumin Dialysis (SPAD) in combination with CytoSorb was applied resulting in a marked decrease in IL-6, bilirubin as well as a reduction of vasopressor need. Orthotopic liver transplantation could be successfully performed on the 4th day on ICU. CytoSorb treatment was safe and well-tolerated, without any adverse events. CytoSorb seems to be promising and new approach for patients with liver failure.

<http://www.ncbi.nlm.nih.gov/pubmed/25233991>

1.3.4. Myoglobinemia

Hemoadsorption in Infection-Associated Rhabdomyolysis

Suefke S, Sayk F, Nitschke M

Ther Apher Dial 2016;20(5):531-3

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Summary:

This case study reports on a 55-year-old patient with history of arterial hypertension who was admitted with complaints of dyspnea and symptoms of respiratory infection. He went on to develop fulminant pneumogenic sepsis and acute respiratory distress syndrome (ARDS) with considerable requirements for fluids and catecholamines for hemodynamic stabilization. Plasma concentrations of myoglobin and creatine kinase increased drastically

on top of his inflammatory response, indicative of severe infection-associated rhabdomyolysis. For treatment of his acute kidney injury grade III (crush kidney) and to lower inflammatory mediator and myoglobin levels CytoSorb was installed in combination with renal replacement therapy (RRT). During the course of the treatment, plasma concentrations of IL-6, procalcitonin, myoglobin and creatine kinase decreased significantly. Levels of leucocytes, thrombocytes, alanine aminotransferase, and aspartate aminotransferase normalized over the 4 consecutive treatments. The clinical situation improved considerably including improvement of the patient's respiratory situation and liver function and he was discharged on day 13 with ongoing renal failure and need for RRT. In this patient, the application of CytoSorb resulted in a significant reduction of cytokines (i.e. IL-6) but also had an important additive effect on myoglobin removal.

<http://www.ncbi.nlm.nih.gov/pubmed/26991687>

Cytosorb™ in a patient with legionella-pneumonia associated rhabdomyolysis

Wiegele M, Krenn CG

ASAIO J 2015;61(3):e14-6

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Summary:

This case study reports on a 44-year-old man presenting with ongoing fever and general malaise for more than 5 days. Respiratory insufficiency led to hospitalization and admission to ICU for intubation and ventilatory support. Chest x-ray and computed tomography confirmed the clinical diagnosis of acute respiratory distress syndrome and he was found to have *Legionella pneumophila*. Despite administration of antibiotics, his liver enzymes and parameters of renal function deteriorated over the following days, indicating a trend toward multiple organ failure. Creatine kinase and myoglobin levels increased in combination with reduced urine excretion. Therefore Cytosorb was run in stand-alone mode on day 6 after admission. Within 8 hours, myoglobin levels decreased from 18,390 to 10,020 ng/ml and with a second cycle it again declined from 13,400 to 8,359 ng/ml. The patient's condition improved subsequently. Renal function completely recovered and hemodialysis was not necessary at any time of hospitalization. No side effects of therapy were observed. This is the first time that a decrease in myoglobin levels following application of Cytosorb have been demonstrated in vivo.

<http://www.ncbi.nlm.nih.gov/pubmed/25635933>

1.3.5. Other indications

Cardiogenic shock in a hemodialyzed patient on flecainide: treatment with intravenous fat emulsion, extracorporeal cardiac life support and CytoSorb hemoadsorption

De Schryver N, Hantson N, Haufroid V, Dechamps M

Case Reports in Cardiology 2019; epub

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Summary

A 67-year-old woman on chronic hemodialysis for end stage renal disease who had received a therapeutic dose of the anti-arrhythmia drug flecainide for

three weeks was admitted to the Emergency Department for malaise, dizziness and ventricular tachycardia. Her hemodynamic condition remained stable so toxicity from the flecainide was not suspected until she developed cardiogenic shock requiring vasopressors 8 hours later. The patient then received sodium bicarbonate and dobutamine but two hours later went into cardiac arrest. She was given intravenous fat emulsion (IFE) which was associated with a return of spontaneous circulation, but as there was a relapse in the cardiovascular shock at the end of the IFE infusion, she was placed on extracorporeal cardiac life support (ECLS), and continuous hemofiltration with hemoadsorption using CytoSorb. Serial determinations of serum flecainide concentrations (initially > 9000 ng/ml, normal range 200 – 1000 ng/ml), were obtained pre and post the CytoSorb so that the clearance rate of flecainide could be calculated. Within 4 hours the flecainide levels had reduced to around 2000 ng/ml. The authors calculated that a mean plasma clearance of 40.3 ml/min was observed using CytoSorb. Although the impact of CytoSorb on the clinical course has to be understood in the context of the other therapeutic interventions including ECLS, this patient was eventually discharged home with no apparent side effects. This is the first case reporting the removal of flecainide with the CytoSorb adsorber.

<https://www.hindawi.com/journals/cric/2019/1905871/>

Cytokine adsorption is a promising tool in the therapy of hemophagocytic lymphohistiocytosis.

Frimmel S, Hinz M, Schipper J, Bogdanow S, Mitzner S, Koball S

Int J Artif Organs 2019; epub

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Summary

This is a case series of two patients with hemophagocytic lymphohistiocytosis (HLH), a life-threatening clinical syndrome caused by severe hyper-cytokemia brought on by a highly stimulated but ineffective immune response. In the first patient with the herpes virus, despite being put on the Molecular Adsorption Recirculation system (MARS) as a bridge to liver transplant, her condition continued to deteriorate (increasing hemodynamic instability) so she was also placed on single-pass albumin dialysis (SPAD®) and then continuous venovenous hemodialysis (CVVHD) into which the CytoSorb was inserted. This resulted in a dramatic decrease in interleukin-6 (IL-6) plasma levels and norepinephrine requirements, and successful liver transplant 20 hours later. The second patient had two episodes of HLH two months apart, most likely triggered by refractory septic shock and then an acute Epstein–Barr virus infection. A CytoSorb adsorber was inserted into his CVVHD circuit, on both occasions for 48 hrs total (2 adsorbers for 24 hours each). With both CytoSorb treatment episodes, his clinical condition stabilized with a marked decrease in his IL-6 and a stabilization or decrease in his norepinephrine requirements. Importantly, the treatment in both patients was safe and well-tolerated, without any adverse events.

<https://www.ncbi.nlm.nih.gov/pubmed/31238776>

Severe quetiapine voluntary overdose successfully treated with a new hemoperfusion sorbent

Giuntoli L, Dalmastrì V, Cilloni N, Orsi C, Stalteri L, Demelas V, Giuliani G, Gordini G, De Ponti F, La Manna G.

Int J Artif Organs 2019; epub

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Summary

Overdose on quetiapine (a psychiatric medication), although rare, is linked to heart arrhythmias, somnolence, coma, hyperglycemia, and eventually hepatotoxicity and myocarditis. Use of extracorporeal techniques for quetiapine removal has been only rarely reported in the literature. In this case report, a 27-year-old healthy woman, admitted to Intensive Care Unit after deliberate quetiapine overdose is described. After 24 hrs of standard treatment including charcoal, diuretics and laxatives, her quetiapine levels were still very high (1850 µg/L, normal range of 70–170 µg/L) so she was treated with CytoSorb hemoperfusion in combination with continuous renal replacement therapy (CRRT), for 48 hrs (2 adsorbers used for 24 hrs each) in order to accelerate quetiapine elimination. After only 12 hrs the level of quetiapine had already reduced by 65% to 648 µg/L. After 96 hrs she was able to be extubated, and eventually discharged to a step down unit after 7 days. This is the first published experience of the application of hemoadsorption therapy (CytoSorb), after a large overdose of quetiapine. Use of CytoSorb resulted in the fast and efficient elimination of quetiapine from the blood and stabilization of a critical situation.

<https://www.ncbi.nlm.nih.gov/pubmed/31006356>

Snake bite induced sepsis with multi organ failure successfully treated with Extracorporeal Cytokine Adsorption Device (ECAD) therapy along with standard of care - a case series

Sathe P, Sakhavalkar P, Borse R, Parathody A, Huparikar A, Rayte N

IJMDAT 2018; 1(2): e158

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Summary

This publication reports on two snake bite patients and describes the use of CytoSorb because of local pain and swelling, disseminated intravascular coagulation (DIC) and Acute Kidney Injury (AKI) caused by the venom from the snake bite. In both patients two CytoSorbs were used and associated with a decrease in IL6 and good overall clinical stabilization. Both patients were able to be discharged from hospital and the authors describe the use of CytoSorb along with standard of care to be a promising and safe treatment modality in order to stabilize and decrease envenomation induced complications, potentially leading to shorter ICU stays and better survival.

<https://www.ijmdat.com/wp-content/uploads/sites/3/2018/10/e158-Snake-bite-induced-sepsis.pdf>

Hemoadsorption in cardiac shock with biventricular failure and giant cell myocarditis: A case report

Dogan G, Hanke J, Puntigam J, Haverich A, Schmitto J.

IJAO 2018; 41(8): 474-9

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Summary

In this case a 57-year-old patient with the autoimmune disorder giant cell myocarditis, developed fulminant right heart failure, respiratory insufficiency, hemodynamic instability and oliguric-anuric renal failure. Extracorporeal life support (ECLS) with an Impella was applied for circulatory support along with continuous veno-venous hemodialysis (CVVHD). Since adequate hemodynamic stabilization could not be achieved despite high catecholamine support and due to increasing inflammatory mediators and bilirubin levels, the decision was made to additionally integrate CytoSorb into the CVVHD system. The following day the patient had a left ventricular assist device (LVAD) inserted, and veno-pulmonary-arterial (VPA) Extra Corporeal Membrane Oxygenation (ECMO) was started. CytoSorb was then inserted into the VPA ECMO circuit. In total 9 CytoSorb treatments were performed over 23 days with a 7-day pause (due to a secondary septic surge). With the last CytoSorb treatment the right ventricular bypass could be explanted and the patient was discharged to a high care program. The combined ECLS treatment including CytoSorb resulted in a clear and steady improvement in hemodynamics and the inflammatory condition with marked reductions in all measured parameters throughout the treatment period. Metabolic acidosis resolved and liver function also improved. The authors describe the combination of all techniques applied as practical, technically feasible, and highly beneficial for the patient.

<https://www.ncbi.nlm.nih.gov/pubmed/29779449>

A rare case of septic shock due to *Neisseria meningitidis* serogroup B infection despite prior vaccination in a young adult with paroxysmal nocturnal haemoglobinuria receiving eculizumab

Reher D, Fuhrmann V, Kluge S, Nierhaus A.

Vaccination 2018; 36(19):2507-2509

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Summary

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired haematopoietic stem cell disease which causes defects in complement inhibiting proteins. Following approval of eculizumab, a humanized antibody for PNH treatment, several cases of invasive meningococcal disease (IMD) have been reported in eculizumab-treated patients. This is a report of a rare case of septic shock due to infection with *Neisseria meningitidis* serogroup B despite prior vaccination in a young PNH patient treated with eculizumab where CytoSorb was used for treatment of excessive hypercytokinemia along with IgM-enriched IgGAM for three days.

<https://www.ncbi.nlm.nih.gov/pubmed/29631884>

Successfully treated necrotizing fasciitis using ECLS combined with hemoadsorption device and continuous renal replacement therapy.

Eid M, Fouquet O, Pierrot M, Kouatchet A, Mercat A, Baufreton C.

IJAO 2018; 41(3): 178 – 82

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Summary:

In this case a 41 yr old patient presented with necrotizing fasciitis and multi organ failure. Extracorporeal life support (ECLS – veno-arterial) was implemented to compensate for his heart failure (ejection fraction 15%) requiring 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 hrs 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.

<https://www.ncbi.nlm.nih.gov/pubmed/29546811>

First-in-Man Fully Percutaneous Complete Bypass of Heart and Lung

Napp LC, Vogel-Claussen J, Schäfer A, Haverich A, Bauersachs J, Kühn C, Tongers J. *JACC Cardiovasc Interv* 2017; 10(24): e231 – 3

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Summary:

This case reports on a 24-year-old man admitted to a regional hospital after an attempted suicide by taking 9 g of the antidepressant venlafaxine. After initial seizures, he developed progressive cardiogenic shock resulting in cardiac arrest from electromechanical dissociation 12 h after ingestion. Emergency femoral venoarterial extracorporeal membrane oxygenation (ECMO) was inserted under continued cardiopulmonary resuscitation and the patient was then transferred to a tertiary hospital. In an attempt to restore pulmonary gas exchange a novel form of mechanical support was initiated by a triple cannulated ECMO and the Impella, resulting in a complete takeover of upper and lower body gas exchange and circulation by the devices. In addition, CytoSorb hemoadsorption was connected to the circuit due to post cardiac arrest syndrome, high demand of catecholamines and venlafaxine intoxication. The result was hemodynamic stabilization accompanied by a significant decrease in catecholamines. Over time the patient could be weaned from mechanical ventilation and was transferred to rehabilitation 28 days after admission.

http://interventions.onlinejacc.org/content/10/24/e231?sso=1&sso_redirect_count=1&access_token=

First application of CVVHDF, plasmapheresis and "CytoSorb absorber" to solve a pediatric haemophagocytic Histocytosis case

Milella L & Ficarella MT

Res Pediatr Neonatal 2017; 1(2): 1-6

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Summary:

This is the case of a 4 yr old girl (body weight 19 kg) with secondary hemophagocytic lymphohistiocytosis (HLH) due to a bacterial infection. She developed septic shock and sepsis with multi-organ failure so was put on mechanical ventilation, high dose catecholamines and fluids to support her cardiovascular system, and dialysis (continuous veno-venous hemodiafiltration CVVHDF) for 20 hrs per day and intermittent plasmapheresis for 4 hrs per day. As she was so critically ill, a CytoSorb adsorber was added to the CVVHDF circuit. After the first 2 hrs of CVVHDF plus CytoSorb, the patient rapidly improved her cardiovascular and respiratory status with complete stabilization after 24 hrs. There was a swift decrease in the hyperammonemia,

improvement in renal and hepatic function and a rapid decrease in inflammatory markers. The patient went on to make a full recovery. The authors state that CytoSorb in this pediatric case seemed to be very helpful in resolving the patient's clinical complications including respiratory, cardiovascular, liver (ascites), renal function and laboratory tests that had confirmed the presence of multi-organ failure in a short time period.

<http://crimsonpublishers.com/rpn/pdf/RPN.000510.pdf>

Pediatric patient with dengue fever and associated multiorgan dysfunction syndrome (MODS) receiving haemoadsorption using CytoSorb - a case report on clinical experience

Mekala N and Damera S

Nephrol Dial Transplant 2017;32(Suppl 3):iii746

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Summary:

In this case report a 10- year old boy with dengue hemorrhagic fever and multi organ dysfunction (including thrombocytopenia, coagulopathy, systemic inflammatory response syndrome, acute fulminant hepatic failure with encephalopathy and oliguria) was treated successfully and safely with a combination of standard care and hemoadsorption with Cytosorb for an 18 hour period. The patient was eventually discharged alive and well.

<https://doi.org/10.1093/ndt/gfx183.MP851>

Cytokine adsorption is a promising tool for therapy of hemophagocytic lymphohistiocytosis (HLH)

Frimmel S, Bogdenow S, Schipper J, Hinz M, Mitzner S, Koball S

Nephrol Dial Transplant 2017; 32(Suppl 3): SP247

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Summary:

In this case series 2 patients with 3 episodes of severe hemophagocytic lymphohistiocytosis (HLH) were treated with Cytosorb. In the first case a 50 yr old woman with acute necrotizing hepatitis caused by Herpes simplex and HLH, CytoSorb was used to help bridge the time to liver transplant. In the second case a 42-year-old male patient with respiratory and circulatory failure, septic shock and acute renal failure was treated for 48 hours with 2 CytoSorb adsorbers. After a second relapse he was again treated with CytoSorb and s went on to make a full recovery. In both cases a marked decrease in IL-6 plasma levels, and vasopressor needs were the major results. Importantly, treatment was safe and well- tolerated, without any adverse events.

<https://doi.org/10.1093/ndt/gfx144.SP247>

Venlafaxine intoxication with development of takotsubo cardiomyopathy: successful use of extracorporeal life support, intravenous lipid emulsion and CytoSorb

Schroeder I, Zoller M, Angstwurm M, Kur F, Frey L

Int J Artif Organs 2017;40(7):358-60

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Summary:

This case report describes a 19 yr old female who ingested 18g of the antidepressant venlafaxine (240 times the daily therapeutic dose) who went on to develop severe takotsubo cardiomyopathy and multi-organ dysfunction

syndrome. As there is minimal clearance of the drug with hemodialysis, and there is no specific antidote available, she was treated with intravenous lipid emulsion (ILE) and CytoSorb to enhance detoxification of the drug, and extracorporeal life support (ECLS) as a bridge to support the cardiac failure. Despite the relatively short use of CytoSorb (9 hours), a massive reduction in venlafaxine and its metabolites was observed under the combined therapy with ILE. Over time other therapies including the ECLS, ventilation, and dialysis could be withdrawn and the patient went on to make a full recovery. <https://www.ncbi.nlm.nih.gov/pubmed/28574114>

Removal of focal segmental glomerulosclerosis (FSGS) factor suPAR using CytoSorb

Schenk H, Müller-Deile J, Schmitt R, Hinrich Bräsen J, Haller H, Schiffer M. *Journal of Clinical Apheresis* 2017; 32(6): 444-52

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Summary

This case looked at the potential effect of suPAR elimination (a circulating factor that causes renal failure) in a 32 yr old woman who developed severe post-partum nephrotic syndrome who went on to develop FSGS (focal segmental glomerulosclerosis). After three treatments with total plasma exchange (TPE - the normal method used to remove suPAR) she was given one 8 hour treatment with CytoSorb and the efficiency of both was compared. CytoSorb hemoadsorption caused a 27.33% reduction in the suPAR level in a single treatment, whereas 3 sessions with TPE caused a reduction of 25.12% (P<0.01). The authors conclude that compared to TPE, plasmapheresis, and immunoabsorption, CytoSorb hemoabsorption is an effective novel treatment alternative for removing circulating factors in patients with idiopathic FSGS or for patients with a recurrence of primary FSGS in the transplanted kidney. <https://www.ncbi.nlm.nih.gov/pubmed/28370393>

Rescue of cytokine storm due to HLH by hemoabsorption in a CTLA4-deficient patient

Greil C, Roether F, La Rosée P, Grimbacher B, Duerschmied D, Warnatz K *Journal of Clinical Immunology* 2017;37(3):273-6

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Summary:

In this letter to the editor the authors describe the use of a CytoSorb in a patient with secondary hemophagocytic lymphohistiocytes (HLH) caused by CTLA-4 deficiency (caused by a heterozygous germ line mutation of the cytotoxic T lymphocytic antigen-4 (CTLA-4) gene leading to a syndrome with prominent features of immune dysregulation). HLH is characterized by fever, splenomegaly, bicytopenia, highly elevated serum levels of ferritin and soluble interleukin-2 receptor (sIL2-R), decreased natural killer (NK) cell activity, hypertriglyceridemia and detection of hemophagocytosis in bone marrow or other tissue. To date, HLH has never been described in a patient with CTLA-4 deficiency. A 50 yr old patient was admitted to ICU with systemic inflammatory response syndrome 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, 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.

<https://www.ncbi.nlm.nih.gov/pubmed/28265964>

(The Use of a Cytokine Adsorber (CytoSorb) in a Patient with Septic Shock and Multi-Organ Dysfunction (MODS) after a Severe Burn Injury)

Houschyar KS, Nietzschmann I, Siemers F

Handchir Mikrochir Plast Chir 2017;49(2):123-6

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Article in German only

Summary:

This case report reports on a 21-year-old patient admitted to hospital immediately following an explosion at home with 2b-3-degree burns to a total of 60% of the body surface area. On admission, he was immediately given bath therapy while he was still hemodynamically stable, with surgical wound treatment of the burned areas. Because of the burn severity, multiple operations were performed, with transplants on his lower abdomen, both upper arms, the upper thorax and both forearms. Further therapy consisted of epifascial debridements, keratinocyte deposits and automatic prone / supine positioning. With sustained elevation of the inflammatory parameters (leukocytes, C-reactive protein and procalcitonin) and renal function, positive blood cultures and wound smears for *Acinetobacter baumannii*, the decision was made to start hemofiltration therapy with additional CytoSorb adsorbers. The CytoSorb adsorber was used daily from the 9th - 17th treatment days and from days 32 - 52. The interleukins IL-6 and IL-10 were significantly reduced during the treatment, catecholamine requirement was significantly reduced and circulatory stabilization could be achieved. However, due to cardiopulmonary insufficiency in the context of a multiorgan failure, the patient died on the 52nd postoperative day.

<https://www.ncbi.nlm.nih.gov/pubmed/27931049>

A clinical experience of using extracorporeal cytokine adsorption device (CytoSorb) in a case of Dengue fever

Khan ZA

J Evid Based Med Healthc 2017;3(87):4779-81

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Summary:

This case study reports on a patient with Dengue fever, septic shock and multiple organ failure (MOF). Dengue is a mosquito-borne viral disease where it is thought that elevated cytokines (tumour necrosis factor alpha - TNF- α , interleukins and interferon gamma - IFN- γ) cause damage to the endothelial cells of the capillaries that results in fluid leakage. Here a 32 year old male patient was admitted to the intensive care unit and because of multiple organ failure, he was mechanically ventilated and put on renal replacement therapy. CytoSorb was used as an adjuvant supportive therapy on days 2, 4 and 6 of admission. The patient also received multiple transfusions to address thrombocytopenia and coagulopathy. The patient showed gradual improvement with a normalization of the central nervous system, improved

oxygenation status, adequate renal function and normal platelet count (APACHE score 27 before and 12 at the end of CytoSorb treatment). Liver function also improved significantly. Serum Glutamic Oxaloacetic Transaminase – GOT (AST) fell from 15,690 U/L to 156 U/L, and Serum Glutamic Pyretic Transaminase - GPT (ALT) fell from 3910 to 84 after CytoSorb treatment). The patient was discharged from ICU on day 13 and subsequently discharged home. The authors note that CytoSorb® seems to be a useful and safe extracorporeal therapy option to stabilize and help dengue shock patients with MODS to recover.

http://www.jebmh.com/abstract.php?at_id=95229

2. Pre-Clinical data

2.1. Animal models

Blood Purification by Non-Selective Hemoadsorption Prevents Death after Traumatic Brain Injury and Hemorrhagic Shock in Rats

McKinley TO, Lei Z, Kalbas Y, White FA, Shi Z, Wu F, Xu ZC, Rodgers RB.

J Trauma Acute Care Surg; 85(6): 1063 - 71

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Summary:

Patients who sustain traumatic brain injury (TBI) and concomitant hemorrhagic shock (HS) are at high risk of inflammation which can lead to poor outcomes and death. To investigate the influence of hemoadsorption (HA) on outcome after TBI and HS, rats were subjected to a combined injury of a controlled cortical impact to their brain and hemorrhagic shock. The rats were then instrumented with an extracorporeal blood circuit and treated with either therapeutic hemoadsorption with a 2 ml cartridge filled with CytoSorb beads (HA-group, 14 rats) or sham intervention (19 rats) for 180 minutes. CytoSorb beads improved survival from 47% in sham treated rats to 86% in HA treated rats. HA resulted in decreases in circulating concentrations in several biomarkers compared to sham treatment, but the majority of cytokines were not affected by HA treatment. In conclusion blood purification by non-selective HA is an effective intervention to prevent death in a combined TBI/HS rat model.

<https://www.ncbi.nlm.nih.gov/pubmed/30211852>

Haemoadsorption reduces the inflammatory response and improves blood flow during ex vivo renal perfusion in an experimental model.

Hosgood SA, Moore T, Kleverlaan T, Adams T, Nicholson ML

J Transl Med 2017; 15(1): 216

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Summary:

Ex-vivo normothermic perfusion strategies are a promising new instrument in organ transplantation and whilst they are designed to be protective, the artificial environment can induce a local inflammatory response. The aim of this study was to determine the effect of incorporating a Cytosorb adsorber into an isolated kidney perfusion system. Porcine kidneys were subjected to 22 h of cold ischaemia then reperfused for 6 h in an ex vivo reperfusion circuit. Pairs of kidneys were randomised to either control (n = 5) or reperfusion with a Cytosorb adsorber (n = 5) integrated into the circuit. Baseline levels of cytokines were similar between groups. Levels of IL-6

and IL-8 in the perfusate significantly increased during reperfusion in the control group but not in the Cytosorb group. Levels of other cytokines were numerically lower in the Cytosorb group. The mean renal blood flow (RBF) was significantly higher in the Cytosorb group. Perfusate levels of prostaglandin E2 and thromboxane were significantly lower in the Cytosorb group. While no effect of hemoadsorption on creatinine clearance or renal function could be shown in this model, it can reduce the inflammatory response and improve renal blood flow during perfusion.

<https://www.ncbi.nlm.nih.gov/pubmed/29070045>

Cytokine filtration modulates pulmonary metabolism and edema formation during ex vivo lung perfusion

Iskender I, Cosgun T, Arni S, Trinkwitz M, Fehlings S, Yamada Y, Cesarovic N, Yu K, Frauenfelder T, Jungraithmayr W, Weder W, Inci I
J Heart Lung Transplant 2017; epub

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Summary:

This study tested the safety and efficacy of cytokine adsorption during ex vivo lung perfusion (EVLP) in an animal model. Pig donor lungs were preserved for 24 hours at 4°C (to induce lung injury) and then randomly divided into 2 groups, the treatment and control groups (n=5 each), for a 12 hour EVLP procedure. In the treatment group, the perfusate ran continuously through CytoSorb via a veno-venous shunt from the reservoir, whereas perfusions were run without additional filtering in the control group. Cytokine filtration with CytoSorb significantly improved airway pressure and dynamic compliance during the perfusion period. Electrolyte imbalance, glucose consumption and lactate production were markedly worse in the control group while cytokine expression profile, tissue myeloperoxidase activity and microscopic lung injury were significantly reduced in the CytoSorb treatment group. Continuous perfusate filtration through CytoSorb was found to be effective and safe during prolonged EVLP and cytokine removal decreased the development of pulmonary edema and modulated pulmonary metabolism through the suppression of anaerobic glycolysis and neutrophil activation.

<https://www.ncbi.nlm.nih.gov/pubmed/28587802>

Effects of Blood Purification on Serum Levels of Inflammatory Cytokines and Cardiac Function in a Rat Model of Sepsis

Lin CM, Chen CR, Wu XQ, Ren JH, Chen SZ, Luo XF, Mei XQ, Shen LY, Guo MX, Ma XD, Yang T
Blood Purif 2017;44(1): 40-50

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Summary:

This sepsis rat model study explored the effects of blood purification, using a modified CytoSorb adsorber, on serum levels of inflammatory cytokines (IL6, TNF, IL10,) and cardiac function. The rat model of sepsis was established by cecal ligation and puncture. Rats were divided into normal control (n=8), sham operation (n=32), model (n=32), sham treatment (n=32), and BP treatment groups (n=32). Cardiac function, inflammatory cytokines, myocardial enzymes, pathological score of cardiac muscle tissue, and myocardial apoptosis of rats in each group were compared. Results showed that the septic rats had higher serum levels of inflammatory cytokines and lower cardiac function than those in the normal control and sham operation groups. Importantly, compared with

the model and sham treatment groups, the CytoSorb treated group showed improved cardiac function, decreased inflammatory cytokines and myocardial enzymes, a lower pathological score, less myocardial apoptosis and a much lower mortality. The authors conclude that blood purification using CytSorb may reduce serum levels of inflammatory cytokines and improve cardiac function in septic rats.

<https://www.ncbi.nlm.nih.gov/pubmed/28241128>

Evaluation of the CytoSorb hemoadsorbptive column in a pig model of severe smoke and burn injury

Linden K, Scaravilli V, Kreyer SF, Belenkiy SM, Stewart IJ, Chung KK, Cancio LC, Batchinsky AI

Shock 2015; 44(5):487-95

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Summary:

The aim of this in vivo study in a porcine model of smoke inhalation and burn injury was to investigate the feasibility, technical safety and efficacy of cytokine and myoglobin removal by early use of CytoSorb. Female Yorkshire pigs (n=15) were injured by wood bark smoke inhalation and deep burn to 40% total body surface area, and observed for 72 hours or death. The animals were randomized to hemoadsorption treatment (n=9) or sham treatment (n=6) before injury and underwent a six hour hemoadsorption or sham session on days one, two and three. Serum cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-alpha) and myoglobin were measured systemically, locally in broncho-alveolar lavage fluid and also in circulating blood before and after the adsorbing column. Use of CytoSorb resulted in a significant removal of IL-1b, IL-6, IL-10 and myoglobin mainly during the first run, while systemic cytokine and myoglobin serum concentrations did not change. The authors conclude that further investigations are needed to optimize the efficiency of mediator clearance to impact on both circulating levels and clinically relevant outcomes.

<http://www.ncbi.nlm.nih.gov/pubmed/26368927>

Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

Peng ZY, Bishop JV, Wen XY, Elder MM, Zhou F, Chuasuwan A, Carter MJ, Devlin JE, Kaynar AM, Singbartl K, Pike F, Parker RS, Clermont G, Federspiel WJ, Kellum JA

Crit Care 2014;18(4):R141

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Summary:

In this in vivo rat study of polymicrobial abdominal sepsis the authors investigated whether the removal of chemokines from the plasma changed chemokine gradients and subsequently enhanced leukocyte localization into the infected compartment, and away from healthy tissues. The results demonstrated the efficacy of CytoSorb to target leukocyte trafficking control by influencing chemokine gradients and thereby reducing leukocyte infiltration into remote organs.

<http://www.ncbi.nlm.nih.gov/pubmed/24992991>

Role of cytokine hemoadsorption in cardiopulmonary bypass-induced ventricular dysfunction in a porcine model

Vocelka CR, Jones KM, Mikhova KM, Ebisu RM, Shar A, Kellum JA, Verrier ED, Rabkin DG

J Extra Corpor Technol 2013;45(4):220-7

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Summary:

This in vivo study in a porcine model undergoing cardiopulmonary bypass investigated the role of hemoadsorption using CytoSorb on left ventricular function, cytokine removal, hemodynamics and non-cardiac organ functions.

<http://www.ncbi.nlm.nih.gov/pubmed/24649569>

Effect of cytokine hemoadsorption on brain death-induced ventricular dysfunction in a porcine model

Mikhova KM, Don CW, Laflamme M, Kellum JA, Mulligan MS, Verrier ED, Rabkin DG

J Thorac Cardiovasc Surg 2013;145(1):215-24

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Summary:

This in vivo study investigated the effect of CytoSorb on cytokine levels (TNF, IL-6), cell injury (liver, kidney) and heart function (cardiac output, ventricular function) in a brain-dead porcine model.

<http://www.ncbi.nlm.nih.gov/pubmed/23127374>

Hemoadsorption Reprograms Inflammation in Experimental Gram-Negative Septic Peritonitis: Insights from In Vivo and In Silico Studies

Namas RA, Namas R, Lagoa C, Barclay D, Mi Q, Zamora R, Peng Z, Wen X, Fedorchak MV, Valenti IE, Federspiel WJ, Kellum JA, Vodovotz Y

Mol Me. 2012;20(18):1366-74

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Summary:

This combined in vivo/in silico study in a rat model of E.coli-induced peritonitis investigated whether CytoSorb hemoadsorption was able to reduce, re-localize and reprogram sepsis-induced acute inflammation (determined by analysis of 14 different cytokines and bacterial count in peritoneal fluid).

<http://www.ncbi.nlm.nih.gov/pubmed/22751621>

Acute removal of common sepsis mediators does not explain the effects of extracorporeal blood purification in experimental sepsis

Peng ZY, Wang HZ, Carter MJ, Dileo MV, Bishop JV, Zhou FH, Wen XY, Rimmelé T, Singbartl K, Federspiel WJ, Clermont G, Kellum JA

Kidney Int 2012;81(4):363-9

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Summary:

This in vivo study in a subacute rat model of intraabdominal sepsis (cecal ligation puncture) investigated the effect of CytoSorb hemoadsorption that did not exert its positive effect as a direct reduction of cytokine plasma concentrations. Levels of cytokines in this model were low, resulting in low removal by CytoSorb (a concentration-dependent technology). However, 7-day survival was significantly improved in the treatment group, with a reduction in latent organ injury. Cytokine removal (TNF α , IL-1 β , IL-6 und IL-10), organ

injury/dysfunction (HMGB-1, ALT, and creatinine), production of cytokines (via NFkB binding in neutrophils) and 7-day survival was analyzed. The effect of exchange blood transfusions (between CytoSorb-treated and sham animals) on IL-6 levels and 7-day mortality was also analyzed.

<http://www.ncbi.nlm.nih.gov/pubmed/21918497>

Effects of hemoadsorption on cytokine removal and short-term survival in septic rats

Peng ZY, Carter MJ, Kellum JA
Crit Care Med 2008;36(5):1573-7

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Summary:

In this in vivo study in a rat model of intraabdominal sepsis (cecal ligation and puncture) the authors explored the effect of hemoadsorption (using CytoSorb) on cytokine adsorption (TNF α , IL-1 β , IL-6 and IL-10), on mean arterial pressure (MAP) and short-term survival.

<http://www.ncbi.nlm.nih.gov/pubmed/18434884>

Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor- κ B DNA binding, and improves short-term survival in lethal endotoxemia

Kellum JA, Song M, Venkataraman R
Crit Care Med 2004;32(3):801-5

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Summary:

This in vivo study in a lethal endotoxemic rat model (in septic shock) investigated the effect of hemoadsorption (using CytoSorb) on cytokine adsorption, inflammation and short-term survival.

<http://www.ncbi.nlm.nih.gov/pubmed/15090965>

Cytokine removal with a novel adsorbent polymer

Song M, Winchester J, Albright RL, Capponi VJ, Choquette MD, Kellum JA
Blood Purif 2004;22(5):428-34

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Summary:

This study characterized the CytoSorb adsorbent polymer in terms of cytokine removal in 50 LPS challenged rats by measuring TNF alpha, interleukin 10 and interleukin 6 concentrations under a variety of conditions to evaluate adsorption kinetics. The authors found that all three cytokines were rapidly removed from the blood with less than 50% of the initial concentrations present after 1 h of circulation through the cartridge pointing towards a high efficiency, while binding was relatively unaffected by a variety of physical conditions.

<http://www.ncbi.nlm.nih.gov/pubmed/15316198>

2.2. In vitro data

Removal of dabigatran using sorbent hemadsorption.

Angheloiu AA, Angheloiu GO
Int J Cardiol. 2019; epub



Summary

Recent studies have demonstrated the safety of drugs including dabigatran and ticagrelor for preventing strokes in patients with atrial fibrillation. However, these drugs place the patient at an increased risk of bleeding complications if emergency surgery is required. In this in-vitro study the authors looked at the use of CytoSorb as a method for removing dabigatran from human blood. Dabigatran was passed through different sized experimental CytoSorb columns and its concentration measured from the affluent and effluent solutions. For testing the effect of dabigatran removal on the aPTT value (coagulation of the blood) one human volunteer was administered oral dabigatran 150 mg. aPTT was measured at baseline prior to and post drug administration. The dabigatran concentration decreased from 1456 to 67 nM ($P = 0.002$) with the smaller CytoSorb column, and with the 40 mL column it dropped to undetectable levels (therapeutic level is 743 nM). The removal rate from only one pass through the adsorber was 99%. In the human volunteer the aPTT was 29.2 s in the baseline samples, 34.7 s after oral dabigatran, and 25 s after plasma was passed through CytoSorb ($p = 0.000025$ and 0.000002). In conclusion, dabigatran is robustly removed by CytoSorb, a method already proven successful for the P2Y12 receptor antagonist ticagrelor. Dabigatran removal restores the aPTT to below baseline values, suggesting that CytoSorb could clinically reverse the anticoagulant effect of this drug.

<https://www.ncbi.nlm.nih.gov/pubmed/31296393>

In vitro removal of anti-infective agents by a novel cytokine adsorbent system

König C, Röhr A, Frey OR, Brinkman A, Roberts JA, Wichmann D, Braune S, Kluge S, Nierhaus A.

International Journal of Artificial Organs 2019; 42(2):57-64



Summary

The aim of this in vitro study was to describe the adsorption of anti-infective drugs (standardized, clinically used concentrations of vancomycin, gentamicin, meropenem, ciprofloxacin, piperacillin, flucloxacillin, voriconazole, rifampicin and fluconazole) by the CytoSorb adsorber in either normal saline 0.9% (1st experiment) or human albumin 5% (2nd experiment) at a flow rate of 1.2L/h for 1.5h. In addition, the antibiotics meropenem and ciprofloxacin were also dissolved in reconstituted blood and run through a CytoSorb cartridge (3rd experiment), which was integrated into a continuous renal replacement therapy (CRRT) circuit with a flow rate of 2L/h for 18h. Samples from the solution, pre- and post-filter, were quantified by high-performance liquid chromatography. The mean clearance of the drugs in normal saline was 1.22 ± 0.07 L/h and in human albumin, 1.29 ± 0.08 L/h. In reconstituted blood, clearance of meropenem decreased from 5.4 to 1.4 L/h and for ciprofloxacin from 6.3 to 4.3L/h within the first 1.5h because of early drug adsorption. Importantly the authors note that during the total observation period of 18 hrs, 394 mg of meropenem and 284 mg of ciprofloxacin were absorbed by CytoSorb, however, in addition 2870 mg of meropenem and 235mg of ciprofloxacin were removed by the concomitant renal replacement therapy alone. In these in-vitro settings, all tested drugs were adsorbed by CytoSorb in relevant amounts however, as noted by the authors, the results, particularly

using saline and albumin cannot be extrapolated into clinical practice as they do not represent what happens in a human body. The identified maximum adsorptive capacity and the rapid decline in concentration during the first 1.5 h of CytoSorb use suggest that the administration of an additional dose within the first hours of CytoSorb treatment may be reasonable. In addition, early therapeutic drug monitoring should be considered.

<https://www.ncbi.nlm.nih.gov/pubmed/30545255>

Removal of Bilirubin with a New Adsorbent System: In Vitro Kinetics.

Gemelli C, Cuoghi A, Magnani S, Atti M, Ricci D, Siniscalchi A, Mancini E, Faenza S. *Blood Purif* 2019; 47(1):10-15

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Summary

Many potentially toxic molecules accumulate in the blood during hepatic dysfunction including bilirubin, however this is difficult to remove, particularly in its unconjugated form when it is strongly bound to albumin. The aim of this in vitro study was to assess bilirubin adsorption using Cytosorb in 4 separate but related experiments with different albumin-bilirubin solutions. Results showed that in all experiments the ability of CytoSorb to adsorb unconjugated bilirubin led to efficient bilirubin removal with a removal rate up to 90% after 24 hrs and with minimal albumin loss. No sign of bilirubin release from the charged adsorber was detected, confirming the irreversibility of the adsorption. The authors conclude that Cytosorb seems a promising artificial liver support, due to its ability to adsorb bilirubin (and other liver toxins) and its proven ability to modulate the cytokines involved in hepatic and other organ dysfunctions.

<https://www.ncbi.nlm.nih.gov/pubmed/30219813>

Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb(R) sorbent porous polymer beads

Gruda MC, Ruggeberg KG, O'Sullivan P, Guliashvili T, Scheirer AR, Golobish TD, Capponi VJ, Chan PP

PLoS One 2018; 13(1): e0191676

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Summary:

In sepsis and septic shock, pathogen-associated molecular pattern molecules (PAMPs), including bacterial exotoxins, cause direct cellular damage and/or trigger an immune response in the host, often leading to excessive cytokine production, a maladaptive systemic inflammatory response syndrome response (SIRS), and tissue damage. The released damage-associated molecular patterns molecules (DAMPs), such as activated complement and HMGB-1, into the bloodstream cause further organ injury. This study quantified the size-selective adsorption of a wide range of sepsis-related inflammatory bacterial and fungal PAMPs, DAMPs and cytokines, in an in-vitro whole blood recirculation system. Purified proteins were added to whole blood and recirculated through a device filled with CytoSorb hemoadsorbent polymer beads or a control (no bead) device in vitro. Except for TNF-alpha trimer, hemoadsorption through CytoSorb reduced the levels of a broad spectrum of cytokines, DAMPs, PAMPs and mycotoxins by more than 50 percent providing an additional means of reducing the uncontrolled inflammatory cascade that

contributes to a maladaptive SIRS response, organ dysfunction and death in patients with a broad range of life-threatening inflammatory conditions such as sepsis, toxic shock syndrome, necrotizing fasciitis, and other severe inflammatory conditions.

<https://www.ncbi.nlm.nih.gov/pubmed/29370247>

Extracorporeal Hemoperfusion as a Potential Therapeutic Option for Critical Accumulation of Rivaroxaban

Koertge A, Wasserkort R, Wild T, Mitzner S.

Blood Purification 2018; 45: 126 - 8

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Summary

Rivaroxaban is widely used as an oral anticoagulant for prevention of stroke, systemic and pulmonary embolism, and deep vein thrombosis. However, there are issues in patients with impaired renal clearance or overdose which potentially leads to an increased risk of bleeding. In this experimental work the authors applied a model device containing 60 mL of the CytoSorb adsorbent in an in-vitro recirculation system to remove high plasma concentrations of rivaroxaban from citrate-anticoagulated human whole blood (1,000 mL, flow rate 40 mL/ min) during 120 min of hemoperfusion. Results showed that within 1 hour of circulation 91.6% of the drug had been removed by the CytoSorb adsorber. The same circulation system without CytoSorb showed only minor depletion and loss over a test period of 5 hrs. The results suggest that CytoSorb hemadsorption columns may offer a suitable means to rapidly reverse the anticoagulant effect of rivaroxaban in-vivo.

<https://www.karger.com/Article/FullText/484923>

Removal of bile acids by extracorporeal therapies: an in vitro study

Hartmann J and Harm S

Int J Artif Organs 2017; 40(1): 4 - 8

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Summary

Bile acids (BAs) that accumulate in the circulation in patients with liver failure are considered to be responsible for direct toxic effects and pruritus. The aim of this study was the in vitro characterization of different BAs regarding their removability with high-flux dialysis and different adsorbents (including CytoSorb). Dialysis experiments were conducted in pediatric circuits with human plasma. For the adsorption studies, batch tests using 10% adsorbent in spiked human plasma were carried out. The study found that with high-flux dialysis, only BAs such as glycocholic and taurocholic acid could be removed efficiently, while all tested BAs were removed by adsorption, including the CytoSorb adsorber. In conclusion, adsorption-based systems offer particular advantages for the removal of hydrophobic bile acids.

<https://www.ncbi.nlm.nih.gov/pubmed/28885663>

Hemadsorption corrects hyperresistinemia and restores anti-bacterial neutrophil function

Bonavia A, Miller L, Kellum JA, Singbartl K

Intensive Care Med 2017;5(1):36

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Summary

Resistin is an inflammatory cytokine and uremic toxin. Elevated levels of resistin (hyperresistinemia) in septic patients have been associated with greater disease severity and worse outcomes. Septic hyperresistinemia impairs neutrophil migration, a crucial first-line mechanism in the body's defense against bacterial infection. In this experimental study the effects of hyperresistinemia on other neutrophil defense mechanisms were studied, as well as the effects of hemoadsorption with CytoSorb (and a second, clinically non-approved, adsorbent material) on hyperresistinemia and neutrophil dysfunction. Thirteen patients with septic shock and six control patients were analyzed for serum resistin levels and the effect on neutrophil migration. Patients with septic shock had higher serum resistin levels than the control patients. In vitro, neutrophils exposed to hyperresistinemia exhibited twofold lower bacterial clearance rate from the cells compared to controls. Hemoadsorption with CytoSorb (and the second adsorbent material) reduced resistin levels and thereby restored normal intracellular bacterial clearance. Cytosorb may therefore provide a therapeutic option to improve neutrophil function during septic hyperresistinemia and ultimately alleviate immunosuppression in this disease state.

<https://www.ncbi.nlm.nih.gov/pubmed/28779451>

Ticagrelor Removal From Human Blood

Angheloiu GO, Gugiu GB, Ruse C, Pandey R, Dasari RR, Whatling C

JACC: Basic to Translational Science 2017;2(2):135–145

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Summary:

The authors devised a method for ticagrelor removal (platelet aggregation inhibitor) from blood using Cytosorbent hemadsorption in two sets of in-vitro experiments. The first was a first-pass experiment using bovine serum albumin (BSA) solution pre-incubated with ticagrelor, whereas the second set, performed in a recirculating manner, used human blood mixed with ticagrelor. In the recirculation set up, Ticagrelor removal from BSA solution and human blood reached values of over 90% after only 3 - 4 hours. CytoSorb hemadsorption was found to robustly remove ticagrelor from both BSA solutions and human blood samples.

<http://www.sciencedirect.com/science/article/pii/S2452302X17300451>

Polystyrene-Divinylbenzene-Based Adsorbents Reduce Endothelial Activation and Monocyte Adhesion Under Septic Conditions in a Pore Size-Dependent Manner

Eichhorn T, Rauscher S, Hammer C, Groger M, Fischer MB

Inflammation 2016;39(5):1737-46

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Summary:

The endothelium is the tissue that acts as a barrier between the blood stream and surrounding tissues. Endothelial activation with excessive recruitment and adhesion of immune cells plays a central role in the progression of sepsis. This study studied endothelial activation induced by plasma from highly septic patients and demonstrated the ability of polystyrene-divinylbenzene-based adsorbents (CytoSorb and Amberchrom) to reduce endothelial activation in a pore size-dependent manner. Blood from septic patients was taken on admission to ICU, 1 hr and 24 hrs later.

Primary monocytes were isolated and their purity and viability determined. Venous blood was obtained from healthy volunteers. Blood from both sets of patients was diluted and passed through the adsorbers. Following this the blood was then passed over an endothelial layer. Results showed that treatment of stimulated whole blood with polystyrene-divinylbenzene-based cytokine adsorbents prior to passage over the endothelial layer resulted in significantly reduced endothelial cytokine and chemokine release, plasminogen activator inhibitor-1 secretion, adhesion molecule expression, and in diminished monocyte adhesion. Plasma samples from septic patients differed substantially in their potential to induce endothelial activation and monocyte adhesion despite their almost identical interleukin-6 and tumor necrosis factor-alpha levels. Data support the potential of porous polystyrene-divinylbenzene-based, including CytoSorb, to reduce endothelial activation under septic conditions by depletion of a broad range of inflammatory mediators.

<http://www.ncbi.nlm.nih.gov/pubmed/27503310>

Removal of bilirubin with a new adsorbent system: in vitro kinetics

Faenza S, Ricci D, Mancini E, Gemelli C, Cuoghi A, Magnani S, Atti M

Crit Care 2016;20(Suppl 2):P192

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Summary:

The authors performed an in vitro study on bilirubin kinetics removal to verify the adsorption capacity of CytoSorb and the ability to remove protein-bound solutes. The study showed the effectiveness of CytoSorb in removing irreversibly bilirubin, without significant loss of albumin. CytoSorb might represent a valid and simple aid in organ dysfunctions, without need of plasma separation. In vivo studies are ongoing to confirm the in vitro results.

<http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1208-6>

Leukocyte capture and modulation of cell-mediated immunity during human sepsis: an ex vivo study

Rimmele T, Kaynar AM, McLaughlin JN, Bishop J, Fedorchak M, Chuasuwan A, Peng Z, Singbartl K, Frederick D, Zhu L, Carter M, Federspiel W, Zeevi A, Kellum JA
Crit Care 2013;26;17(2): R59

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Summary:

This ex vivo study using human whole blood tested the hypothesis whether leukocyte capture modulates inflammatory cytokines and immune cell function. Specially designed miniaturized extracorporeal blood purification devices (including mini cartridges with CytoSorb beads in two different sizes) were capable of capturing not only inflammatory mediators but also activated leukocytes (primarily neutrophils and monocytes). The effects of this therapy on inflammation and immune function were examined.

<http://www.ncbi.nlm.nih.gov/pubmed/23531333>

Modeling competitive cytokine adsorption dynamics within hemoadsorption beads used to treat sepsis

Kimmel JD, Harbert EM, Parker RS, Federspiel WJ

J Chromatogr A 2011;1218(44):8013-20

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Summary:

This study investigated in vitro whether competitive adsorption of serum solutes affected cytokine removal dynamics (IL-6) within the CytoSorb beads and found that competitive adsorption effects seem negligible at physiologic cytokine concentrations (<1 ng/ml).

<http://www.ncbi.nlm.nih.gov/pubmed/21962329>

Characterizing accelerated capture of deoligomerized TNF within hemoadsorption beads used to treat sepsis.

Kimmel JD, Lacko CS, Delude RL, Federspiel WJ

J Biomed Mater Res B Appl Biomater 2011;98(1):47-53

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Summary:

This in vitro study examined the dynamics of TNF capture within the CytoSorb beads and quantified how perturbation of TNF oligomeric structure accelerated TNF removal within the device. The authors found that dissociation of TNF into its smaller monomeric constituents significantly accelerated TNF capture rates and therefore propose strategies to promote localized TNF deoligomerization at the sorbent surface.

<http://www.ncbi.nlm.nih.gov/pubmed/21504054>

IL-6 adsorption dynamics in hemoadsorption beads studied using confocal laser scanning microscopy

Kimmel JD, Gibson GA, Watkins SC, Kellum JA, Federspiel WJ

J Biomed Mater Res B Appl Biomater. 2010;92(2):390-6

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Summary:

In this in vitro study the authors used confocal laser scanning microscopy (CLSM) to directly examine adsorption dynamics of fluorescently labeled IL-6 within hemoadsorption beads.

<http://www.ncbi.nlm.nih.gov/pubmed/19904819>

Characterization of a Novel Sorbent Polymer for the Treatment Of Sepsis

Isabella Elfriede Valenti

Master Thesis

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Summary:

Objective of this in vitro study was to characterize the CytoSorb polymer with respect to its adsorption properties of cytokines in different media with increasing complexity (buffer, serum, whole blood).

http://d-scholarship.pitt.edu/8528/1/Valenti_MS_2010.pdf

A simple mathematical model of cytokine capture using a hemoadsorption device

DiLeo MV, Kellum JA, Federspiel WJ

Ann Biomed Eng. 2009 37(1):222-9

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Summary:

In this in silico study the authors presented a bio-mathematical model which can calculate adsorption/removal-dynamics of different cytokines (TNF, IL-6, IL-10) in the CytoSorb cartridge. They state that the removal rate of individual

cytokines only depends on a single cytokine-polymer specific parameter (Γ_i). The model and the theoretically calculated removal dynamics correlated well with experimental data from an in vivo-performed reference study (rats with endotoxemia).

<http://www.ncbi.nlm.nih.gov/pubmed/18949559>

In-Vitro Myoglobin Clearance by a Novel Sorbent System

Kuntsevich VI, Feinfeld DA, Audia PF, Young W, Capponi V, Markella M and Winchester JF

Artif Cells Blood Substit Immobil Biotechnol 2009;37(1):45-7

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Summary:

Rhabdomyolysis (excessive break-down of muscle tissue due to crush injury, infection, drugs etc.) can result in acute kidney injury from myoglobinuria when the myoglobin released into the blood from damaged muscle passes through the glomerular filter and accumulates in the renal tubules. The aim of this in vitro study was to investigate, whether hemoadsorption (using CytoSorb) was potentially useful to effectively reduce myoglobin levels (myoglobin dissolved in 1) Normal saline and 2. In serum of three donors)

<http://www.ncbi.nlm.nih.gov/pubmed/19132637>

Hemoadsorption to improve organ recovery from brain-dead organ donors: a novel therapy for a novel indication?

Venkataraman R, Song M, Lynas R, Kellum JA

Blood Purif. 2004;22(1):143-9

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Summary:

The usefulness of CytoSorb for in maintaining organ function (liver, kidney, heart) in brain-dead donors is discussed in this study. As a 'proof of concept' in vitro experiment the authors tested the ability of hemoadsorption to remove S100B (released from damaged brain cells exhibiting cytokine-like properties) using two human glioblastoma cell lines.

<http://www.ncbi.nlm.nih.gov/pubmed/14732823>

Sorbents in acute renal failure and end-stage renal disease: middle molecule and cytokine removal

Winchester JF, Silberzweig J, Ronco C, Kuntsevich V, Levine D, Parker T, Kellum JA, Salsberg JA, Quartararo P, Levin NW

Blood Purif 2004;22(1):73-7

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Summary:

This study discusses the use of hemoadsorption in acute and chronic renal failure (both inflammatory states) to reduce cytokine- and middle molecule levels. CytoSorb is discussed in detail. Data are presented that show the use of CytoSorb as well as CytoSorb plus conventional high-flux dialysis in patients with chronic renal failure. Results confirm that removal of β_2 – microglobulin, angiogenin, leptin and IL-18 is much more effective when using combined therapy (CytoSorb plus conventional high-flux dialysis). Levels of leucocytes, thrombocytes and albumin were hardly affected.

<http://www.ncbi.nlm.nih.gov/pubmed/14732814>

***In vitro* removal of therapeutic drugs with a novel adsorbent system.**

Reiter K, Bordoni V, Dall'Olio G, Ricatti MG, Soli M, Ruperti S, Soffiati G, Galloni E, D'Intini V, Bellomo R, Ronco C
Blood Purif 2002;20(4):380-8

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Summary:

Aim of this in vitro study was to investigate the potential of CytoSorb to effectively eliminate therapeutically administered drugs (mainly in intensive care) of middle molecular weight from uremic blood. In addition, the authors emphasize the good biocompatibility of CytoSorb.

<http://www.ncbi.nlm.nih.gov/pubmed/12169849>

3. Background & Reviews

NEW: Recommendations for the management of hemophagocytic lymphohistiocytosis in adults

La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, Kumar A, van Laar JAM, Lachmann G, Nichols KE, Ramanan AV, Wang Y, Wang Z, Janka G, Henter JI.
Blood 2019; 133(23): 2465 – 77

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Summary

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by over-activated macrophages and cytotoxic T cells. The primary (genetic) form is most common in children, whereas the secondary (acquired) form is most frequent in adults. Secondary HLH is commonly triggered by infections or malignancies but may also be induced by autoinflammatory/autoimmune disorders, in which case it is called macrophage activation syndrome (MAS; or MAS-HLH). HLH in adults may present with a phenotype indistinguishable from sepsis or multiple organ dysfunction syndrome. Treatment algorithms targeting hyperinflammation are frequently based on pediatric protocols, which may result in overtreatment and unnecessary toxicity in adults. In adults, HLH-associated mortality remains high, especially in patients with underlying malignancies. Although the drugs used in pediatric HLH are effective in adult HLH, there is still a need for novel agents and interesting trials testing alternative therapeutic approaches have been initiated. In this paper, expert consensus recommendations derived from an interdisciplinary working group on adult HLH are presented, to facilitate knowledge transfer between physicians caring for pediatric and adult patients with HLH, with the aim to improve the outcome for adult patients affected by HLH. Noted with a couple of case references in the section, 'Salvage treatment of relapsed and refractory HLH' is the comment that 'the use of cytokine adsorption columns may aid in rescuing critically ill patients from a deleterious cytokine storm'.

<https://www.ncbi.nlm.nih.gov/pubmed/30992265>

Rationale of Hemoadsorption during Extracorporeal Membrane Oxygenation Support

Napp LC, Ziegeler S, Kindgen-Milles D.
Blood Purif 2019; epub

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Summary

In this review the role of CytoSorb with the use of extracorporeal membrane oxygenation (ECMO) and extracorporeal life support (ECLS) is explored. ECMO and ECLS are increasingly being used for treating various forms of shock, lung failure, and life support including resuscitation. However, most patients on ECMO are affected by a systemic inflammatory response caused by the underlying disease as well as the ECMO support itself, which contributes to vasoplegia, multi-organ failure, deterioration and death. The rationale, available data and technical aspects of CytoSorb use is described with ECMO and ECLS, as a way of reducing excessive levels of inflammatory molecules such as interleukins, cytokines as well as damage- and pathogen-associated molecular patterns. Finally, the authors give recommendations based on their existing experience.

<https://www.ncbi.nlm.nih.gov/pubmed/31096211>

Cytokine removal in human septic shock: Where are we and where are we going?

Honore PM, Hoste E, Molnar Z, Jacobs R, Joannes-Boyau O, Malbrain M, Forni LG. *Ann Intensive Care* 2019; 9(1): 56

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Summary

The use of blood purification therapies to improve immune homeostasis and therefore mortality in septic patients has recently become more available. In this executive summary of an expert meeting held at the 6th International Fluid Academy Days in Antwerp, Belgium (Nov 23-25, 2017), the current understanding regarding the use of such adsorbers, and in particular, CytoSorb in humans with septic shock was explored in detail. All available literature was summarized, and the topics discussed included; pathophysiology of the inflammatory response, rationale for cytokine removal, and whether the use of CytoSorb in patients with sepsis or septic shock demonstrate any clinical benefit.

Results from the consensus meeting included discussion regarding which patient benefits most from cytokine removal, when to start CytoSorb, for how long, in which study population, which severity of patient, which biomarkers to observe and recommendations for future research. The authors conclude that while clinical results are thus far not yet satisfactory, more research is needed to answer various open questions.

<https://www.ncbi.nlm.nih.gov/pubmed/31089920>

What Have We Learned about the Use of Cytosorb Adsorption Columns?

Ankawi G, Xie Y, Yang B, Xie Y, Xie P, Ronco C
Blood Purif. 2019; epub

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Summary

The aim of this review was to summarize the published literature on the use of Cytosorb (CS). The authors describe the main studies that use CytoSorb in sepsis (Schädler 2013 & 2017, Friesecke and Kogelmann) where they note that observational data suggest improved hemodynamics and a trend towards improved mortality. They also summarize the main cardiac surgery papers

(Träger 2016, Bernardi, Träger 2017, Calabro) before reporting on the Nemeth and Kellum 2008 studies in regards to organ transplantation, the use of CytoSorb in liver failure, in drug removal including ticagrelor, and finally the Registry.

The authors note that the body of evidence to support the safety and effectiveness of CS continues to grow and that sorbents offer clear advantages compared to other extracorporeal techniques: the capacity for removal of a wide range of molecular weights; enhanced clearance due to large surface area of sorbents material; and that sorbents do not rely on the removal of fluid for the clearance of toxins, potentially avoiding the time limitations of dialysis and the replacement fluid requirements of hemodiafiltration.

CytoSorb adsorption therapy may be of utmost benefit when applied early in the clinical course, for an adequate duration, and frequently repeated until hemodynamic stability is achieved. Among the important potential side effects associated with the use of sorbents in general, including CytoSorb, is the removal of antibiotics, and other beneficial molecules, which should be carefully monitored with drug levels (when possible), and supplemented with additional doses as needed.

Finally, although evidence to support the use of extracorporeal blood purification techniques (in general) in sepsis/other acute conditions is insufficient at this point, potential benefits (in particular, control of the exaggerated immune response, which typically translates into hemodynamic stability) cannot be ignored. Overall, CytoSorb therapy seems to be safe and effective, with further studies to expand the knowledge on novel indications, such as management of the cytokine release syndrome, which complicates adoptive immunotherapies such as chimeric antigen receptor T cells (CAR T cells) warranted.

Comments by CytoSorbents

- It should be noted, that the article states that 25 (and not 20) patients were included in the Friesecke study, and that the Schädler 2013 data is reported as a separate patient study rather than interim analysis for the 2017 publication.
- The article states that CytoSorb does not remove IL-10. The reference used for this is Kellum et al., 2008 where they reported that systemic levels of IL-10 did not decrease over 1 hr of CytoSorb use in 8 brain dead subjects. However, the same article proves that there is indeed IL-10 removal by CytoSorb, as shown by the comparison of simultaneous pre- and post adsorber measurements. So, despite a lack of decrease of systemic levels in these subjects, there is clear evidence that CytoSorb removes IL-10.

<https://www.ncbi.nlm.nih.gov/pubmed/30253409>

Why do we need extracorporeal blood purification for sepsis and septic shock?

Simoni J

Artif Organs 2019; 43(5):444-447



Summary

In this invited editorial the author discusses the fact that there are still a lot unknowns in the field of sepsis and septic shock, mortality remains unacceptably high, there is a lack of efficacious drugs and a cure impossible given current knowledge. As an adjunctive therapy, blood purification technology is logical and urgently needed for the removal of sepsis and septic shock mediators: (i)

pathogenic microorganisms, (ii) microbial toxins, (iii) inflammatory mediators (eg, anaphylatoxins, cytokines, other activators of leukocytes and platelets, (iv) vasoactive substances (eg, NO), and (v) other factors (eg, plasma free Hb, bilirubin, ammonia, uremic toxins, etc). The primary goal of blood purification is hemodynamic stabilization and attenuation of systemic inflammation and subsequent immunosuppression. In this review various forms of hemoadsorption are described including Polymxin B, oXiris, and CytoSorb. The lesson today is that “monotherapy” directed at attenuating a single molecule or a very narrow group of molecules, cannot overcome the damaging effects of an entire cascade of sepsis and septic shock mediators. To overcome this problem a much broader approach is necessary including safe and effective blood purification devices. According to the author, despite the present lack of data on significant outcome improvements, their positive role in the treatment of septic shock patients remains undisputed.

<https://www.ncbi.nlm.nih.gov/pubmed/30908693>

Hemoadsorption with CytoSorb((R))

Poli EC, Rimmele T, Schneider AG

Intensive Care Med 2019; 45(2):236 - 9

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Summary

This review article focuses solely on hemoadsorption with CytoSorb. The authors describe how CytoSorb works and that it is currently marketed in 53 countries. Scientific evidence of CytoSorb use in sepsis is given, including the RCT from Schädler et al., where it is noted that the short treatment time may have limited findings. The CytoSorb Registry is also mentioned along with the studies from Friesecke et al. and Kogelmann et al. Use of CytoSorb is also discussed in cardiac surgery, including the Bernardi et al. study, where it is again noted that the cytokine levels in these patients were not particularly high, perhaps explaining the lack of cytokine removal. Drug removal is also discussed however it is noted that potential removal of antibiotics should be monitored. Beneficial removal of medications in situations of intoxication (venlafaxine, dabigatran, ticagrelor, rivaroxaban) is briefly discussed. Finally, the recent approval for use for CytoSorb for removal of myoglobin and bilirubin is also mentioned. The review notes that post marketing surveillance in over 20,000 patients has not reported any major adverse events. Future studies, the authors feel, should focus on patients with very high inflammatory responses, ideally pre-confirmed before inclusion in order to determine the ideal target population. The authors conclude that, until more evidence from RCTs becomes available, the users of CytoSorb in clinical practice should be aware that there are still some open questions to be answered concerning clear evidence of benefit and potential undesired effects.

<https://www.ncbi.nlm.nih.gov/pubmed/30446798>

Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls.

Ankawi G, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C.

Crit Care 2018; 22(1): 262

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Summary

Understanding the complex pathophysiology behind a sepsis induced

dysregulated immune response (caused by both pathogen- and damage – associated molecular patterns – PAMPS and DAMPS that trigger both pro- and anti-inflammatory cytokines) has led to the development of therapeutic strategies aimed at restoring a balanced immune response by eliminating and/or deactivating these inflammatory mediators. Different extracorporeal techniques have been studied in recent years in the hope of maximizing the effect of renal replacement therapy in modulating the exaggerated host inflammatory response, including high volume hemofiltration (HVHF), high cut-off (HCO) membranes, adsorption alone, and coupled plasma filtration adsorption (CPFA). This review provides a comprehensive overview of the technical aspects, clinical applications, and associated side effects of these techniques. In regards to CytoSorb, the evidence is described as limited at the moment, but growing. Literature suggests an improvement in hemodynamics and trend towards decreased mortality, with reductions in IL6 levels observed. Reasons for the to date neutral results from the CytoSorb randomized controlled trials are clearly explained, while a table summarizes the available main studies that report on the effectiveness and limitations of the adsorber.

<https://www.ncbi.nlm.nih.gov/pubmed/30360755>

Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review

Bonavia A, Groff A, Karamchandani K, Singbartl K.

Blood Purif 2018; 46(4): 337-349

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Summary:

Extracorporeal cytokine hemoadsorption is an emerging technology utilized in the treatment of dysregulated inflammatory states such as sepsis. In this review article the authors assess the literature relating to cytokine hemoadsorption in the context of sepsis. Three blood purification techniques are available including filtration, dialysis and adsorption however, this article focuses on adsorption and primarily CytoSorb in particular. The CytoSorb therapy is described in depth, its mode of action, as well as a review of literature supporting its various fields of application. Whilst larger and in particular randomized control trials are lacking, the authors provide a table describing the clinical reports relating to CytoSorb therapy in peer reviewed articles. They also discuss ongoing trials, including the REFRESH II randomized controlled multicenter trial in the USA, as well as the CytoSorb Registry. The latest interim analysis of the registry showed that none of the patients were affected by any device-associated side effects. Given the widespread reported use of this technology thus far, the authors are hopeful that the rate of clinician self-reporting increases in the future.

<https://www.ncbi.nlm.nih.gov/pubmed/30176653>

Neonatal and Pediatric General and Cardiac Anaesthesia and ICU: what's new in 2017/2018 ? -Bari Pediatric Hospital Experience-Italy

Milella L

Journal of Pediatrics and Neonatal Care 2018; 8(1): 00309

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Summary:

This is a review of the current protocols and studies, recently published or in progress at the Neonatal and Pediatric General and Cardiothoracic Intensive Care Unit in Bari, Italy. In recent years pediatric units have adapted some of the techniques used to treat adults, including hemodiafiltration and new blood purification techniques for septic shock and sepsis treatment. The article describes some of these adaptations, such as how it successfully used the CytoSorb in a patient with hemophagocytotic lymphohistiocytosis (HLH). As a result a pilot study has been conducted with CytoSorb used in patients with sepsis, systemic inflammatory response syndrome (SIRS) and multi-organ failure or inflammatory changes caused by ECMO or ventricular assist devices. Cytokine levels were measured in the blood before, during and after CytoSorb use with results appearing to confirm its reliability and effectiveness. <http://medcraveonline.com/JPNC/JPNC-08-00309.pdf>

Extracorporeal membrane oxygenation and cytokine adsorption

Datzmann T and Traeger K

Journal of Thoracic Disease 2018: Suppl 5:S653-S660

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Summary:

Extracorporeal membrane oxygenation (ECMO) is increasingly used for mechanical support of respiratory and cardio-circulatory failure, but its use may lead to a similar excessive systemic inflammatory response as observed during sepsis and after cardiopulmonary bypass which may lead to multiple organ damage and failure. Therefore, controlling these excessively increased cytokines may be considered a valuable treatment option. This review article describes the mechanism of hemoadsorption therapy with CytoSorb to decrease cytokine levels, as well as removal of other substance such as myoglobin, free hemoglobin and bilirubin. They describe how controlling the pro-inflammatory response with hemoadsorption may have a positive impact on the endothelial glycocalix, and maintenance of the vascular barrier function. The authors acknowledge that whilst published data thus far on the use of CytoSorb in ECMO is based on individual cases, it appears to offer a promising new option for the treatment of overwhelming inflammatory response, leading to faster hemodynamic and metabolic stabilization, finally resulting in preserved organ function.

<http://jtd.amegroups.com/article/view/17003/13575>

Extracorporeal Sorbent Technologies: Basic Concepts and Clinical Application

Clark WR, Ferrari F, La Manna G, Ronco C

Contrib Nephrol 2017;190:43-57

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Summary:

In this review article the basic principles that apply to sorbents are discussed, including composition, structure, fundamental mechanisms of solute removal and the importance of sorbent biocompatibility. The clinical application of sorbents is discussed. New sorbent-based clinical approaches for acute conditions are presented, including a chapter on CytoSorb which is described and its use summarized in brief.

<https://www.ncbi.nlm.nih.gov/pubmed/28586767>

Continuous hemoadsorption with a cytokine adsorber during sepsis - a review of the literature

Houschyar KS, Pyles MN, Rein S, Nietzsche I, Dusche D, Maan ZN, Weissenberg K, Philipps HM, Strauss C, Reichelt B, Siemers F
Int J Artif Organs 2017;40(5):205-11

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Summary

Sepsis is a well-recognized worldwide healthcare issue, ultimately resulting in significant mortality, morbidity and resource utilization. In its most severe form, sepsis causes multi-organ dysfunction. Sepsis induces the activation of complement factor and the release of inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-1beta (IL-1 β), resulting in a systemic inflammatory response. This review article analyzes the efficacy of CytoSorb in reducing the inflammatory response during sepsis. CytoSorb is known to have excellent adsorption rates for inflammatory cytokines such as IL-1 β , IL-6, IL-8, IL-10, and TNF- α . Studies have demonstrated that treatment with CytoSorb has beneficial effects on the survival rate and inflammatory responses in animal septic models. Several cases have been reported in which treatment with CytoSorb is very effective in the stabilization of organ failure and hemodynamics in critically ill patients. Therefore, treatment with CytoSorb may play an important role in the treatment of sepsis in the future.
<https://www.ncbi.nlm.nih.gov/pubmed/28525674>

Extracorporeal renal replacement therapies in the treatment of sepsis: where are we?

Forni LG, Ricci Z, Ronco C
Semin Nephrol 2015;35(1):55-63

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Summary:

This review outlines the use of extracorporeal therapies in the treatment of sepsis and septic AKI, considering the classic aspects of extracorporeal renal replacement therapy including indications, timing, and delivered dose but also discussing the various techniques that are currently used to achieve immune homeostasis. The authors discuss evidence accumulated to date and suggest possibilities for the future treatment of these patients. In this context, CytoSorb therapy is mentioned as one of the most promising approaches, due to its improved biocompatibility and therefore the opportunity for whole blood perfusion, its efficiency in removing multiple inflammatory mediators shown in animal studies as well as in case reports, and its beneficial effects on chemokine gradients which may restore gradients towards infected tissue and away from healthy organs through leukocyte trafficking control.
<http://www.ncbi.nlm.nih.gov/pubmed/25795499>

Blood Purification and Mortality in Sepsis: A Meta-Analysis of Randomized Trials

Zhou F, Peng Z, Murugan R, Kellum JA
Crit Care Med 2013;41(9):2209-20

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Summary:

This is a systematic review and meta-analysis of randomized trials to determine the association between various blood purification techniques including hemofiltration, hemoperfusion, plasma exchange, and hemodialysis and all-cause mortality in humans with sepsis. A key finding of the review is that blood purification techniques were associated with lower mortality in patients with sepsis. These results were driven mainly by hemoperfusion and plasma exchange. Noteworthy, polymyxin B hemoperfusion studies from Japan had the biggest influence on the results.

<http://www.ncbi.nlm.nih.gov/pubmed/23860248>

Newly Designed CRRT Membranes for Sepsis and SIRS-A Pragmatic Approach for Bedside Intensivists Summarizing the More Recent Advances: A Systematic Structured Review

Honore PM, Jacobs R, Joannes-Boyau O, De Regt J, De Waele E, van Gorp V, Boer W, Verfaillie L, Spapen HD
ASAIO J 2013; 59(2):99-106

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Summary:

Since continuous renal replacement therapy (CRRT) in the treatment of sepsis and systemic inflammation response syndrome (SIRS) have shown relatively negative results, attention is now drawn to new membranes and sorbents that may better eliminate massive amounts of unbound mediators in a wider spectrum and also in greater magnitudes. This review summarizes the use and evidence of these newly designed technologies i.e. high cutoff CRRT membranes, high non-selective adsorptive CRRT membranes, high selective adsorptive CRRT membranes and cytokine-adsorbing columns. The authors state, that "CytoSorb might be seen as the most promising although not having the ability to fix endotoxin".

<http://www.ncbi.nlm.nih.gov/pubmed/23438770>

Moving from a Cytotoxic to a Cytokinic Approach in the Blood Purification Labyrinth: Have We Finally Found Ariadne's Thread?

Honore PM, Jacobs R, Joannes-Boyau O, Boer W, De Waele E, Van Gorp V, De Regt J, Spapen HD
Mol Med. 2012;18:1363-5

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Summary:

In this article the authors discuss the new "cytokinik" approach introduced by Namas et al. potentially explaining the mode of action of hemoadsorption using large surface-area polymer (i.e. CytoSorb) compared to the hitherto propagated "cytotoxic" hypotheses.

<http://www.ncbi.nlm.nih.gov/pubmed/23052299>

New membranes for extracorporeal blood purification in septic conditions

Bello G, Di Muzio F, Maviglia R, Antonelli M
Minerva Anestesiol 2012;78(11):1265-81

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Summary:

This review discusses the use of available technologies for extracorporeal blood purification (hemoadsorption, coupled plasma filtration adsorption, high

cut-off- and hemofiltration membranes) in sepsis. The authors specifically address the medical/scientific evidence of CytoSorb, but also of all other procedures.

<http://www.ncbi.nlm.nih.gov/pubmed/22772857>

Clinical review: blood purification for sepsis

Rimmelé T, Kellum JA

Crit Care 2011;15(1):205

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Summary:

This review discusses the latest advances in blood purification for sepsis and how they relate to current concepts of disease. The authors review the underlying mechanisms and the current medical/scientific evidence for high-volume hemofiltration, cascade hemofiltration, hemoabsorption, coupled plasma filtration adsorption, high-adsorption hemofiltration and high-cutoff hemofiltration/hemodialysis. Though all technologies are biocompatible and effective (reduction of cytokines and in part bacterial toxins, improvement of physiological parameters such as hemodynamics and oxygenation), there is an urgent need for confirming large multi-center trials evaluating the ability of these therapies to improve clinical outcomes. Regarding CytoSorb, the authors mainly discuss the two Kellum in vivo studies (endotoxin and cecal ligation and puncture model).

<http://www.ncbi.nlm.nih.gov/pubmed/21371356>