

# 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

#### 1.2.4 COVID-19

**NEW; Extracorporeal Cytokine Hemadsorption in Severe COVID-19 Respiratory Failure**

Damiani M, Gandini L, Landi F, Borleri G, Fabretti F, Gritti G, Riva I  
*Respiratory Medicine* 2021; 185: 107477

### 1.3 Case Reports

#### 1.3.1 Sepsis

**NEW; Hemoadsorption with CytoSorb and the early course of linezolid plasma concentration during septic shock**

Köhler T, Schwier E, Kirchner C, Winde G, Henzler D, Eickmeyer C.  
*J Artif Organs* 2021; epub

#### 1.3.6 COVID-19

**NEW; Hemadsorption as a Treatment Option for Multisystem Inflammatory Syndrome in Children Associated With COVID-19. A Case Report.**

Ruiz-Rodríguez JC, Chiscano-Camón L, Palmada C, Ruiz-Sanmartin A, García-de-Acilu M, Plata-Menchaca E, Perurena-Prieto J, Hernandez-Gonzalez M, Pérez-Carrasco M Soler-Palacin P, Ferrer R.  
*Frontiers in Immunology* 2021; 12: 665824

**NEW; Successful Treatment of Suspected Donor-derived Human Herpesvirus-8 Infection in a Liver Transplant Patient With Coronavirus Disease-19**

Peri AM, Magro B, van den Bogaart L, Dalla Pria A, Giuffrida P, Gianatti A, Fabretti F, Maria Barbui A, Tebaldi A, Rizzi M, Faggioli AS.  
*Transplantation* 2021; 105(6): e65-e67

### 3. Background and Reviews

**NEW; Sepsis-Pathophysiology and Therapeutic Concepts**

Jarczak D, Kluge S, Nierhaus A.  
*Front Med (Lausanne)* 2021; 2021: 8: 628302

## 1. Clinical data

### 1.1. Studies

#### 1.1.1. Sepsis

#### **High-dose CytoSorb hemoadsorption is associated with improved survival in patients with septic shock: A retrospective cohort study**

Schultz P, Schwier E, Eickmeyer C, Henzler D, Köhler T.

*Journal of Critical Care* 2021; 64: 184 - 92

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#### **Summary**

In this retrospective cohort study, data from 70 patients with septic shock and/or non-infectious systemic hyperinflammation (SIRS), who were treated with CytoSorb incorporated into their renal replacement therapy were analyzed. The 28-day mortality was compared to predicted mortality. On average, CytoSorb hemoadsorption was used for 85.6 hrs (number of adsorbers per patient 3.2) and started within 24 hrs after diagnosis. The APACHE II score was 30.2±6.3 with a predicted mortality of 73.3%, while the observed mortality was significantly lower (50%, p<0.05). Interleukin 6 decreased significantly (2144 – 445 pg/ml) after 72 hrs. For all patients, lactate decreased from 2.29 – 1.35 mmol/l after 72 hrs, and PaO<sub>2</sub>/FiO<sub>2</sub> index increased from 212 – 269. The authors also studied the amount of blood purified (= duration of CytoSorb treatment \* blood flow / body weight) and found that the higher the amount purified the better survival (8.5±4.4 vs. 6.1±3.6 l/kgBW, p=0.017). The authors identified three clusters of patient body weights (<6l/kgBW, 6-13l/kgBW and ≥13l/kgBW) with a linear dose response relation between blood purification volume and survival that was best in the highest volume cluster (83.3%; p=0.045). The application of CytoSorb appears to be effective and without associated side effects in various conditions of septic shock and SIRS. In the investigated cohort of severely ill patients the observed mortality rate was reduced if the blood purification volumes had exceeded 6 l/kg. The results suggest that hemoadsorption might improve survival in these severely ill patients provided that the applied dose is high enough.

<https://pubmed.ncbi.nlm.nih.gov/33962219/>

#### **Improved Survival beyond 28 Days up to 1 Year after CytoSorb Treatment for Refractory Septic Shock: A Propensity-Weighted Retrospective Survival Analysis**

Brouwer WP, Duran S, Ince C.

*Blood Purif* 2020; epub

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#### **Summary**

This publication is the long-term follow-up retrospective analysis of patients with septic shock who were treated with continuous renal replacement therapy (CRRT) + CytoSorb (n = 67) or CRRT alone (n = 49) (original publication *Brouwer et al., Crit Care* 2019; 317 in which patients were analyzed for all cause 28-day mortality). In this 2<sup>nd</sup> study the median follow-up for the **total** cohort was 30 days after ICU admission, and **333 days** for those who survived beyond 28 days (n = 59). The same statistical analysis was used in both studies. As with the first study factors associated with time to event were analyzed both weighted by stabilized inverse probability of treatment weights (sIPTW), as well as unweighted stratified by therapy received. Results showed that survival beyond 28 days was sustained up to 1 year after ICU admission for both treatment regimens: 80% vs. 87% for CytoSorb vs. CRRT, respectively. Using the statistical analysis approach of sIPTW, CytoSorb treatment showed a significantly higher survival rate compared to CRRT. Independent factors associated with long-term outcome in CytoSorb-treated patients were baseline lactate levels, age in the presence of comorbidity, and presence of abdominal sepsis. A lactate level above 6.0 mmol/L at the start of CytoSorb therapy had a positive predictive value of 79% for mortality. This is the first ever CytoSorb longitudinal study. It shows that survival achieved with CytoSorb and CRRT for patients with septic shock beyond 28 days from ICU admission may be improved with CytoSorb treatment. Lactate levels above 6.0 mmol/L at the start of CytoSorb therapy are predictive of worse outcome with high specificity and positive predictive value.

<https://www.ncbi.nlm.nih.gov/pubmed/33352555>

#### **Multicentred prospective investigator initiated study to evaluate the clinical outcomes with extracorporeal cytokine adsorption device (CytoSorb) in patients with sepsis and septic shock**

Paul, R, Sathe P, Kumar S, Prasad S, Aleem Ma, Sakhalvalkar P.

*World Journal of Critical Care Medicine* 2021; 10(1): 22 - 34

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#### **Summary**

This prospective, multicentre, observational study included 45 patients with septic shock (diagnosed <48 hrs prior to enrolment). Before and at the end of CytoSorb treatment a number of data were recorded and compared. A minimum of two adsorbers per patient were used in either hemodialysis mode (12 hours), or continuous renal replacement therapy mode (24 hrs). Post CytoSorb therapy, 26 patients survived. In the survivor group there was a (non-significant) tendency to require less vasopressors (norepinephrine 51.4%, epinephrine 69.4%, vasopressin 13.9% decrease). In the non-survivor group the use of vasopressors either remained unchanged or increased. In the survivor group lymphocytes, serum creatinine and lactate levels decreased significantly, and interleukin (IL) 1 and 6 levels decreased by 52.3% (non-significant). In the survivors the APACHE II and SOFA scores both significantly reduced by the end of treatment. Survivors spent 4.44 days in ICU and non survivors 8.5 days. There were no adverse events noted including no significant changes to albumin and platelets. There was a 75% survival rate in patients given treatment within 24 hrs of admission. Overall, the authors observed improved clinical outcome in terms of reduced mortality as compared to predicted, improved hemodynamics as indicated by MAP, and reduced use of vasopressors and their doses. They conclude that CytoSorb might be an effective adjuvant therapy in stabilizing septic shock patients, particularly if it is started within less than 24 hours after the onset of sepsis.

<https://pubmed.ncbi.nlm.nih.gov/33505870/>

### **Hemoadsorption with CytoSorb in Septic Shock Reduces Catecholamine Requirements and In-Hospital Mortality: A Single-Center Retrospective ‘Genetic’ Matched Analysis**

Rugg C, Kloese R, Hornung R, Innerhofer N, Bachler M, Schmid S, Fries D, Ströhle M.  
Biomedicines 2020; 8(12):539

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#### **Summary**

In this retrospective single-center study, septic shock patients receiving CytoSorb in addition to renal replacement therapy (n = 42) were analyzed and compared to closely matched control patients (n = 42). A generalized propensity-score and Mahalanobis distance matching method (‘genetic’ matching) was applied. Baseline comparability was high although the CytoSorb group had higher Sequential Organ Failure Assessment (SOFA) scores (13 vs. 12) scores, and requirements for norepinephrine (0.54 vs. 0.25 ug/kg/min). CytoSorb was started on average 21 hours after ICU admission, with most patients (38/42) receiving one treatment (24 hrs). While remaining fairly constant in the controls, the catecholamines levels were approximately halved to 0.26 ug/kg/min within 24 h after initiation of CytoSorb therapy. In-hospital- as well as 28-day - mortality was significantly lower in the CytoSorb group (35.7% vs. 61.9%, p=0.015 and 21.4% vs. 47.6%, p=0.029, respectively). Risk factors for mortality within the CytoSorb group were high lactate levels (7.5 mmol/L) and low thrombocyte counts prior to initiation suggesting that this might indicate an absence of CytoSorb benefit. This study shows that the addition of CytoSorb to standard care in septic shock patients requiring renal replacement therapy approximately halved catecholamine requirements within 24 hrs. In-hospital as well as 28-day mortality were significantly reduced when compared to a generalized propensity-score and Mahalanobis distance matched group.

<https://pubmed.ncbi.nlm.nih.gov/33255912/>

### **Combined Use of CytoSorb® and ECMO in patients with severe pneumogenic sepsis**

Akil A, Ziegeler S, Reichelt J, Rehers S, Abdalla O, Semik M, Fischer S.  
*The Thoracic and Cardiovascular Surgeon* 2021; 69(3):246-251

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#### **Summary**

In this prospective case series, 13 patients with pneumogenic sepsis on high flow veno-venous extracorporeal respiratory support (vv-ECMO) and CytoSorb were compared to retrospective data from 7 patients treated with ECMO alone. All patients in the CytoSorb group survived to 30 days (57% mortality in the ECMO only group). The use of CytoSorb resulted in the rapid and significant reduction in inflammatory markers (procalcitonin and C Reactive Protein). Patients in the CytoSorb group could also be weaned off high dose catecholamine therapy within 48 hrs which was not the case in the ECMO only group. The authors conclude that the use of CytoSorb in combination with ECMO is an effective therapy to prevent the escalation of sepsis, with rapid weaning off high dose catecholamines.

<https://www.ncbi.nlm.nih.gov/pubmed/32252114>

### **Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study**

Brouwer WP, Duran S, Kuijper M, Ince C.  
*Crit Care* 2019; 317

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## Summary

In this investigator-initiated retrospective study, patients with septic shock were treated with continuous renal replacement therapy (CRRT) + CytoSorb (n = 67) or CRRT alone (n = 49). Patients were weighted by stabilized inverse probability of treatment weights (sIPTW), a statistical method applied to overcome differences in baseline patient characteristics and to make these independent from treatment assignment, with the target to mimic a randomized controlled trial. The primary endpoint was the 28-day all-cause mortality compared for CytoSorb versus CRRT alone. Secondary endpoints included the comparison between the observed 28-day mortality rate in the CytoSorb treatment group versus the predicted mortality according to the SOFA score, and variables that predict mortality in the CytoSorb group. This represents the largest cohort of septic shock patients treated with CytoSorb therapy to date in which mortality was assessed as a primary outcome. At the start of therapy, CytoSorb-treated patients had higher lactate levels ( $p < 0.001$ ), lower mean arterial pressure ( $p = 0.007$ ) and higher levels of noradrenaline ( $p < 0.001$ ) compared to the CRRT group. For CytoSorb, the mean predicted mortality rate based on a SOFA of 13.8 (n = 67) was 75%, while the actual 28-day mortality rate was 48% (mean difference - 27%,  $p < 0.001$ ). By sIPTW analysis, patients treated with CytoSorb had a significantly lower 28-day mortality rate compared to CRRT alone (53% vs. 72%, respectively,  $p = 0.038$ ). Independent predictors of 28-day mortality in the CytoSorb group were the presence of pneumosepsis, higher levels of lactate at the start of CytoSorb and older age. In this study, measurements of antibiotic levels were not available. Nonetheless, there were no observations or indications of excessive need for antibiotics or persistence of infections in the CytoSorb group. In summary, this study has demonstrated in the largest cohort of septic shock patients investigated to date, that CytoSorb treatment was associated with a statistically significant improvement of 28-day survival, both on the basis of observed versus predicted mortality rates, as well as compared to a control group with CRRT alone.

<https://www.ncbi.nlm.nih.gov/pubmed/31533846>

## 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  $7.8 \pm 3.7$  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 during Cardiopulmonary Bypass in Patients with Endocarditis Undergoing Valve Surgery: A Retrospective Single-Center Study**

Santer D, Miazza J, Koechlin L, Gahl B, Rrahmani B, Hollinger A, Eckstein FS, Siegemund M, Reuthebuch OT.

*J Clin Med* 2021; 10(4): 564

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#### **Summary**

The aim of this retrospective single centre study was to evaluate the outcomes of infectious endocarditis patients undergoing valve surgery with CytoSorb during cardiopulmonary bypass. Over a ten-year period from 2009 until 2019, 241 patients underwent valve surgery due to endocarditis and those who received CytoSorb during surgery ( $n = 41$ , 17%) were compared to those without ( $n = 200$ ), using inverse probability of treatment weighting in order to achieve balanced distributions of baseline characteristics. Even with this statistical approach, standardized difference with respect to the intake of platelet inhibitors did not drop below 0.2, indicating residual confounding. The results showed that in-hospital mortality, major adverse cardiac and cerebrovascular events and postoperative renal failure were similar in both groups. However, demand for norepinephrine, milrinone, red blood cell concentrates, and platelets were higher in the CytoSorb group. In addition, there was also a higher incidence of reoperation for bleeding and a prolonged length of in-hospital stay observed in the CytoSorb group. The authors conclude that there were no benefits of CytoSorb-therapy observed in these patients with infective endocarditis undergoing valve surgery.

<https://pubmed.ncbi.nlm.nih.gov/33546164/>

#### **Haemoadsorption – effective in reducing circulating fragments of the endothelial glycocalyx during cardiopulmonary bypass in patients undergoing on-pump cardiac surgery?**

Hohn A, Baumann A, Pietroschinsky E, Franklin J, Illerhaus A, Buchwald D, Hinkelbein J, Zahn P.K., Annecke T.

*Min Anest 2021; 87(1): 35 - 42*

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## **Summary**

Damage-associated molecular patterns (DAMPs) have been shown to enhance the inflammatory process and induce further the ischemia/reperfusion injury and endothelial glycoalyx degradation. This article included 15 patients undergoing on-pump cardiac surgery where the CytoSorb adsorber was integrated into the cardiopulmonary bypass circuit. Pre- and post adsorber levels of DAMPs heparan sulphate (HEP), syndecan-1 (SYN) and hyaluronan (HYA) and the atrial natriuretic peptide (ANP) were measured at 10 (T1), 30 (T2), and 60 (T3) minutes after aortic cross-clamping and the end of CPB. Use of CytoSorb significantly reduced concentrations of HEP, however concentrations of HYA, SYN and ANP could not be reduced.

<https://www.ncbi.nlm.nih.gov/pubmed/32643361>

## **Influence of hemoadsorption during cardiopulmonary bypass on blood vesicle count and function.**

Wisgrill L, Lamm C, Hell L, Thaler J, Berger A, Weiss R, Weber V, Rinoesl H, Hiesmayr MJ, Spittler A, Bernardi MH.

*J Transl Med 2020; 18(1): 202*

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## **Summary**

Microvesicles (MV) have recently been found to be responsible for part of the cellular communication network during inflammation. In this 2<sup>nd</sup> subgroup analysis of a previously published paper (Bernardi et al., Crit Care 2016; 1:96) the effect of circulating MVs during cardiopulmonary bypass (CPB) was assessed in a total of 18 patients with (n = 9) and without (n = 9) CytoSorb inserted into the CPB. Levels of apoptotic bodies (AB – a vesicle that contains parts of a dying cell) was also assessed. MV and AB counting was conducted via flow cytometry and procoagulatory potential was measured by tissue factor-dependent MV assays. Both study groups exhibited comparable counts and post-operative kinetics in MV and AB subsets. Tissue factor-dependent pro-coagulatory potential was not detectable in the plasma at any timepoint. Post-operative course and laboratory parameters showed no correlation with MV or AB counts in these patients undergoing CPB surgery. This study confirms that adding additional artificial surfaces into the CPB-circuit with the CytoSorb device had no effect on the systemic immune cell activation in the circulation further confirming the safety of the device.

<https://www.ncbi.nlm.nih.gov/pubmed/32414386>

## **Assessing efficacy of CytoSorb haemoadsorber for prevention of organ dysfunction in cardiac surgery patients with infective endocarditis: REMOVE-protocol for randomised controlled trial**

Diab M, Platzer S, Guenther A, Sponholz C, Scherag A, Lehmann T, Velichkov I, Hagel S, Bauer M, Brunkhorst FM, Doenst T.

*BMJ Open 10(3): e031912*

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## **Summary**

This protocol describes the design of the REMOVE study (*Revealing mechanisms and investigating efficacy of hemoadsorption for prevention of vasodilatory shock in cardiac surgery patients with infective endocarditis*), an interventional randomised controlled multicenter trial for assessing efficacy of CytoSorb in patients undergoing cardiac surgery for infective endocarditis. The change in mean total Sequential Organ Failure Assessment (SOFA) score between pre- and post-operative care is the primary endpoint with data on 30-day mortality, changes in cytokines levels, duration of mechanical ventilation, length of intensive care unit and hospital stay, and postoperative stroke as the secondary endpoints. An interim analysis will be conducted after including 25 participating patients per study arm (focusing on feasibility of recruitment as well as differences in cytokines and cell-free DNA levels). The protocol was approved by the institutional review board and ethics committee of the University of Jena, Germany, as well as by the corresponding ethics committee of each participating study centre. ClinicalTrials.gov registry (NCT03266302).

<https://www.ncbi.nlm.nih.gov/pubmed/32234739>

## **Extracorporeal Hemadsorption versus Glucocorticoids during Cardiopulmonary Bypass: A Prospective, Randomized, Controlled Trial**

Taleska Stupica G, Sostaric M, Bozhinovska M, Rupert L, Bosnic Z, Jerin A, Ihan A, Klokocovnik T, Podbregar M.

*Cardiovascular Therapeutics 2020: 1-15*

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## Summary

In this randomized control trial, intraoperative hemadsorption (CytoSorb) or methylprednisolone was compared to usual care in sixty complex cardiac surgery patients on cardiopulmonary bypass (CPB). Allocation was into three groups: Methylprednisolone (n 20), CytoSorb (n 20), and Control group (usual care, n 20). Proinflammatory (TNF- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-8) and anti-inflammatory (IL-10) cytokines with complement C5a, CD64, and CD163 expression by immune cells were analyzed for the first five postoperative days, in addition to hemodynamic and clinical outcome parameters. The methylprednisolone group, compared to CytoSorb and control groups had significantly lower levels of TNF- $\alpha$  (until the end of surgery,  $p < 0.001$ ), IL-6 (until 48 h after surgery,  $p < 0.001$ ), and IL-8 (until 24 h after surgery,  $p < 0.016$ ). CD64 expression on monocytes was the highest in the CytoSorb group and lasted until the 5th postoperative day ( $p < 0.016$ ). IL-10 concentration (until the end of surgery) and CD163 expression on monocytes (until 48 h after surgery) were the highest in the Methylprednisolone group ( $p < 0.016$ , for all measurements between three groups). There were no differences between groups in the cardiac index or clinical outcome parameters. Methylprednisolone was reported to more effectively ameliorate inflammatory responses after CPB surgery compared to CytoSorb or usual care however, this did not translate into better short-term outcomes. Use of CytoSorb had a beneficial effect intraoperatively, with patients from the CytoSorb group having the lowest need for norepinephrine, and patients in the Methylprednisolone group having the highest; however, this was seen only during surgery and did not reach statistical significance. CytoSorb use compared with usual care caused higher prolonged expression of CD64 on monocytes and higher expression of CD163 on granulocytes, which however lasted only until the end of surgery. Hemadsorption with CytoSorb was safe and well tolerated. The authors note that the effects of hemadsorption with CytoSorb might have been more pronounced if the duration of CPB was longer (median bypass time was around 140 mins), or if only high-risk patients had been included (i.e., aortic arch surgery with hypothermic arrest and selective perfusion of brain, endocarditis surgery, and higher EuroSCORE II).

<https://www.ncbi.nlm.nih.gov/pubmed/32292492>

## Cytokine Removal in Critically Ill Patients Requiring Surgical Therapy for Infective Endocarditis (RECRATE): An Investigator-initiated Prospective Randomized Controlled Clinical Trial Comparing Two Established Clinical Protocols.

Gisler F, Spinetti T, Erdoes G, Luedi MM, Pfortmueller CA, Messmer AS, Jenni H, Englberger L, Schefold JC.

*Medicine (Baltimore) 2020; 99(15): e19580*

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## Summary

Infective endocarditis (IE) can induce significant changes in the immune response with patients developing persistent functional immunological phenotypes characterized by a profound anti-inflammation and/ or functional "anergy" particularly in patients with unresolved infectious foci (previously referred to as "injury-associated immunosuppression" (IAI)). IAI can be assessed by monocytic human leukocyte antigen-DR (mHLA-DR) expression, a global functional marker of immune competence. Persistence of IAI is associated with prolonged intensive care unit length of stay, increased secondary infection rates, and death. Immunomodulation to reverse IAI has been shown to be beneficial in early immunostimulatory (randomized controlled) clinical trials.

This protocol (RECRATE) is a prospective 1:1 randomized controlled clinical study to compare the course of mHLA-DR in patients scheduled for cardiac surgery for IE. Fifty-four patients will be randomized to receive either best standard of care plus CytoSorb adsorption during surgery while on cardiopulmonary bypass (protocol A) versus best standard of care alone, that is, surgery without CytoSorb (cytokine) adsorption (protocol B). The primary endpoint is a change in quantitative expression of mHLA-DR from baseline (preoperation visit 1) to day 1 post-OP (visit 4). This protocol was registered in ClinicalTrials.gov NCT03892174.

<https://www.ncbi.nlm.nih.gov/pubmed/32282706>

## Intraoperative hemoadsorption in patients with native mitral valve infective endocarditis

Haidari Z, Wendt D, Thielmann M, Mackowiak M, Neuhäuder M, Jakob H, Ruhparwar A, El Gabry M.

*The Annals of Thoracic Surg 2020; 110(3): 890 - 6*

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## Summary

This retrospective non-randomized study included 58 consecutive patients with infective endocarditis of the native mitral valve who were undergoing surgery between January 2014 and July 2018. Thirty patients who received intraoperative CytoSorb therapy were compared to 28 patients who didn't. The two groups of patients were comparable in their baseline characteristics prior to surgery. Results showed that postoperative sepsis occurred in only 5 patients in the CytoSorb (hemoadsorption) group and in 11 patients in the control group ( $p=0.05$ ). There were no sepsis-associated deaths in the CytoSorb group, whereas five septic patients died in the control group ( $p=0.02$ ). Thirty-day-mortality was 10% in the hemoadsorption group versus 18% in the control group (statistically non-significant). Patients in the CytoSorb group also showed greater hemodynamic stability (less need for norepinephrine and epinephrine). The authors conclude that the data suggest that intraoperative hemoadsorption with CytoSorb may improve surgical outcome in patients with mitral valve endocarditis.

<https://www.ncbi.nlm.nih.gov/pubmed/32059855>

### **Plasma Levels of Myocardial MicroRNA-133a Increase by Intraoperative Cytokine Hemoadsorption in the Complex Cardiovascular Operation.**

Wagner R, Soucek P, Ondrasek J, Fila P, Sterba J, Spacilova H, Michalcikova A, Freiburger T, Nemecek P

*J Clin Med Res* 11(12): 789-797

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#### **Summary**

This study evaluated if intraoperative cytokine reduction by CytoSorb modulates the systemic inflammatory response syndrome (SIRS) and affects myocardial injury as measured by some relatively new markers for myocardial injury (miRNA-126, 223 and miRNA-1, 133a), respectively. Twenty-eight patients were assigned to CytoSorb ( $n = 15$ ) or a control ( $n = 13$ ) group. CytoSorb was integrated into the extracorporeal circuit. MiRNA-133a plasma levels were increased postoperatively in both groups but were higher in the CytoSorb group at 3 hrs ( $P = 0.037$ ) and 18 h ( $P = 0.017$ ) after reperfusion. MiRNA-1 and miRNA-223 plasma levels were significantly increased postoperatively, but did not differ between groups. The vascular miRNA-126 was not affected. Intraoperative CytoSorb use in these patients increased the plasma levels of miRNA-133a, suggesting higher myocardial injury. There was no difference in inflammatory mediators such as C-reactive protein, leukocytes, platelets and fibrinogen levels, and a marked reduction in procalcitonin in the CytoSorb group that did not however reach statistical significance. There were no differences in clinical outcomes between groups (including need for vasoconstrictors and inotropes, time to extubation, time in intensive care and to hospital discharge).

<https://www.ncbi.nlm.nih.gov/pubmed/31803323>

### **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; 31(4): 783 - 93

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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 > 3hrs) 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  $\geq 3$ h. 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.

*Crit 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://www.ncbi.nlm.nih.gov/pubmed/30944029>

### **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; 56(4):731-737

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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 $\alpha$ serum levels in cardiac surgery: a randomized controlled trial.**

Garau I, März A, Sehner S, Reuter DA, Reichensperner H, Zöllner C, Kubitz JC.

*Minerva Anesthesiol.* 2019; 715 - 23

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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  $\alpha$  (TNF $\alpha$ ) 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 $\alpha$  levels were also below those in the CG at both the end of and 6h after CPB (p=0.034). After 24 hours, TNF $\alpha$  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 $\alpha$  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* 2019; 65(7): 738 - 43

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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-Gefäßschir* 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.

[Link to Article](#)

## **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](http://www.ncbi.nlm.nih.gov/pubmed/26971164)

### **1.1.3. Other indications**

#### **Effect of Cytokine Adsorption on Survival and Circulatory Stabilization in Patients Receiving Extracorporeal Cardiopulmonary Resuscitation**

Supady A, Zahn T, Rieder M, Benk C, Lothar A, Bode C, Wengenmayer T, Staudacher D, Kellum JA, Duerschmied D.

*ASAIO J* 2021; epub

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#### **Summary**

In this study 23 patients who received extracorporeal cardiopulmonary resuscitation (ECPR) plus CytoSorb hemoadsorption due to cardiac arrest, were compared to a propensity-matched cohort of 23 ECPR patients without cytokine adsorption. Survival, lactate clearance, vasopressor need, and fluid demand in both groups were compared. Cytokine adsorption was started after a mean of 14 hours after ECPR and the CytoSorb cartridge was renewed after 24 hours, with treatment being continued for at least 72 hours. Survival to discharge from intensive care unit (ICU) was similar in both groups at around 20%. A decrease of serum-lactate, need for vasopressors, and fluid demand during the first 72 hours after ECPR was observed and there were no significant between-group differences. Impella 2.5 or CP percutaneous ventricular assist devices for left-ventricular unloading were used more often in the cytokine adsorption group. For platelet count and international normalized ration (INR) values there were no significant differences discovered between cytokine adsorption and control groups. Duration of veno-arterial (V-A) Extracorporeal Membrane Oxygenation (ECMO) therapy was significantly longer in the cytokine adsorption group than in the control group ( $5.4 \pm 5.1$  vs.  $2.6 \pm 2.1$  days,  $p=0.02$ ) due to longer survival. Due to small case numbers and the retrospective design of the study, the authors state that the results should be interpreted cautiously and neither disprove nor confirm a clinically relevant treatment effect of cytokine adsorption.

<https://www.ncbi.nlm.nih.gov/pubmed/33883508>

## Early use of hemoadsorption in patients after out-of hospital cardiac arrest - a matched pair analysis)

Akin M, Garcheva V, Sieweke JT, Flierl U, Daum HC, Bauersachs J, Schafer A.  
*PLoS One* 2020; 15(11): e0241709

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### Summary

This study aimed to assess the effect of cytokine adsorption on mortality in patients following out-of-hospital cardiac arrest by comparing a patient cohort with hemoadsorption after resuscitation for out-of-hospital cardiac arrest (24 pts) matched in a 1:2 fashion to a control cohort without adsorption (48 pts). Patients were matched according to age, gender, time to return of spontaneous circulation, initial left-ventricular ejection fraction, extracorporeal membrane-oxygenation or left-ventricular unloading by Impella, need for renal replacement therapy, admission lactate, pH, glomerular filtration rate. The CytoSorb group had a higher (non-significant) requirement for vasopressors prior to the start of CytoSorb, suggesting they were sicker. In the hemoadsorption group, use of CytoSorb was within 4 hours of admission to ICU, and was attempted for three days. There were no adverse events caused by the use of CytoSorb. While there was no significant difference in baseline parameters, 30-day mortality was higher in patients treated with hemoadsorption than in the matched control group (83% vs 65%, Log rank  $p = 0.011$ ). The authors point out the small number of patients examined and that the CytoSorb patients may have been sicker, which may have contributed to the increased mortality. They conclude that hemoadsorption should be investigated more closely in randomised controlled trials of suitable size.

<https://www.ncbi.nlm.nih.gov/pubmed/33141843>

## 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* 2019; 114(8): 699 - 707

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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>

#### **1.1.4 COVID-19**

### **Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial**

Supady A, Weber E, Rieder M, Lothar A, Niklaus T, Zahn T, Frech F, Müller S, Kuhl M, Benk C, Maier S, Trummer G, Flügler A, Krüger K, Sekandarzad A, Stachon P, Zotzmann V, Bode C, Bieber PM, Staudacher D, Wengenmayer T, Graf E, Duerschmied D.

*The Lancet Respiratory Medicine* 2021; epub

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#### **Summary**

This single-centre, open-label, randomised, controlled trial investigated cytokine adsorption in adult patients with severe COVID-19 pneumonia requiring veno venous extracorporeal membrane oxygenation (vv ECMO). Patients were randomly assigned to receive cytokine adsorption or not. The CytoSorb device was incorporated into the ECMO circuit and replaced every 24 hrs and removed after 72 h. 34 patients were assessed for eligibility, and 17 (50%) were treated with cytokine adsorption and 17 (50%) without. Median interleukin (IL)-6 decreased from 357.0 pg/mL to 98.6 pg/mL in patients randomly assigned to cytokine adsorption and from 289.0 pg/mL to 112.0 pg/mL in the control group after 72 h. One patient in each group died before 72 h (during treatment). Survival after 30 days was three (18%) of 17 with cytokine adsorption and 13 (76%) of 17 without cytokine adsorption with most patients dying between day 10 and 20, so several days after the end of the 72-h period of cytokine adsorption. Causes of death were respiratory failure, pulmonary haemorrhage, septic shock, multiorgan failure and intracranial haemorrhage. The authors summarize that early initiation of cytokine adsorption in patients with severe COVID-19 and vv ECMO did not reduce serum IL-6 and had a negative effect on survival and that therefore cytokine adsorption should not be used during the first days of ECMO support in COVID-19.

<https://pubmed.ncbi.nlm.nih.gov/34000236/>

### **Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation: protocol for a randomised, controlled, open-label intervention, multicentre trial.**

Rieder M, Schubach F, Schmoor C, von Spee-Mayer C, Wengenmayer T, Rilinger J, Staudacher D, Bode C, Duerschmied D, Supady A.

*BMJ Open* 2021; 11(1); e043345

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#### **Summary**

This is the published protocol of a 1:1 randomised, controlled, parallel group, open-label intervention, superiority multicentre trial to evaluate the effect of extracorporeal cytokine adsorption using CytoSorb in severe COVID-19 related acute respiratory distress syndrome (ARDS) patients treated with veno-venous Extracorporeal Membrane Oxygenation (v-v ECMO). The hypothesis is that use of CytoSorb in



these patients effectively reduces interleukin (IL)-6 levels by 75% or more after 72 hours compared with the baseline measurement, and also reduces time to successful v-v ECMO explantation. The adsorber is usually installed in the system as part of the preparation of the ECMO system before the system is connected to the patient circuit, but at the latest within 4 hours after initiation of the ECMO. A total of 80 patients at nine centres in Germany are planned. The protocol of this study was approved by the ethical committee of the University of Freiburg as the leading institution (EK 285/20) with additional votes to be obtained at all participating centres. Trial registration numbers are NCT04385771 and DRKS 00021248.

<https://pubmed.ncbi.nlm.nih.gov/33455938/>

## **Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation**

Rieder M, Wengenmayer T, Staudacher D, Duerschmied D, Supady A.

*Crit Care* 2020; 24:435

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### **Summary**

In this letter to the editor, the randomized controlled data from four patients with COVID-19 on veno-venous (vv) Extracorporeal Membrane Oxygenation (ECMO) and CytoSorb adsorbers was compared to 4 control patients on vvECMO without CytoSorb. The adsorber was exchanged every 24 hrs and integrated into the ECMO circuit which was found to be both feasible and safe. Results showed that the reduction in interleukin (IL)-6 was more pronounced in the CytoSorb group, although the initial level was much higher in this group. The letter then goes on to describe the planned multicentre randomized control trial established to compare cytokine adsorption in ECMO treatment plus CytoSorb for COVID-19 with a control group receiving standard care without CytoSorb (CYCOV-II study (Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation, ClinicalTrials.gov number NCT04385771)).

<https://www.ncbi.nlm.nih.gov/pubmed/32664996>

## **1.2. Case series**

### **1.2.1. Sepsis**

#### **Adsorption therapy in critically ill with septic shock and acute kidney injury: a retrospective and prospective cohort study.**

Schittek GA, Zoidl P, Eichinger M, Orlob S, Simonis H, Rief M, Metnitz P, Fellingner T, Soukup J.

*Annals of Intensive Care* 2020; 10(1);154

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### **Summary**

The case series looked at whether hemoadsorption with CytoSorb could influence intensive care unit (ICU) and hospital length of stay (LOS) and mortality as well as therapeutic support in patients with severe septic shock and sepsis associated acute kidney injury (SA-AKI) using a retrospective control group and prospective intervention group. All patients were treated in accordance with the local sepsis treatment protocol, however, to be included in the study, still had to have increasing catecholamine dependency (above 20 µg/min norepinephrine), elevated interleukin(IL) 6 levels >500 pg/ml, and required continuous veno-venous hemodiafiltration (CVVHDF) due to AKI (KDIGO stage 3). In the historical control group 33 patients were finally identified out of 672 patients with septic shock treated between 1/2012 and 12/2013. From 1/2015 to 5/2018 2,102 patients were treated with septic shock out of which 43 patients fulfilled the inclusion criteria for the CytoSorb group. Severity of illness, as depicted by APACHE II, was higher in patients treated with hemoadsorption (39 versus 35), as was catecholamine dependency (norepinephrine 64 µg/min vs. 44 µg/min) and procalcitonin (28 v 7 ng/l). Approximately one cartridge per patient was utilised as the median (IQR 1, 2) for 35.5 h (17, 47). In univariate analysis of all patients, the authors found that LOS, ventilatory support, duration of CVVHDF and duration of catecholamine administration were significantly lower for patients in the hemoadsorption group (p < 0.01), however these differences did not remain significant in multivariate analysis.

<https://pubmed.ncbi.nlm.nih.gov/33206229/>

## **Standard renal replacement therapy combined with hemoadsorption in the treatment of critically ill septic patients**

Popescu M, Dima S, David C, Tudor A, Simionescu M, Tomescu D.

*Ther Apher Dial* 2020; epub

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## **Summary**

The aim of this prospective observational study was to assess clinical and paraclinical effects that hemoadsorption with CytoSorb had on organ dysfunction, severity scores and 28 days survival in 55 septic intensive care patients. Each patient underwent three consecutive 24-hour sessions of renal replacement therapy in combination with hemoadsorption, with clinical and paraclinical variables measured after the treatment. Use of hemoadsorption was associated with a significant increase in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, urine output and Glasgow Coma Score and a significant decrease in white blood cell count, C-reactive protein, procalcitonin levels and platelet count. Overall, the use of hemoadsorption was associated with an improvement in neurological and renal function and a decrease in inflammatory markers. Acute Respiratory Distress Syndrome (ARDS) improved significantly, based on relevant improvements in one third of the patients.

<https://www.ncbi.nlm.nih.gov/pubmed/33270367>

## **Cytokine Adsorption in Severe Acute Respiratory Failure Requiring Veno-Venous Extracorporeal Membrane Oxygenation.**

Rieder M, Duerschmied D, Zahn T, Lang C, Benk C, Lothar A, Biever P, Bode C, Wengenmayer T, Staudacher D, Supady A.

*ASAIO J 2020; epub*

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## **Summary**

Veno-venous extracorporeal membrane oxygenation (V-V ECMO) is a last resort treatment option for patients with acute respiratory failure (acute respiratory distress syndrome [ARDS]). This is a report of a single-center registry data from nine all-comers with severe ARDS predominately from infectious cause, treated with V-V ECMO and cytokine adsorption using the CytoSorb adsorber, compared with a control group of nine propensity score matched patients who had undergone V-V ECMO support without cytokine adsorption. Even though scores (SOFA - Severity of Organ Failure Assessment, RESERVE – Predicting Death for Severe ARDS on V-V ECMO) both predicted a higher mortality in the cytokine adsorption group, mortality was reduced in the CytoSorb plus V-V-ECMO group compared with V-V ECMO alone. In total, 5 patients in the CytoSorb plus V-V-ECMO group survived (55.6%), compared with 2 (22.2%) from the V-V- ECMO alone group. The need for fluid resuscitation and vasopressor support as well as lactate levels dropped significantly in the cytokine adsorption group within 72 hours, whereas vasopressor need and lactate levels did not decrease significantly in the control group. Therefore, the authors conclude that cytokine adsorption might be beneficial in patients with severe ARDS requiring V-V ECMO support by contributing to hemodynamic stabilization and, in turn impacting on survival.

<https://www.ncbi.nlm.nih.gov/pubmed/33181544>

## **Effect of a novel extracorporeal cytokine apheresis method on endocan, copeptin And interleukin-6 levels in sepsis: An observational prospective study**

Kaya Ugur B, Cicek H, Kul S, Mete O, Yilmaz M.

*Transfus Apher Sci 2020; 59(6):102919*

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## **Summary**

The aim of the study was to evaluate the effect of each CytoSorb hemoadsorption therapy course on several blood levels of inflammatory biomarkers of sepsis (endocan, copeptin, interleukin-6, procalcitonin, C-reactive protein). A total of 178 samples belonging to 34 sepsis patients who received CytoSorb therapy either in hemoperfusion mode or as part of the renal replacement circuit were analysed. Arterial blood samples were obtained both before and after each CytoSorb course (8 hours per session, range of adsorbers per patient 1 – 19). Levels of copeptin, interleukin-6, procalcitonin, C-reactive protein, erythrocyte sedimentation rate, white blood cell count, and creatinine were measured and all were significantly decreased after the CytoSorb course when compared with levels before therapy ( $p = 0.039, 0.001, 0.010, 0.001, 0.002$  and  $0.001$ , respectively). There was no significant difference between white blood cell count and creatinine levels before and after CytoSorb courses. The authors speculate that decreasing plasma levels of inflammatory cytokines may help alleviate the cytokine storm and may have a role in improving outcomes.

<https://www.ncbi.nlm.nih.gov/pubmed/32912735>

## **Elimination of glycopeptide antibiotics by cytokine hemoadsorption in patients with septic shock: A study of three cases**

Dimski T, Brandenburger T, MacKenzie C, Kindgen-Milles D.

*Int J Artif Organs*: 2020; 43(12): 753 - 7

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## **Summary**

In this short case series, glycopeptide antibiotic serum levels (vancomycin and teicoplanin) of three patients were measured pre and post CytoSorb adsorber which was inserted into a hemodialysis circuit in hemoperfusion mode in all cases for one 8 hour cycle. All patients had septic shock and were critically ill. In two patients, teicoplanin and vancomycin were given via a 60-min infusion and, in the third patient vancomycin was given via a continuous infusion. Results for the short infusions (60 min bolus), showed that both vancomycin and teicoplanin were removed immediately by the adsorber. However, the adsorptive capacity of the device was saturable with serum levels of vancomycin, but not teicoplanin, decreasing to subtherapeutic levels. With the continuous infusion of vancomycin, removal was less and serum levels remained in the therapeutic range. After 240 mins a difference between pre and post adsorber concentrations was not detectable. This information shows that the dose of these antibiotics should be adjusted appropriately, and early therapeutic drug monitoring is highly recommended. The authors suggest administering these antibiotics at the upper limit of recommended dosing regimens. Vancomycin should be administered as a high loading dose followed by a continuous infusion. The adsorptive capacity of the device (for the investigated substances) seems limited and saturation occurs within 120– 240 min.

<https://www.ncbi.nlm.nih.gov/pubmed/32342769>

## **Hemoperfusion with Cytosorb in pediatric patients with septic shock: A retrospective observational study.**

Bottari G, Guzzo I, Marano M, Stoppa F, Rava L, Di Nardo M, Cecchetti C.

*Int J Artif Organs* 2020; 43(9): 587 - 93

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## **Summary**

This retrospective case series included eight consecutive pediatric patients who received CytoSorb with standard Continuous Renal Replacement Therapy (CRRT) within 24 hours of proven or suspected septic shock refractory to standard treatment. The ages of the children ranged from 1-13 years, and weight from 10-45 kg. The source of the septic shock included three with secondary hemophagocytic lymphohistocytosis. Four of patients also received extracorporeal membrane oxygenation (3 VA-ECMO, 1 VV-ECMO). The Vasoactive-Inotropic Score (VIS) was measured before and after CytoSorb treatment. Time course of cytokines IL-6, IL-10, and tumor necrosis factor-alpha (TNF $\alpha$ ) were measured at time 0, then every 12 h until the end of blood purification treatment (72 or 96 h). CytoSorb use with CRRT was associated with a rapid and significant decrease in catecholamine demand and hemodynamic stabilization with an improved VIS following CytoSorb (pre: 40.00 post: 8.89  $p=0.0076$ ). Overall the pediatric intensive care unit survival was 88.75%. Measurement of cytokine levels showed a significant reduction of IL-6 (7977.27-210.18 pg/mL,  $p=0.0077$ ) and IL-10 (from 687.19 to 36.95 pg/mL,  $p=0.0180$ ). There were no adverse events noted during the use of CytoSorb therapy.

<https://www.ncbi.nlm.nih.gov/pubmed/32003289>

## **Experience with hemoadsorption (CytoSorb) in the management of septic shock patients.**

Mehta Y, Mehta C, Kumar A, George JV, Gupta A, Nanda S, Kochhar G, Raizada A.

*World J Crit Care Med* 2020 9(1): 1 - 12

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## **Summary**

This retrospective case series included 100 adult patients who were admitted to intensive care between 2016 and 2018 in an Indian hospital following the diagnosis of sepsis or septic shock, who had been treated with dialysis and CytoSorb combination therapy. The authors used a new CytoSorb scoring (CS) system that was developed by a group of Indian clinicians for initiating CytoSorb therapy on the basis of their practical experience so far. The scoring system was derived from five parameters (hemodynamic, renal, respiratory, lab and sepsis scores), representing five different organ system which get affected in sepsis patients. This study proposes that the CytoSorb therapy should be recommended to the patients with scores between 8-13. In summary, results showed a reduction in the vasopressor dose, a significant reduction in cytokine levels, remarkable reduction in diagnostic markers such as PCT, CRP, bilirubin and serum lactate after the usage of CytoSorb therapy. Early (preferably within <48 h after onset of septic shock) initiation could result in better clinical outcomes. CytoSorb was found to be safe and a well-tolerated rescue therapy option in patients with septic shock.

[Lhttps://www.ncbi.nlm.nih.gov/pubmed/32104647](https://www.ncbi.nlm.nih.gov/pubmed/32104647)

## **Hemadsorption by extracorporeal cytokine adsorption therapy (CytoSorb) in the management of septic shock: A retrospective observational study**

Singh YP, Chhabra SC, Lashkari K, Taneja A, Garg A, Chandra A, Chhabra M, Singh GP, Jain S.  
*The Int J Artif Organs* 2020; 43(8): 372 - 8

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### **Summary**

This retrospective, observational study included 36 patients with septic shock who also received CytoSorb therapy. After CytoSorb therapy there was a significant decrease in procalcitonin (PCT) within 24 hours of therapy. The leucocyte count also decreased within this time frame. The sepsis related organ failure assessment (SOFA) score decreased after the use of CytoSorb. Shock reversal was seen in 8 patients within 24 hrs of treatment. The authors confirm that CytoSorb may be a safe, effective and well tolerated rescue therapy, decreasing vasopressor requirements and stabilizing hemodynamics in septic shock patients.

<https://www.ncbi.nlm.nih.gov/pubmed/31868078>

## **A retrospective analysis of efficacy of hemoadsorption (CytoSorb®) in refractory septic shock patients as an adjuvant**

Surendra M, Cherukuri B, Kumar S, Harithra N, Kantham L, Silpa, Bhavya, Srikanth, Jyothi Y.  
*International Journal of Scientific Research* 2019; 8(19): 1 – 3

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### **Summary**

This retrospective study included eight patients with refractory septic shock (defined as unresponsive to inotropic and vasopressor support - dopamine <sup>3</sup>15mcg/kg/min, noradrenaline <sup>3</sup>0.25 mcg/kg/min) treated with CytoSorb. Patients were relatively young (age range 19 – 39 yrs) with a variety of causes for their sepsis. Six out of the 8 patients could be stabilized after 24hrs of CytoSorb treatment, completely recovered and survived. CytoSorb treatment appeared to be well tolerated in this patient population. Total leucocyte count, mean arterial blood pressure, lactate and vasopressor requirements all improved after 24 hours of CytoSorb therapy. This study reports that the use of CytoSorb as an adjunctive therapy along with standard therapy in a high risk group of septic shock patients with organ damage appears to improve their outcome.

[Link to Article](#)

## **Changes in Cytokines, Haemodynamics and Microcirculation in Patients with Sepsis/Septic Shock Undergoing Continuous Renal Replacement Therapy and Blood Purification with CytoSorb.**

Zuccari S, Damiani E, Domizi R, Scorcella C, D'Arezzo M, Carsetti A, Pantanetti S, Vannicola S, Casarotta E, Raghino A, Donati A, Adrario E  
*Blood Purif* 2020; 49(1-2): 107 - 113

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### **Summary**

This prospective observational pilot study evaluated changes in cytokines, hemodynamics and microcirculation during blood purification with Cytosorb adsorber in nine septic patients who were on renal replacement therapy (RRT) for acute renal failure. Measurements were taken at baseline, after 6 and 24 hrs and included hemodynamic parameters, arterial and central venous blood gases, plasma levels of tumour necrosis factor alpha, and interleukin (IL) 1-beta, IL-6, IL-8 and IL-10. The sublingual microcirculation as well as tissue oxygenation and microvascular reactivity were also assessed.

Despite being hemodynamically stable, microvascular perfusion was significantly impaired at the time of enrolment. Hemodynamics remained stable throughout the observation, however, microvascular perfusion improved over time with a significant increase in microvascular density and a trend towards an improvement in blood flow quality. Plasma levels of IL-8 decreased at 24 h (p < 0.05 versus 6 h). The Sequential Organ Failure Assessment (SOFA) score decreased from 12 to 10 at 24 hrs (p = 0.039). This study shows that in septic patients undergoing RRT, use of Cytosorb seems to show a potential beneficial effect of treatment on the microcirculatory perfusion going beyond just cytokine removal, with a decrease in plasma levels of IL-8, and an improvement in the microcirculation despite no significant variation in macro-hemodynamics in this study.

<https://www.ncbi.nlm.nih.gov/pubmed/31434083>

## **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* 2020; 43(1): 10 - 16

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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* 2020; 21(2): 183 - 90

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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://pubmed.ncbi.nlm.nih.gov/32489416/>

## **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.

[Link to Article](#)

## **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.

[Link to Article](#)

## **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 hemoadsorption 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.

<https://www.ncbi.nlm.nih.gov/pubmed/28979423>

## **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.

[Link to Article](#)

## 1.2.2. Cardiac surgery

### Impact of CytoSorb on kinetics of vancomycin and bivalirudin in critically ill patients)

Scandroglio AM, Pieri M, Nardelli P, Fominskiy E, Calabro MG, Melisurgo G, Ajello S, Pappalardo F. *Artif Organs* 2021; epub

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#### Summary

This retrospective case series included 89 critically ill patients treated with 109 CytoSorb adsorbers. Reasons for treatment included 1. hyperinflammation caused by out of hospital - and in hospital - cardiac arrest, 2. acute respiratory distress syndrome, and both 3. post-cardiotomy and acute-cardiogenic shock. To assess the impact of CytoSorb on two commonly used drugs (the antibiotic vancomycin and the thrombin inhibitor bivalirudin) blood plasma levels were recorded daily and 8 hourly respectively. During treatment with CytoSorb, a decrease in lactate dehydrogenase (LDH, p=0.007), troponin T (p=0.022) and creatine phosphokinase (CPK, p=0.013) was seen. The vancomycin dose required significant adjustments during treatment (p<0.001), but no significant change was necessary after the first 3 days which was similar for the requirements of bivalirudin. Furthermore, it is reported that from a total of 11 patients that were brain dead after extracorporeal cardiopulmonary resuscitation (eCPR) and considered for organ donation, that all transplanted organs (kidneys in 7 patients and liver in 4 patients) showed good functional status after transplant.

In conclusion, CytoSorb therapy did not significantly modify the administered dose of vancomycin and bivalirudin after reaching initial stabilization in a large population of severely critically ill patients. The authors conclude that CytoSorb treatment appears to have further application also in the context of organ donation and may be worth further evaluation as an adjunctive tool to reduce ischemic damage and cytokine burden in potential organ donors, as it might contribute to end-organ preservation and ultimately affect outcome.

<https://www.ncbi.nlm.nih.gov/pubmed/33686696>

### Extracorporeal cytokine adsorption: Significant reduction of catecholamine requirement in patients with AKI and septic shock after cardiac surgery

Boss K, Jahn M, Wendt D, Haidari Z, Demircioglu E, Thielmann M, Ruhparwar A, Kribben A, Tyczynski B.

*PLoS One* 2021; 16(2): e0246299

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#### Summary

The purpose of this retrospective large case series was to investigate the effects of extracorporeal cytokine adsorption with CytoSorb on hemodynamic parameters in 98 patients with acute kidney injury (AKI) on continuous renal replacement therapy (CRRT) who developed septic shock after cardiac surgery (44 emergency and 54 elective cases with 92 requiring cardiopulmonary bypass). All patients were initially treated following the Surviving Sepsis Guidelines. If there was no decrease in catecholamine demand after maximum standard therapy, extracorporeal cytokine adsorption was applied within 24 h of septic shock diagnosis. CytoSorb was then used for at least 15 hours and at least one adsorber was used per patient (range 15 – 40 hours, 1 – 4 adsorbers). To compare cumulative catecholamine dose to maintain a mean arterial pressure (MAP) of  $\geq$  65 mmHg, the vasoactive score (VAS) was recorded for each patient before and after CytoSorb use. Before CytoSorb the mean VAS was 56.7 points and after use it was 27.7 points (p< 0.0001). Before use, the mean noradrenaline dose to reach a MAP of  $\geq$  65 mmHg was 0.49  $\mu$ g/kg/min. This decreased to 0.24  $\mu$ g/kg/min (p<0.0001) post CytoSorb use. The mean adrenaline dose also decreased significantly. There was also a significant reduction in serum lactate after treatment (7.2 – 3.5 mmol/l, p< 0.0001). The mean predicted in-hospital mortality rate based on the mean SOFA-score was 77%, and 73% on APACHE II-score, while the all-cause in-hospital mortality rate of the patients in this study was 59.2%. In conclusion, the present study

showed a stabilization in hemodynamic parameters in patients with AKI on CRRT and sepsis after cardiac surgery with a significant reduction in the catecholamine requirements and serum lactate level. This was also observed in patients with very high predicted mortality scores. Additionally, observed versus predicted in-hospital mortality SOFA- and APACHE II-score rates were decreased.

<https://www.ncbi.nlm.nih.gov/pubmed/33556101>

### **Modulating the Inflammatory Response With Hemadsorption (CytoSorb) in Patients Undergoing Major Aortic Surgery.**

Mehta Y, Singh A, Singh A, Gupta A, Bhan A.

*J Cardiothorac Vasc Anesth* 2021 ;35(2):673-675

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#### **Summary**

In this retrospective pilot study, 8 patients undergoing elective major aortic surgery with CytoSorb installed in the cardiopulmonary bypass (CPB) circuit were compared to 8 patients who received standard care. Despite the relatively short time on CPB (166 mins for the control group and 174 mins for the CytoSorb group), patients who received CytoSorb had significant reductions in interleukin-6 (IL-6) and procalcitonin levels. CytoSorb use also preserved the mean arterial pressure better, with less norepinephrine requirements, and resulted in a better PaO<sub>2</sub>/FiO<sub>2</sub> (PF) ratio and shorter durations of mechanical ventilation, intensive care unit stay, and hospital stay. The results may add important information to those who are planning to design prospective, randomized trials in this patient population.

<https://www.ncbi.nlm.nih.gov/pubmed/32620492>

### **Hemoadsorption treatment with CytoSorb in patients with ECLS therapy – a case series**

Traeger K, Skrabal C, Fischer G, Schroeder J, Marenski L, Liebold A, Reinelt H, Datzmann T.

*The International Journal of Artificial Organs* 2020; 43(8): 422 - 9

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#### **Summary**

This retrospective case series described the use of extracorporeal life support (ECLS, specifically veno-arterial extracorporeal membrane oxygenation – VA ECMO) and CytoSorb hemoadsorption in 23 cardio-thoracic intensive care patients with a wide range of complex disease states. The trigger for initiation of CytoSorb was presence of renal replacement therapy (RRT) and the presence of one or more of the following - severe hyperinflammatory activation, severe reperfusion injury, extended cardiopulmonary bypass times with post-cardiotomy low cardiac output, and refractory vasoplegic response with rapid progressive organ dysfunction. The CytoSorb was integrated into the renal replacement therapy system, and patients had, on average 2 x 24 hour treatments (range 1-3). APACHE II and SOFA scores were high for these patients (28 and 13 respectively), representing a very severely sick patient population. Both interleukin (IL)-6 and IL-8 decreased pre and post CytoSorb as did procalcitonin (PCT). Patients stabilized hemodynamically, with a reduction in vasopressor requirements (epinephrine, norepinephrine) and a sustained mean arterial pressure (MAP). ECLS flow rate was maintained, and lactate, pH, and base excess could all be stabilized and normalized during and after the treatment period. The combination of CytoSorb hemoadsorption and RRT in ECLS patients appeared to be well tolerated and there were no device related technical issues or adverse events during or after treatment.

<https://www.ncbi.nlm.nih.gov/pubmed/31868089>

### **Comparison of intra-operative versus intra- plus postoperative hemoadsorption 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.

[Link to Article](#)

### **1.2.3. Other indications**

#### **Successful elimination of bilirubin in critically ill patients with acute liver dysfunction using a cytokine adsorber and albumin dialysis: a pilot study**

Scharf C, Liebchen Uwe, Paal M, Becker-Pennrich A, Irlbeck, M, Zoller M, Schroeder I.

*Scientific Reports* 2021; 11(1); 10190

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### **Summary**

In this retrospective case series, 39 patients with acute liver dysfunction (ALD) and corresponding high levels of bilirubin (>10 mg/dl) were given either CytoSorb integrated into high flux dialysis (n. 33), or the advanced organ support system ADVOS (n. 6). The reasons for admission to the Intensive Care Unit in these extremely ill patients treated with CytoSorb were: Acute Respiratory Dysfunction Syndrome (24.2%), septic shock (15.2%), polytrauma (15.2%), liver transplantation (12.1%), Acute Liver Failure (12.1%), lung transplantation (6.1%), cardiogenic shock (6.1%), and other reasons (9.0%). The reasons for admission in patients treated with ADVOS were acute liver failure (50.0%), cardiogenic shock (33.3%), and liver transplantation (16.7%). Laboratory parameters were evaluated before starting therapy (d-1 and d0) and 12–24 h thereafter (d1). The median bilirubin at d-1 was 14.2 and 18.5 mg/dl, at d0 16.9 and 17.7 mg/dl and at d1 13.2 and 15.9 mg/dl, in the CytoSorb and ADVOS groups, respectively, showing a significant increase in total bilirubin in the period prior to CytoSorb treatment. There was a significant bilirubin reduction during CytoSorb treatment ( $p < 0.001$ ) and during ADVOS treatment ( $p = 0.028$ ). Significant decreases of AST (92 kDa), ALT (110 kDa), and GGT (64 kDa), observed during CytoSorb treatment might reflect an improvement of liver function, as direct adsorption is unlikely due to molecular size. The authors note that in addition to the lower than expected mortality (92% v 82.2%), there was also a significant reduction in norepinephrine demand with the use of CytoSorb, resulting in hemodynamic stabilization. The significant reduction in SAPS II during CytoSorb is another indicator of an improvement in the patient's outcome. The authors conclude liver support systems play an important role in the supportive therapy of patients with ALD. While both ADVOS and CytoSorb led to a significant and comparable decrease in bilirubin in critically ill patients, the easy use of CytoSorb might be an advantage compared to other procedures. They note that because CytoSorb is able to be easily integrated into high flux dialysis, for example, it may be possible to use in smaller, less resourced hospitals.

<https://www.ncbi.nlm.nih.gov/pubmed/33986443>

#### **Multicentric Castleman's disease in HIV patients: a single-center cohort diagnosed from 2008 to 2018**

Gliga S, Orth HM, Lubke N, Timm J, Luedde T, Jensen BO.

*Infection* 2021; epub

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## Summary

This is a retrospective, descriptive study on a cohort of nine patients with multicentric Castleman's Disease (MCD) admitted to the infectious diseases or intensive care unit over a ten year period. Included patients had a previous or new HIV diagnosis and clinical signs resembling MCD. All patients received rituximab, and three also received tocilizumab. Other treatment options included: splenectomy (2/9), valganciclovir (2/9), vincristine and siltuximab (1/9), ruxolitinib and Cytosorb (2/9). CytoSorb was used to reduce cytokine levels associated with a cytokine storm, and control sepsis (in one of the patients). The authors conclude that the most effective first-line therapy and retreatment option remains rituximab and that the effectiveness of other treatment options such as splenectomy or different immunotherapeutic approaches require confirmation in larger-scale studies.

<https://www.ncbi.nlm.nih.gov/pubmed/33945103>

## Use of CytoSorb in cases of acute amitriptyline intoxication

Paland M

*Journal of Clinical Pharmacy and Therapeutics 2021; epub*

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## Summary

This is a report of two patients with potentially lethal amitriptyline overdose levels. As treatment options for this type of tricyclic antidepressant overdose are limited, continuous renal replacement therapy was also started along with CytoSorb hemoadsorption. In the first patient three adsorbers were used over 22 hours with plasma levels assessed pre and post the adsorber. Measurements showed the direct and highly efficient removal of amitriptyline so that CytoSorb treatment resulted in the rapid and sustained decrease in plasma levels to non-toxic levels within only a few hours (186 µg/l to 54.7 µg/l). In the second patient a toxic range of 844 µg/l at the start of treatment dropped to 290 µg/l at its discontinuation 8.5 hours later. As noted by the author, the ability of CytoSorb to address hyperinflammation and/or to remove bilirubin and other liver toxins and myoglobin might also justify its use in intoxications in which clinical complications such as shock states, rhabdomyolysis or liver failure are present, despite the non-confirmed direct removal of the overdose substances. In cases presented here, CytoSorb was primarily used with the idea of effective and early detoxification, which is thought to have prevented the occurrence of clinical complications. The author concludes that the use of CytoSorb therapy in amitriptyline intoxication as a detoxification approach should be encouraged.

<https://www.ncbi.nlm.nih.gov/pubmed/33768556>

## Use of Hemoadsorption in Patients With Severe Intoxication Requiring Extracorporeal Cardiopulmonary Support-A Case Series.

Zickler D, Nee J, Arnold T, Schroder T, Slowinski T, Eckardt KU, Korner R, Kruse JM.

*ASAIO J 2021; epub*

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## Summary

This is a case series that includes four cases of acute intoxication requiring Venous Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) support used as extracorporeal cardiopulmonary resuscitation after intoxication-induced out-of-hospital cardiac arrest (OHCA). All patients were additionally treated with CytoSorb hemoadsorption in combination with renal replacement therapy. Drugs included the anti-hypertensives - amlodipine, bisoprolol, and the antidepressant amitriptyline. The number of days of treatment ranged from 1 – 7. Combined treatment was associated with a considerable decrease in plasma levels of all the overdosed drugs. Additionally, the combination of applied techniques was safe, practical, and technically feasible with no adverse or any device-related side effects documented during or after the treatment sessions. Taking the pathophysiology of post cardiac arrest syndrome and its elevated levels of cytokines into account, CytoSorb, might also have had some additional beneficial immunomodulatory properties in these cases next to potential detoxification effects. In summary and based on the reported dramatic decline in drug levels during treatment the authors strongly suggest to further investigate the potentially lifesaving role of CytoSorb therapy in patients with acute intoxications requiring multiple organ support techniques.

<https://www.ncbi.nlm.nih.gov/pubmed/33587468>

## Blood purification with a cytokine adsorber for the elimination of myoglobin in critically ill patients with severe rhabdomyolysis

Scharf C, Liebchen U, Paal M, Irlbeck M, Zoller M, Schroeder I

Crit Care 2021; 41

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## Summary

This retrospective observational case series included 43 patients with anuric renal failure with the need of renal replacement therapy, who additionally received CytoSorb therapy because they had rhabdomyolysis resulting in potentially damaging high levels of myoglobin (recognised as >5,000 ng/ml, study median was >25,000 ng/ml). The reason for the rhabdomyolysis included several factors including septic shock, trauma and hypovolemic or cardiogenic shock. Due to the severity of their illness (SOFA – sequential organ failure assessment score - on treatment day was 19 with an expected mortality of >90%), around 33% of all patients also needed ECMO (extracorporeal membrane oxygenation). Levels of myoglobin were measured pre- and post-CytoSorb treatment. Patients were divided into those with persistent rhabdomyolysis (ongoing creatinine kinase (CK) and myoglobin production from ongoing muscle injury) and those in which rhabdomyolysis was resolving (assuming that there is no direct removal of CK by CytoSorb due its large molecular weight of 80kDa, as was indicated by decreasing CK levels). Overall, myoglobin levels decreased by 29% with a higher reduction of 38% seen in patients without ongoing rhabdomyolysis. Since all patients had anuric renal failure, renal elimination of myoglobin cannot be assumed and, in the authors' view, the reduction of myoglobin was largely due to the use of CytoSorb and not due to the high-flux dialyzer. There was no significant difference in myoglobin elimination in patients with or without ECMO indicating that ECMO therapy might not have any impact on the elimination performance of the CytoSorb adsorber. In hospital mortality was 67.4%. In summary, myoglobin removal with the CytoSorb integrated into a high-flux dialyzer can be recommended for clinical routine due to its existing CE mark, ease of use and absence of side effects. This is the first case series in severe rhabdomyolysis patients showing the benefit of CytoSorb therapy for removal of myoglobin, thereby averting permanent kidney damage.

<https://www.ncbi.nlm.nih.gov/pubmed/33509234>

## Haemoadsorption by CytoSorb in patients with acute liver failure: A case series

Tomescu D, Popescu M, David C, Sima R, Dima S.

*Int J Artif Organs* 2020; *epub*

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## Summary

The aim of this case series was to assess the clinical effects of CytoSorb on a range of biochemical parameters in 28 patients with acute liver failure (ALF). Causes of ALF included acetaminophen (paracetamol) overdose, acute viral hepatitis, mushroom poisoning and Wilsons disease. Patients were treated with three consecutive 24 hr sessions of continuous venovenous haemodiafiltration (CVVHDF) in combination with CytoSorb. Use of CytoSorb was associated with a significant decrease in serum creatinine, bilirubin, ammonia and C-Reactive Protein (CRP). Twelve patients had a decrease in SOFA score after the use of CytoSorb that was mostly due to a decrease in serum bilirubin levels. A decrease was also noted in the platelet count but this was not associated with any significant bleeding episodes. The authors note that the decrease in the platelet count in patients with ALF may be attributed to both the intrinsic mechanism in liver disease and to the use of renal replacement therapy. In accordance with previously published cases, the use of CytoSorb can be considered as a therapeutic option for the management of liver impairment in patients with ALF, as providing biochemical control of liver function tests may aid in bridging such patients to liver transplantation, or until spontaneous remission is assured. Thrombocytopenia remains one of the side effects of this treatment requiring consideration on a patient by patient basis. A higher survival rate was observed in patients in whom a decrease in Sequential Organ Failure Assessment (SOFA) was observed.

<https://www.ncbi.nlm.nih.gov/pubmed/33302765>

## First experiences of hemoadsorption in the Donation after Circulatory Death

Baroni S, Melegari G, Brugioni L, Gualdi E, Barbieri A, Bertellini E

*Clinical Transplant* 2020; 34 (6): e13874

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## Summary

In this letter to the editor, the authors describe a recent new application of the use of CytoSorb with extracorporeal membrane oxygenation (ECMO) in cases of Donation after Circulatory Death (DCD). Particular to Italy, determination of death requires a 20-minute flat electrocardiogram, resulting in absence of circulation and any subsequent "Warm Ischemia Time (WIT)", which results in high levels

of cytokines, such as Tumor Necrosis Factor-Alpha (TNF $\alpha$ ). This is a case report of three DCD donors. The abdominal organs were re-perfused using normothermic regional perfusion (nRP) in combination with CytoSorb (included in the side arm of the regional ECMO circuit) in an attempt to increase the number of organs suitable for transplantation (liver and kidneys). Kidneys and liver were re-perfused with a blood flow always higher than 3 L/min, while blood flow through CytoSorb was 300ml/min during extracorporeal circulation. Blood sampling from the circuit showed a significant removal of TNF $\alpha$  by CytoSorb. During the first week after transplantation the creatinine serum mean value was almost 1.0 mg/dl, bilirubin 3.0 mg/dl, INR 1.2, only serum transaminase reached value upper 2000 U/L followed by physiological decrease. No cases of liver or kidney graft syndrome or recipient death at day 30 were reported.

The authors state that nRP in combination with CytoSorb has the potential to limit irreversible organ damage, to restore organ function and to be used as a bridge to transplantation, potentially mitigating cytokine release and harmful inflammatory mediators, especially TNF $\alpha$ , thereby reducing the risk of any adverse scenarios or graft dysfunction.

<https://pubmed.ncbi.nlm.nih.gov/32339334>

#### Impact of Cytokine Adsorption Treatment in Liver Failure

Acar U, Gokkaya Z, Akbulut A, Ferah O, Yenidunya O, Acik ME, Tokat Y, Yentur E *Transplant Proc* 2019; 51(7):2420-2424

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#### Summary

This case series included four patients with sepsis / septic shock plus severe liver failure, and tested the effect of CytoSorb use on liver function and liver toxins. In total, nine CytoSorb cartridges were used with continuous venovenous hemodialysis in 12-hour sessions. The biochemical values of the patients before and after the use of the adsorber were recorded. According to the results the authors note that CytoSorb can be considered as an option to lower bilirubin levels in cases of liver failure however, in their patients the authors were not able to detect a decrease in ammonia levels. Although further studies are needed, cytokine adsorption systems (including CytoSorb) may be considered in the treatment of sepsis and hyperbilirubinemia in liver failure patients with sepsis.

<https://www.ncbi.nlm.nih.gov/pubmed/31405742>

#### 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.

[Link to Article](#)

### **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://www.ncbi.nlm.nih.gov/pubmed/30638101>

### **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>

#### **1.2.4 COVID-19**

### **NEW; Extracorporeal Cytokine Hemadsorption in Severe COVID-19 Respiratory Failure**

Damiani M, Gandini L, Landi F, Borleri G, Fabretti F, Gritti G, Riva I  
*Respiratory Medicine* 2021;185: 107477

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## Summary

The letter to the editor reports on 11 patients admitted with COVID-19 over a 2 week period in March 2020. All patients were mechanically ventilated and admitted to intensive care. Along with standard therapy at the time, CytoSorb was included in the continuous veno-venous hemodiafiltration circuit. Most patients had 2 x 24 hr treatment. After a median follow up of 16 days (range 6 – 30 days), nine patients survived (82%) and were discharged from intensive care. Inflammatory mediators (including interleukin – IL-6) were measured before and after treatment, and 7 days from treatment end. Markedly elevated levels in particular of IL6 and IL8 were observed, with a significant reduction in IL-6, IL-8, IL-10 and IL1 $\beta$  at treatment end. C-Reactive Protein also significantly reduced and median P/F ratio increased indicating improved respiratory function. CytoSorb proved to be safe in these COVID-19 patients and no unexpected adverse events were observed. Clinical improvement was seen in most treated patients despite the severity of the disease.

<https://pubmed.ncbi.nlm.nih.gov/34102594/>

## Longitudinal Cytokine Profiling in Severe COVID-19 Patients on ECMO and Haemoadsorption

Lebreton G, Dorgham K, Quentric P, Combes A, Gorochov G, Schmidt M  
*Am J Respir Crit Care Med* 2021; 203(11):1433-1435

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## Summary

This letter to the editor included 22 COVID-19 patients who were put on extracorporeal membrane oxygenation (ECMO) due to the severity of their condition. The first group of 11 consecutive patients had a CytoSorb adsorber placed in the ECMO circuit. These patients were unselected otherwise, as was the timing for the initiation of the CytoSorb adsorber. These patients were then compared to the next 11 patients on ECMO who were not given CytoSorb (control group). Various biomarkers for inflammation were recorded pre ECMO, 4 hours after ECMO start (before CytoSorb start), then 12 and 48 hours after CytoSorb and ECMO use (or ECMO alone for control group). Biomarkers included interleukin- IL-1 $\beta$ , IL-6, IL-8, IL-22, IL-10, IL-17A, IL-18, GM-CSF, IFN- $\alpha$ , IFN- $\gamma$ , TNF- $\alpha$ , and IFN- $\beta$ . Analysis of the cytokines tested did not show an increase after four hours of ECMO indicating that ECMO itself does not exacerbate cytokine release in COVID-19 patients. IL-10 and IFN- $\gamma$  concentrations decreased significantly after 48 hours of CytoSorb. IL-6 also decreased but not significantly. IL-6, IL-8 and IL-10 also decreased significantly in the control group. Eight patients survived to 60 days in the CytoSorb group (73%), compared to seven patients in the control group (64%). In conclusion, ECMO does not exacerbate cytokine release in COVID-19 patients where IL-6, IL-8, and IL-10 decrease after 48 hours on ECMO with ultra-protective mechanical ventilation. To what extent combining a Cytosorb adsorber with ECMO could enhance the decrease of these cytokines and improve outcomes, warrants further investigations.

<https://pubmed.ncbi.nlm.nih.gov/33725469/>

## Effects of tocilizumab versus hemoadsorption combined with tocilizumab in patients with SARS-CoV-2 pneumonia: Preliminary results

Berlot G, Pintacuda S, Moro E, Paluzzano G, Scamperle A, Chillemi A, Longo I, Dattola R, Roman-Pognuz E, Tomasini A.  
*Int J Artif Organs* 2021; epub

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## Summary

In this retrospective analysis of four patients with SARS-CoV-2 pneumonia, two treated with Tocilizumab (TCZ) alone were compared to two patients treated with CytoSorb hemoadsorption (HA) and TCZ. TCZ alone was administered in patients with only pulmonary involvement and blood levels of C-Reactive Protein (CRP)  $\geq$  100 mg/L and of interleukin (IL)-6  $>$  11 pg/m, whereas HA was added to the TCZ in the presence of arterial hypotension and/or signs of organ dysfunction (OD) other than the lung. In both of the two CytoSorb patients, three procedures were performed for 24 hrs each. All patients were mechanically ventilated with the blood values of IL-6, CRP and PaO<sub>2</sub>/FiO<sub>2</sub> ratio measured before, during and after treatment. In all patients, the IL-6 increased during the treatment; after its termination, its values sharply decreased only in those treated with HA. According to the authors the increase of the IL-6 of can be ascribed to its displacement from cellular and soluble receptors, whereas its decrease is likely due to the scavenging effect exerted by the HA. Conversely, CRP decreased in all patients; the PaO<sub>2</sub>/FiO<sub>2</sub> increased in three patients and remained stable in one. Both the TCZ and CytoSorb adsorber were well tolerated; all patients were weaned from the mechanical ventilation and discharged from the hospital. The authors note that although the use TCZ and HA could be valuable in the

treatment of the Cytokine Release Storm (CRS) associated with SARS-CoV-2, that CytoSorb could be more effective as it neutralizes a wider panel of inflammatory mediators.

<https://www.ncbi.nlm.nih.gov/pubmed/33573449>

## **Hemoperfusion with CytoSorb as Adjuvant Therapy in Critically Ill Patients with SARS-CoV2 Pneumonia**

Rampino T, Gregorini M, Perotti L, Ferrari F, Pattonieri EF, Grignano MA, Valente M, Garrone A, Islam T, Libetta C, Albertini R, Bruno R, Belliato M  
Blood Purification 2020; epub

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### **Summary**

In this article the authors conducted an observational study on nine consecutive COVID-19 positive patients hospitalized in their COVID Intensive Care Unit. Five of the patients were treated with hemoperfusion (HP) using a CytoSorb adsorber. Due to the emergency overload it was impossible to deliver blood purification in the other four patients. All patients had severe pneumonia requiring continuous positive airway pressure. HP was started in all five patients 6–7 days after hospital admission. The treated patients (T) received 2 consecutive sessions of the CytoSorb adsorber. The results showed a better clinical course for these CytoSorb treated patients compared to the control patients (C). All five CytoSorb patients except 1 survived, and only 2 of them had to be intubated, while all control patients required intubation and unfortunately died. Lymphocytopenia worsened in the controls but not in CytoSorb treated patients. C-reactive protein decreased in both patients, but to a greater extent in the CytoSorb group. Interleukin (IL)-6, IL-8, and TNF- $\alpha$  decreased after CytoSorb, IL-10 did not change. Respiratory function remained stable and did not worsen in the CytoSorb group compared to the controls. As the authors note, this experience suggests a potential therapeutic role of adjuvant CytoSorb in the early course of COVID-19 pneumonia by improving respiratory function and lowering mortality. The authors are currently conducting a randomized clinical trial which is ongoing.

<https://www.ncbi.nlm.nih.gov/pubmed/33181508>

## **Continuous renal replacement therapy with the addition of CytoSorb® cartridge in critically ill patients with COVID-19 plus acute kidney injury: a case-series**

Alharthy A, Faqih F, Memish ZA, Balhamar A, Nasim N, Shahzad A, Tamim H, Alqahtani SA, Brindley PG, Karakitsos D.

*Artificial Organs* 2021; 45(5):E101-E112

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### **Summary**

This case series retrospectively analyzed 50 patients with severe COVID-19 induced acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) along with CytoSorb. Patients also had to have sepsis/septic shock, acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS). This was given in around 10% of all COVID-19 patients admitted to ICU in the study period of June 1 to July 30, 2020. In addition to CRRT with CytoSorb all received ARDS-net ventilation, prone positioning, plus empiric ribavirin, interferon beta-1b, antibiotics, hydrocortisone, and prophylactic anticoagulation. These patients were critically ill according to the ICU scores (mean APACHE II 22.5, SOFA 9.4) with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 117.46. Duration of mechanical ventilation was 17.38 days, ICU length-of-stay 20.70 days, and mortality at 28 days post-ICU admission being 30%. Non-survivors (30% of total patients) had higher levels of inflammatory biomarkers (interleukin – IL 6), and more unresolved shock, ARDS, AKI, and pulmonary emboli (8% vs. 4 %, p<0.05) compared to survivors (70% of patients). After 2 $\pm$ 1 CRRT sessions with CytoSorb (adsorber changed 24 hrly), survivors had decreased Sequential Organ Failure Assessment (SOFA) scores, lactate dehydrogenase, ferritin, D-dimers, C-reactive protein, and interleukin (IL)-6; and increased PaO<sub>2</sub>/FiO<sub>2</sub> ratios, and lymphocyte counts (all p<0.05). Survivors were also able to have vasopressors weaned off and renal function improved. Statistical analysis showed that post therapy values of IL-6 (cutoff point > 620 pg/ml) predicted in-hospital mortality for these patients (AUC 0.87). No side effects of CytoSorb therapy were recorded. The authors conclude that CytoSorb provided a safe rescue therapy in life threatening COVID-19 associated sepsis, AKI, ARDS, and hyperinflammation and appears to mitigate hyperinflammation.

<https://pubmed.ncbi.nlm.nih.gov/33190288/>



## 1.3. Case reports

### 1.3.1. Sepsis

#### **NEW; Hemoadsorption with CytoSorb and the early course of linezolid plasma concentration during septic shock**

Köhler T, Schwier E, Kirchner C, Winde G, Henzler D, Eickmeyer C.

*J Artif Organs* 2021; epub

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#### **Summary**

This is a case of a 61-year-old female patient with Ulrich Turner syndrome who was treated with CytoSorb and linezolid during her intensive care treatment for septic shock. The patient was admitted post operatively and after developing septic shock, CytoSorb was started to stabilize her hemodynamic situation and provide liver support. Five adsorbers were used (18 hrs each) with good clinical results (norepinephrine reduced by 60%, and interleukin 6 levels decreased by 93%, stable bilirubin levels). However, after detection of staphylococcus epidermidis, it was necessary to start linezolid. After establishment of a new CytoSorb adsorber, 600 mg of linezolid was administered over 1 h and levels measured before the adsorber inlet (cpre) and after the adsorber outlet (cpost) at 0, 15, 60, 120 and 480 mins after starting infusion. Linezolid plasma concentrations (cpre) after 60 min (3.25 mg/l) and 120 min (4.7 mg/l) showed sufficiently high linezolid levels (therapeutic range 3-9 mg/l), however, after 480 min, cpre had decreased to 2.8 mg/l. With cpost levels starting to increase over time after 60 minutes (up to 1.85 mg/l after 480 min), the calculated CytoSorb clearance rate decreased to 67.86 ml/min (from 200 ml/min at 60 min). The authors recommend an additional loading dose of 600 mg and suggest that linezolid therapy under hemadsorption with CytoSorb requires a clear indication and close monitoring of levels to avoid underdosing.

<https://www.ncbi.nlm.nih.gov/pubmed/34047868>

#### **Use of CytoSorb(R) as a therapeutic option in a critically ill patient with acute respiratory distress syndrome caused by influenza A (H1N1) pneumonia: A case report**

Kovacevic P, Tomic B, Kovacevic T, Dragic S.

*Int J Crit Illn Inj Sci* 2020; 10(4): 216-219

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#### **Summary**

This is a case of a previously healthy 29-year-old male patient who was admitted to the Medical Intensive Care Unit (MICU) with multiple organ dysfunction and pneumonia caused by influenza type A. Due to acute respiratory failure and altered state of consciousness, the patient was intubated and mechanically ventilated immediately after admission. The initial computed tomography scan showed massive bilateral pneumonia, and few days later the patient's condition progressively worsened, and he developed signs of multi-organ failure. Given the patient's progressing hemodynamic instability (norepinephrine increased to 0.6 µg/kg/min) and systemic inflammatory response (C-Reactive Protein – CRP 519 mg/L, procalcitonin 1.28 ng/ml, leucocytes 14.8 x 10<sup>3</sup>/µl), a CytoSorb adsorber was added into the continuous renal replacement therapy (CRRT) circuit on day 7. Immediately after the first session the norepinephrine requirement decreased to 0.15 µg/kg/min and was able to be discontinued 2 days later. However, the patient's condition started to deteriorate on day 10, so CytoSorb was again used. Overall, the inflammatory markers decreased during combined CRRT plus CytoSorb (CRP to 330 mg/L, PCT to 0.7 ng/ml, leucocytes to 9.2 x 10<sup>3</sup>/µl). Lactate also improved from 4.4 mmol/L to 0.7 mmol/L. The ventilation parameters and lung function also gradually improved. After 48 days in the MICU, he was discharged to the wards, and then to a rehab clinic a few days later. The authors conclude that the combination of pharmacotherapy, supportive measures, and application of CytoSorb resulted in complete recovery of the patient with CytoSorb use associated with rapid hemodynamic stabilization and control of inflammatory response.

<https://www.ncbi.nlm.nih.gov/pubmed/33850832>

#### **CytoSorb in the management of severe septic shock after coronary artery bypass graft surgery**

Prakash A, Garg V, Mittal DK, Upadhyay AB.

*Heart India* 2020; 8: 151 - 153

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#### **Summary**

This is a case of acute septic shock that developed post coronary artery bypass graft surgery in a 58 year old male. The patient was admitted to intensive care postoperatively on moderate inotropic support, however, within 12 – 24 hrs, he had developed refractory hypotension with signs of multiple organ failure. After the progressive deterioration in his hemodynamic state (requirement for epinephrine, norepinephrine and vasopressin), he was started on continuous renal replacement

therapy (CRRT) with CytoSorb. After a single 24 hr session, there was an improvement in end-organ dysfunction (decreased requirements for vasopressors, improved urine output, decreased ventilatory requirements, improved liver function, and normal temperature). Hence, inotropic and organ support could be gradually withdrawn and the hemodynamic status remained stable with improvements in the inflammatory and other laboratory parameters. The authors note that CytoSorb was an effective, safe and easy option in the management of severe septic shock post cardiac surgery and seems to be a promising tool in stabilizing hemodynamics in refractory vasoplegia. In patients with known risk factors, CytoSorb therapy could be used during surgery. They concluded that septic shock increases the risk of multiple organ failure and also adds to the financial burden, which was reduced by CytoSorb therapy.

[Link to Article](#)

## **Sequential Extracorporeal Therapy Collaborative Device and Timely Support for Endotoxic, Septic, and Cardiac Shock: A Case Report**

De Rosa S, Samoni S, Ronco C  
*Blood Purif* 2020; 49(4): 502 - 8

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### **Summary**

The authors report the case of a patient with a severe bacterial infection (*Neisseria meningitidis*) who was admitted to the ICU due to septic shock. In addition to the critical care management, 2 treatments with Polymyxin B hemoperfusion were performed. The treatment resulted in a marked decrease in the serum endotoxin level but without any improvement in tachycardia and circulatory insufficiency progressed. Therefore, considering the involvement of septic cardiomyopathy and cardiogenic shock, and aiming to reduce excessive levels of inflammatory mediators, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was initiated on day 3 from admission and Cytosorb was integrated into the VA-ECMO circuit for 48 h without an evident considerable improvement. Therefore, a 72-h continuous veno-venous hemodialysis session was started in which a high cutoff filter was used. Tachycardia and myocardial dysfunction improved under the combined therapy and VA-ECMO was withdrawn. Subsequently, nutrition management and rehabilitation were performed, and the patient was transferred to the department of respiratory medicine on day 80, he was discharged from the hospital on day 113. The authors concluded that the sequential extracorporeal therapy may be beneficial when concomitant with circulatory assistance in uncontrollable cases of septic shock using catecholamines.

<https://www.ncbi.nlm.nih.gov/pubmed/31865323>

## **Cytokine adsorption as a promising option for septic shock and multiple organ failure due to *Candida* infection and decompensated type 1 diabetes mellitus**

Klinkmann G, Stope MB, Meyer A.  
*Artif Organs* 2020; 44(5): 522-5

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### **Summary**

This is the case report of a 19 year old female patient with type 1 diabetes mellitus (T1DM) and candidiasis associated with severe metabolic acidosis who was admitted to the intensive care unit in septic shock with hemodynamic instability. Continuous renal replacement therapy (CRRT) was initiated in the first 24 hrs due to the metabolic acidosis (initial pH 6.69) and increased retention parameters. When she remained hemodynamically unstable despite high dose catecholamine therapy, and because of the significantly elevated interleukin(IL) -6 levels (>1000 pg/ml), a CytoSorb cartridge was inserted into the CRRT circuit for a 20 hr period. This resulted in a rapid improvement in her hemodynamics and resolution of the metabolic acidosis. The vasopressor support could be reduced during the treatment (norepinephrine 0.9 – 0.2 ug/kg/min). The hyperinflammation could also be rapidly controlled and all parameters reduced during the course of treatment (including procalcitonin and leukocytes). Treatment with CytoSorb was found to be safe and feasible without technical problems. Notably, this is the first case description reporting on the effects of CytoSorb in a patient with fungal septic shock and T1DM.

<https://www.ncbi.nlm.nih.gov/pubmed/31738446>

## **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; 42(12): 765 - 9

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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.

[Link to Article](#)

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

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

*Case Reports in Critl 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.

[Link to Article](#)

## **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, Zeriyuh 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://www.ncbi.nlm.nih.gov/pubmed/27436098>

## **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

[Link to Article](#)

## **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 Crit 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.

[Link to Article](#)

## **Septic shock secondary to $\beta$ -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  $\beta$ -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.

<https://www.ncbi.nlm.nih.gov/pubmed/23949887>

## **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.ncbi.nlm.nih.gov/pubmed/23920222>

### **1.3.2. Cardiac surgery**

#### **The effect of hemoadsorption on rivaroxaban blood plasma concentration in emergency cardiac surgery**

Krüger B, Renner T, Van Hemelrijck M, Sromicki J, Ouda A, Mestres CA

*Indian Journal of Thoracic and Cardiovascular Surgery* 2021; epub

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### **Summary**

CytoSorb hemoadsorption was used in a 59-year-old patient with an acute type A aortic dissection, who was on rivaroxaban and dual antiplatelet therapy with clopidogrel and acetylsalicylic acid prior to the event, in order to expeditiously remove rivaroxaban preoperatively. After 2.5 hrs of hemoadsorption, the rivaroxaban blood plasma concentration (RBPC) decreased from 89.4  $\mu\text{g/l}$  to 42.1  $\mu\text{g/l}$  where it plateaued. Nineteen hours after the onset of symptoms the patient underwent successful ascending aorta replacement. A second CytoSorb was used intraoperatively. Sixteen hours after surgery and a total of 13 h of hemoadsorption, the RBPC was 40.1  $\mu\text{g/l}$ . Thereafter, the RBPC spontaneously decreased to 24.7  $\mu\text{g/l}$  within 14 h. The patient survived the emergency surgery and it was possible to control bleeding after surgery. He could be discharged from hospital on day 40 and is, eighteen months after surgery, alive and active without impairing sequelae. In this patient,

hemoadsorption with CytoSorb may have enhanced rivaroxaban removal at higher RBPC (cutoff value 40–50 µg/l). So if used preoperatively, hemoadsorption may reduce the time of delay of emergency surgery. <https://pubmed.ncbi.nlm.nih.gov/33907356/>

## **Cytosorb® hemoadsorption of apixaban during emergent cardio-pulmonary bypass: a case report**

Mendes V, Colombier S, Verdy F, Bechtold X, Schlaepfer P, Scala E, Schneider A, Kirsch M.  
*Perfusion 2020; epub*

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### **Summary**

An 83-year-old woman treated with the new oral anticoagulant Apixaban (2.5 mg twice a day) because of a recent lower limb deep vein thrombosis underwent emergent redo mitral valve replacement for prosthetic valve endocarditis. The last dose of apixaban was taken seven hours before surgery. Due to the increased risk of bleeding complications and subsequent need for multiple transfusions, a CytoSorb cartridge was added to the cardio-pulmonary bypass (CPB) circuit and an Apixaban-specific anti-factor Xa activity (AFXaA) was measured peri-operatively. After 100 minutes of CPB, a 50% AFXaA rate decrease was noted compared to pre-CPB values. Furthermore, the authors noticed reductions of 39% and 44% in AFXaA levels in comparison to the expected levels in patients with normal or altered renal function, respectively. The postoperative course was uneventful, there were no bleeding complications and the patient was hemodynamically stable. The patient left the intensive care unit after 2 days, and hospital on day 26. The authors conclude that insertion of CytoSorb in the CPB was safe and was associated with the rapid correction of Apixaban-associated anticoagulation.

<https://www.ncbi.nlm.nih.gov/pubmed/33106093>

## **Experience of using an extracorporeal cytokine hemoadsorber (CytoSorb®) in systemic inflammatory response syndrome after heart transplantation.**

Krishan, K., Dutta R, Chand R, Malhotra R  
*Indian Journal of Transplantation 2020; 14(2): 166 - 9*

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### **Summary**

This is a case report of a 28 year male who had a heart transplant due to end stage heart failure. Post operatively he developed an hyperinflammatory response and renal dysfunction, so CytoSorb was initiated together with SLED (sustained low-efficiency dialysis). In total he had 3 cycles of CytoSorb of 6 – 12 hours each. With the use of CytoSorb his hemodynamic picture improved, showing - in comparison to before and after CytoSorb therapy: mean arterial pressure 90 v 100 mmHg, norepinephrine 8 v 4.7 µg/min, dobutamine 4.5 v 0 ml/hour and vasopressin 2 v 1.5 ml/hour. His inflammatory parameters also improved, procalcitonin decreased from 169 to 34 ng/dL, and C-reactive protein 13.7 to 6 mg/dL. The tacrolimus levels were regularly monitored and no modifications were needed. Generally there were no adjustments made to his immunosuppressive therapy because of the use of CytoSorb and the patient showed no signs of rejection either clinically or with biopsy. The patient gradually recovered his renal function and was able to be discharged from intensive care and then hospital. The authors state that use of CytoSorb prevented clinical deterioration and helped to regain control of the hyperinflammation resulting in a relatively short ICU and hospital stay, reducing the financial burden.

[Link to Article](#)

## **Ticagrelor and Rivaroxaban Elimination With Cytosorb Adsorber Before Urgent Off- Pump Coronary Bypass**

Mair H, Jilek C, Haas B, Lamm P  
*The Annals of Thoracic Surg 2020; ; 110(5):e369-e370*

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### **Summary**

This is a case report of a 58 year old male with severe coronary artery disease who was at high risk of bleeding due to treatment of coronary artery disease with ticagrelor and atrial fibrillation with rivaroxaban. The patient had an acute dissection of the left anterior descending artery during a percutaneous coronary intervention so was scheduled for urgent off pump coronary arterial bypass (OPCAB) operation. In order to reduce the risk of bleeding, CytoSorb therapy was performed one hour before the operation and continued for a further 1.5 hrs during the operation in order to eliminate the coagulative active medications (ticagrelor and rivaroxaban). The CytoSorb was inserted into an extracorporeal circuit with hemofilter and dialysate using citrate for anticoagulation. Blood flow rate

was between 130-150 ml/min and no ultrafiltration was used. His intra- and postoperative course was uneventful with adequate bleeding control and good recovery of the patient. At six months follow up the patient continued to do well. This case highlights a novel approach for managing antiplatelet drugs and anticoagulants such as ticagrelor and rivaroxaban prior to OPCAB with CytoSorb appearing to be effective for assisting bleeding control. There were no device-related adverse events or device malfunctions reported.

<https://www.ncbi.nlm.nih.gov/pubmed/32407851>

### **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; 42(9): 521 - 4

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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**

#### **Pericarditis Caused by *Enterococcus faecium* with Acute Liver Failure Treated by a Multifaceted Approach including Antimicrobials and Hemoadsorption**

Köhler T, Pletz MW, Altmann S, Kirchner C, Schwier E, Henzler D, Winde G, Eickmeyer C, Akinci SB.

*Case Reports in Critical Care* 2021: 8824050

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### **Summary**

This case report describes a 29 yr old female with Crohn's disease and cachexia who developed a complex case of peritonitis with pericarditis caused by *Enterococcus faecium*, and acute liver failure caused by septic shock. Potentially hepatotoxic antibiotic therapy levels were monitored using the liver maximum capacity (LiMAx) test, and standard treatment was supplemented by adjunctive hemoadsorption with CytoSorb. Three CytoSorb adsorbers were initially given over 73 hours resulting in rapid hemodynamic stabilization (norepinephrine reduced to 8.3% of the maximum dose), and the patient could be extubated. However, the patient's condition began to deteriorate again over time, and another 13 CytoSorb adsorbers were used from day 22 onwards, over the following 16 days. Inflammatory parameters improved consistently over the course of the next week, the catecholamine dose was reduced, and invasive ventilation was changed to assisted ventilation. An efficient and sustained reduction in plasma bilirubin levels was also noted while maintaining liver function. After further improvement, the patient was discharged in a stable clinical condition from the ICU to the normal ward 53 days after her initial admission. This case shows how complex infectious diseases with an atypical infectious focus resulting in septic shock can be successfully treated. A combination of antimicrobial (tigecycline and caspofungin) and long-term adjunctive hemoadsorption CytoSorb therapy was administered while hepatotoxic antibiotic medication was monitored by LiMAx liver function testing. CytoSorb as an individual adjuvant treatment concept in both cycles allowed medical staff to gain control of the hyperinflammation and to clearly decrease vasopressor requirements.

<https://pubmed.ncbi.nlm.nih.gov/33815848/>

## **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 4<sup>th</sup> 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**

#### **Successful Reduction of Creatine Kinase and Myoglobin Levels in Severe Rhabdomyolysis Using Extracorporeal Blood Purification (CytoSorb(R)).**

Dilken O, Ince C, van der Hoven B, Thijsse S, Ormskerk P, de Geus HRH.  
*Blood Purif* 2020; 49(6): 743 – 7

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### **Summary**

This case describes a 56-year-old man with severe traumatic rhabdomyolysis of the lower extremities and abdominal wall due to a crush injury (initial myoglobin and creatinine kinase – CK levels 79,931mg/l and 15,032 U/L respectively). As he was unresponsive to high dose continuous renal replacement therapy (CRRT) with a high cut off EMiC-2 dialysis filter, a CytoSorb adsorber was added into the circuit on the 2<sup>nd</sup> ICU day. Within 4 hours myoglobin and CK levels had reduced from 110,000 to 90,000 mg/l and 115,000 – 65,000 U/L respectively. The adsorber was changed after 12 hours due to evidence of saturation. This reduced myoglobin and creatine kinase levels further despite ongoing tissue ischemia. Treatment with CytoSorb improved the microcirculatory perfusion despite abnormal macro-hemodynamic parameters, however, this was not enough, resulting in the eventual demise of the patient due to severity of the injury. This report indicates that myoglobin was efficiently removed with CytoSorb following exchange with the conventional high cut-off filter in continuous venovenous hemodialysis in severe traumatic rhabdomyolysis. The authors emphasise the need to install CytoSorb early for removal of inflammatory cytokines and myoglobin.

<https://www.ncbi.nlm.nih.gov/pubmed/32114569>

## **Successful treatment of a severe case of rhabdomyolysis following heart transplantation by hemoadsorption**

Immohr MB, Lichtenberg A, Boeken U, Akhyari P.  
*J Card Surg* 2020; 35(4): 940 - 1

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### Summary

This is a case reporting on a 61 yr old male patient, who post orthotopic heart transplantation developed cardiogenic shock and cardiac arrhythmias requiring support with veno-arterial extracorporeal membrane oxygenation (va-ECMO). The patient stabilized, however, 2 days later an enormous increase in plasma creatine kinase (CK) level was seen (>100,000U/L). His myoglobin concentration also increased to 380,000 mg/L and rhabdomyolysis most probably caused by the combination of statin and immunosuppressive therapies was diagnosed. Conventional therapies failed and the patient further developed acute renal failure requiring continuous veno-venous hemodialysis. A CytoSorb adsorber was then installed into the va-ECMO circuit and continued for the next 4 days. Plasma concentrations of immunosuppressive drugs and antibiotics were closely monitored (the patient received treatment with tacrolimus, mycophenolate mofetil, prednisolone, amphotericin, levofloxacin and cotrimoxazole). As soon as the CytoSorb adsorber was installed the patient stabilized. His CK and myoglobin rapidly and continuously decreased (at end of treatment CK 45,866U/L, myoglobin 53,700 µg/L). Plasma drug concentrations remained stable throughout the treatment period with no problems concerning pharmacokinetics seen. At six-month follow up there were no further postoperative complications, and he had full kidney function despite this episode of severe rhabdomyolysis. The authors state that CytoSorb was a safe and feasible technique (to purify the blood to preserve kidney function).

<https://www.ncbi.nlm.nih.gov/pubmed/32101624>

### Cytosorb for Management of Acute Kidney Injury due to Rhabdomyolysis in a Child.

Padiyar S, Deokar A, Birajdar S, Walawalkar A, Doshi H.  
*Indian Pediatr* 2019; 56(11): 974-976

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### Summary

This is a case report of a previously healthy 6-year-old girl that presented with rhabdomyolysis following a febrile illness. Diagnostics revealed positive findings for Influenza B and enterovirus with very high serum creatine kinase (CK) and myoglobin levels (around 3,000 ng/ml). She developed myoglobinuria with oliguria leading to acute kidney injury so was put on intermittent and then continuous renal replacement therapy (CRRT) because of hemodynamic instability. A Cytosorb adsorber was added to remove the myoglobin and CK. After three days of CytoSorb her myoglobin had dropped to under 600 ng/ml and after two more days of CRRT she was able to be switched back to intermittent dialysis which she received until day 33. The patient was eventually discharged home. This is the first published case of the use of CytoSorb for removal of myoglobin in a pediatric patient.

<https://www.ncbi.nlm.nih.gov/pubmed/31729332>

### 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**

### **Novel diagnostic and therapeutic techniques reveal changed metabolic profiles in recurrent focal segmental glomerulosclerosis**

Muller-Deile J, Sarau G, Kotb AM, Jaremenko C, Rolle-Kampczyk UE, Daniel C, Kalkhof S, Christiansen SH, Schiffer M.

*Sci Rep* 2020; 11(1): 4577

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### **Summary**

Idiopathic forms of the condition Focal Segmental Glomerulosclerosis (FSGS) are most likely caused by circulating permeability factors, which can lead to early recurrence of FSGS and kidney failure after kidney transplantation. In this case report a 24 yr old woman was given a kidney transplant from her mother after a three-year history of progressive renal failure resulting in end stage renal disease and regular hemodialysis. Initially the patient did well, but after a month her condition rapidly deteriorated. The patient received intravenous corticoid treatment and two doses of rituximab (1 g) within 2 weeks, but proteinuria did not improve. Interestingly, the classically published circulating factors were all in normal range in this patient, but due to the early recurrence of the primary disease, and the severity of the original disease it was decided to start CytoSorb apheresis as a compassionate use approach for the potential removal of circulating factors that might cause FSGS. CytoSorb was given daily for four days with good response so the frequency of CytoSorb was reduced to once per week. However, her proteinuria rapidly relapsed (327 mg/g – 4235 mg/g) so CytoSorb was given daily again until the patient went into clinical remission. After a period of stabilization, the patient's condition started to deteriorate once more so she was given CytoSorb daily again. Over time treatment was able to be tapered to once per week, with the patient currently receiving CytoSorb 2<sup>nd</sup> weekly for, what is now two years post-transplant with excellent transplant function. Weaning from CytoSorb apheresis, however, is still not possible and also attempts to increase the time between treatment cycles have failed so far. The authors performed additional cell-based ex-vivo models to detect morphological changes in podocytes caused by FSGS serum. Further novel innovative analysis revealed changed lipid metabolome profiles associated with idiopathic FSGS that might reflect a new subtype of the disease. This is the first case of acute and chronic use of CytoSorb in a post renal translation patient for the successful ongoing management of their kidney disease.

<https://www.ncbi.nlm.nih.gov/pubmed/33633212>

## **Hemoadsorption to treat severe iatrogenic intoxication to Patent Blue: A Case Report**

Taccone FS, Gardette M, Creteur J, Brasseur A, Lorent S, Grimaldi D.

*Journal of Medical Case Reports* 2021; 15:63

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### **Summary**

This is a case report concerning a 27 yr old female admitted with ecstasy (MDMA) intoxication resulting in multi-organ failure (acute respiratory distress syndrome – ARDS; metabolic acidosis;

capillary leakage syndrome; renal failure; and shock refractory to standard resuscitation). She was started on continuous renal replacement therapy (CRRT) and veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) and it was decided to also prescribe Methylene blue to reverse the vasoplegia and high norepinephrine requirements. Instead of Methylene Blue, Patent Blue V was erroneously administered, resulting in a severe clinical picture of methemoglobinemia and tissue hypoxia. CytoSorb hemoadsorption was initiated into the CRRT circuit resulting in a rapid and significant reduction in plasma methemoglobin, accompanied by an improvement in hemodynamics and normalization in plasma lactate levels. Two adsorbers were used (15 hours and 20 hours). After a prolonged recovery period the patient was eventually discharged home on day 75. According to the authors there is a potential role for CytoSorb in wider drug intoxications, which, however, needs to be verified in larger series.

<https://www.ncbi.nlm.nih.gov/pubmed/33557948>

### **Cytokine adsorption therapy in lymphoma-associated hemophagocytic lymphohistiocytosis and allogeneic stem cell transplantation**

Rademacher J-G, Wulf G, Koziolok, MJ, Zeisberg M, Wallbach M.

*Journal of Artificial Organs 2021; epub*

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#### **Summary**

This is a report of a 57 yr old female patient with aggressive lymphoma secondary to chronic lymphocytic leukemia with rapidly progressive Hemophagocytic lymphohistiocytosis (HLH) upon conditioning chemotherapy prior to allogeneic stem cell transplantation (ASCT). Continuous hemodiafiltration (CHDF) was initiated for the treatment of shock with acute renal failure, lactacidosis and need for high-dose catecholamine therapy. A CytoSorb adsorber was added to reduce cytokine levels for a total of 7 x 24 hr sessions. This was followed by a scheduled allogeneic stem cell transplantation on day 3 of CHDF and CytoSorb. A marked decrease in interleukin-6 plasma levels was observed (peak 622 pg/ml to 54.8 pg/ml) which was associated with a reduced need for vasopressor therapy and organ function stabilization. Hematopoietic engraftment was present at day 14 post-ASCT, leading to disease-free discharge at day 100 post-transplantation. The authors conclude that cytokine adsorption may serve as a safe adjunct to HLH/sepsis treatment during allogeneic stem cell transplantation. In summary, cytokine adsorption may have contributed to the mitigation of lymphoma-associated HLH under conditioning therapy, allowing successful ASCT.

<https://pubmed.ncbi.nlm.nih.gov/33459910/>

### **Case Report: Successful Use of Extracorporeal Therapies After ECMO Resuscitation in a Pediatric Kidney Transplant Recipient**

Rybalko AS, Pytal AV, Kaabak M, Rappoport N, Bidzhiev A, Lastovka V.

*Frontiers in Pediatrics 2020; 8: 593123*

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#### **Summary**

In this case report a 30-month old, 6.4 kg child, resuscitated with extracorporeal membrane oxygenation (ECMO), after a cardiac arrest during kidney transplantation surgery was additionally treated with a number of extracorporeal blood purification methods (plasma exchange - PE, CytoSorb, and lipopolysaccharide – LPS/endotoxin - adsorption), in the setting of immunosuppression therapy. Following three PE sessions, and, as the therapeutic effect was not as hoped (slight decrease in liver enzymes, and rise in inflammatory parameters), CytoSorb was started for a total of 21 hours. Use of CytoSorb resulted in a decrease in inflammatory parameters but, due to an occult and untreated infection, the inotropic requirements still increased. Once the infection was treated properly hemodynamics quickly stabilized and the patient gradually recovered and was able to be discharged from intensive care and then the hospital 116 days after his initial admission. This case report shows the successful use of multimodal extracorporeal therapies with a good patient outcome. As the authors note, the lack of response to CytoSorb therapy from a hemodynamic perspective could be seen as an indication for the need for ongoing investigation for an (as yet) unidentified infection and is not necessarily failure of treatment.

<https://pubmed.ncbi.nlm.nih.gov/33384974/>

### **Hemoadsorption cartridge and coronavirus disease 2019 infections: A case report and brief literature review**

Melegari G, Bertellini E, Melegari A, Trenti T, Malaguti S, Barbieri A.

*Artif Organs 2021;45(5):E130-E135*

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## **Summary**

In this case report a 71 year old man with COVID-19 was admitted after a 5 day history of high temperature, general weakness and difficulties breathing. He was admitted to intensive care with severe acute respiratory syndrome in COVID-19 and acute renal failure - for intubation and mechanical ventilation, and renal replacement therapy (RRT). Despite maximum therapeutic interventions, his clinical condition continued to deteriorate so hemoadsorption with CytoSorb was added to his renal circuit in order to reduce the cytokine release syndrome. RRT plus CytoSorb was continued for 5 days and two treatments with CytoSorb were performed for 48 hrs. each. During this time the interleukin (IL) 6 was reduced from 123.53pg/ml to between 18.51 and 22.64 pg/ml and the patient's respiratory function improved allowing him to be weaned from the ventilator. He was discharged home after 2 months in the hospital with normal respiratory function but chronic renal failure. The authors conclude that CytoSorb is compatible with the concomitant use of antiviral drugs, chloroquine, or antirheumatic drugs, with a possible synergistic relationship. The safety and versatility of adsorption treatments highlight their interesting features and potential applications in critically ill patients, including COVID-19 patients, especially with the concomitant use of ECMO or RRT, in order to reduce cytokine hyperproduction and their related life-threatening effects.

<https://www.ncbi.nlm.nih.gov/pubmed/33084021>

Successful treatment of a severe digitoxin intoxication with CytoSorb® hemoadsorption  
Breuer TGK, Quast DR, Wiciok S, Labedi A, Ellrichmann G.

*Blood Purification 2021; 50(1): 137 - 40*

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## **Summary**

In this case report an 81 year old female was admitted to intensive care with severe digitoxin intoxication, acute renal failure and a urinary tract infection (UTI). Continuous renal replacement therapy (CRRT) was started combined with a CytoSorb hemoadsorption. The patient stabilized hemodynamically within the first 4 hours of treatment and all catecholamines could be stopped within 24 hrs. Pre- and post CytoSorb adsorber drug level measurements showed a rapid elimination of digitoxin. Antibiotic treatment with piperacillin/tazobactam was initiated and the UTI successfully treated without dose adaptations. After three days of CytoSorb treatment, digitoxin plasma levels were stable and almost normalized with no clinical signs of intoxication present. Five days after presentation, the patient was transferred from ICU in a stable condition. The authors describe CytoSorb hemoadsorption as maybe a more cost efficient and easily available option than treatment with the Fab fragment, which is the currently recommended therapy for digitalis intoxications. Therefore, the use of CytoSorb might represent an alternative treatment for life-threatening complications of digitoxin intoxications.

<https://pubmed.ncbi.nlm.nih.gov/32937619/>

## **Use of the CytoSorb adsorption device in MDMA intoxication: a first-in-man application and in vitro study**

Lang CN, Sommer M, Neukamm M, Staudacher DL, Supady A, Bode C, Duerschmied D, Lothar A.  
*Intensive Care Med Exp 2020; 8(1): 21*

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## **Summary**

MDMA (3,4-Methylenedioxymethamphetamine, "ecstasy") abuse and overdose has been known to cause severe and eventually lethal multi-organ failure in some cases. To date, there is no treatment for MDMA intoxication or removal. This case presents the first-in-man experience and in-vitro data that supports the potential role of CytoSorb in severe MDMA overdose. A 21 yr old male presented with severe MDMA intoxication and multi-organ failure, including neurological impairment, hyperpyrexia, rhabdomyolysis, oliguric renal failure, liver failure, and coagulopathy with disseminated gastrointestinal and intramuscular bleeding. Use of CytoSorb integrated into the hemodialysis circuit was associated with a decline in MDMA concentrations in serum from 540 to 140 ng/ml within the first 24 h, a decrease of interleukin 6 (48,129 to 4991 pg/ml) and myoglobin levels (75,420 to 18,400 ng/ml), and subsequent clinical improvement. Effective elimination of MDMA by CytoSorb was then confirmed in vitro, where the device lowered MDMA concentrations measured distal of the adsorber, to non-detectable levels indicating full removal. The authors conclude that early integration of CytoSorb use may enhance the management of severe MDMA intoxication, although it is not proven whether clinical

improvement in this case was directly related to elimination of MDMA or the beneficial effects on rhabdomyolysis, hyperinflammation, or liver failure by the CytoSorb adsorber.

<https://www.ncbi.nlm.nih.gov/pubmed/32542550>

## **Paediatric patient with dengue fever and associated multi-organ dysfunction syndrome (MODS) receiving hemoadsorption using Cytosorb®; A case report on clinical experience**

Kumar S, Damera S.

*IJMDAT 2020; 3: e233*

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### **Summary**

In this case report a 10 year old patient with dengue haemorrhagic fever and systemic inflammatory response syndrome was admitted to hospital. He also had acute fulminant hepatic failure, with encephalopathy and oliguria. Despite liver protective measures (N-Acetyl Cystine infusion), his liver function and other organs became increasingly worse so CytoSorb was initiated on day 3 of admission. The adsorber was inserted in a post dialyser position in hemodiafiltration mode with a blood flow of 40 ml/min without anticoagulation for a total of 18 hours. After this time his liver function including bilirubin levels improved (7.2 – 4.8 mg/dL). Over five days his platelet count increased from 17,000 to 108,000 (per  $\mu$ L). His condition continued to improve, and he was eventually discharged in a stable condition. CytoSorb along with standard care is described as a safe and advantageous extracorporeal therapy option for paediatric dengue patients with multiple organ dysfunction.

[Link to Article](#)

## **Extracorporeal cytokine adsorption for treating severe refractory cytokine release syndrome (CRS).**

Wallet F, Bachy E, Vassal O, Friggeri A, Bohe J, Garnier L, Salles G, Allaouchiche B.

*Bone Marrow Transplant 2020; 55(10): 2052 - 5*

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### **Summary**

In this case report a 79 year old otherwise well patient from the hematology ward with aggressive large B-cell lymphoma refractory to several lines of therapy. He was treated with a T-cell-engaging bispecific antibody linking CD3+ T cells to CD20+ malignant B cells. After several hours he developed a reaction to the treatment (Cytokine Release Syndrome - CRS, initially grade 2 then grade 4), and had to be admitted to intensive care for management. Despite receiving tocilizumab, steroids and aggressive fluid management during the next 24 hrs his condition continued to deteriorate, his cytokine levels remained unchanged and he required rapidly increasing doses of norepinephrine (up to 1.5  $\mu$ g/kg/min), intubation and mechanical ventilation and continuous venovenous hemodialysis (CVVHD). After two days on ICU, CytoSorb therapy was added to the dialysis circuit. Within 6 hours of commencement the noradrenaline could be reduced and stopped after the second 24 hr treatment. No more fluid expansion was needed after the initiation of CytoSorb epuration. Interleukin (IL)-6 was reduced by 75% two hours after CytoSorb was initiated (11813 to 2941 pg/mL), and IL-10 by 63% (170 to 63 pg/mL). After 24 hours, IL-6 had reduced further to 841 pg/mL and IL-10 to 15 pg/mL. The patient received two 24 hour treatments with CytoSorb, and after another 48 hours his condition had improved enough for him to be extubated. Unfortunately, a few days later the patient went on to develop an invasive fungal infection with septic shock and multi-organ failure, and treatment was withdrawn in accordance with the families wishes. After CytoSorb treatment, his cytokine levels did not massively rebound indicating that the CRS was under control. During his CytoSorb treatment some of the levels of antimicrobials used were measured. Piperacillin trough concentrations ranged from 70 to 123 (mean  $\pm$  standard deviation [SD] 89.36 mg/L  $\pm$  20.24), and caspofungin trough concentrations ranged from 0.54 to 0.93 (0.74 mg/L  $\pm$  0.19), all within the expected range indicating there was no need to adjust levels because of the CytoSorb adsorber. There were no serious adverse effects associated with CytoSorb use.

<https://www.ncbi.nlm.nih.gov/pubmed/32277144>

## **Extracorporeal cytokine removal in severe CAR-T cell associated cytokine release syndrome**

Stahl K, Schmidt BMW, Hoepfer MM, Skripuletz T, Mohn N, Beutel G, Eder M, Welte T, Ganser A, Falk CS, Koenecke C, David S.

*J Crit Care 2020; 57: 124-129*

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### **Summary**

In this case report a 65 yr old male with relapsed diffuse large B-cell lymphoma was admitted to ICU after he was treated with CD-19 Chimeric antigen receptor - T (CAR-T) cells and then developed

grade 4 cytokine release syndrome (CRS) with refractory shock and severe capillary leakage. He was treated with IL-6 blockade (tocilizumab), methylprednisolone and additionally CytoSorb. During the next 24 hrs, the patient became more hemodynamically unstable, so the CytoSorb was then changed 8 hrly. Within hours the shock completely reversed, vasopressor dose could be decreased to 10% of the peak dose, and inotropic support stopped completely. Plasma was obtained before and 8 hrly following the start of CytoSorb treatment. While multiple soluble inflammatory factors were elevated and most of them decreased by more than 50% following Cytosorb, markers of endothelial injury increased steadily (e.g. Angpt-2/Angpt-1) leading to profound endothelial activation and leakage in ex vivo assays. This is the first reported use of cytokine adsorption for CRS showing efficacy in absorption of various cytokines but not endothelial growth factors. Findings suggest the possibility that removal of excessive circulating cytokines rather than pharmacological blockage of a single key cytokine alone might be a more effective treatment strategy for CRS. The authors are currently recruiting to a randomized controlled trial to evaluate additional CytoSorb treatment in CRS.

<https://www.ncbi.nlm.nih.gov/pubmed/32113143>

### **Multimodal Therapeutic Approach of Cytokine Release Syndrome Developing in a Child Given Chimeric Antigen Receptor-Modified T Cell Infusion.**

Bottari G, Merli P, Guzzo I, Stoppa F, Ruggeri A, Di Nardo M, Del Bufalo F, Galaverna F, Corrado C, Locatelli F.

*Critical Care Explorations* 2020; 2(1): e0071

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#### **Summary**

In this case report a 14-year-old boy with refractory B cell precursor acute lymphoblastic leukemia who was treated with chimeric antigen receptor (CAR) cells then developed severe (grade 4) cytokine release syndrome 7 days after the drug infusion, with progressive respiratory failure. He was admitted to the pediatric intensive care unit (PICU) with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, hemodynamic instability requiring vasopressors, and also secondary hemophagocytic lymphohistiocytosis (HLH) with extremely high ferritin levels. The patient was treated with five CytoSorb adsorbers (first two changed 12 hrly, then 24 hrly) in combination with continuous renal replacement therapy (CRRT). Tocilizumab was given 6 hours before admission to PICU and on the 3<sup>rd</sup> and 4<sup>th</sup> days after start of CytoSorb. This treatment resulted in a decrease of the inflammatory biomarkers over the first 96 hours (e.g. ferritin from 146,095 to 6,934 ng/mL and interleukin-6 from 4,048 – 247 pg/mL,) which was associated with progressive improvement in his ARDS (Pao2/Fio2 ratio). The patient was able to be discharged from PICU after 19 days. This case suggests that CytoSorb treatment with CRRT and tocilizumab is safe and potentially effective in pediatric patients with severe cytokine release syndrome.

<https://www.ncbi.nlm.nih.gov/pubmed/32166291>

### **A case report to highlight the impact of extracorporeal cytokine elimination therapy in viper snakebite induced septic shock with acute kidney injury**

Parikh K, Patel H, Kothari M, Maheshwari L, Shetty V, Khadke SS

*IJMDAT* 2020; 3: e222

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#### **Summary**

In this case a 40-year-old male patient developed hypotensive and circulatory shock post viper snakebite. He went on to develop septic shock and multi organ failure, with acute respiratory distress syndrome followed by acute kidney injury despite full standard care. Due to high inflammatory markers indicative of a cytokine storm, CytoSorb was initiated along with hemodialysis for 8 hours. Post CytoSorb, noradrenaline dose could be reduced and eventually terminated, mean arterial pressure improved, and ventilatory support could be weaned. Circulatory shock was resolved, alongside normalization of hemoglobin, platelet and leukocyte counts. Procalcitonin dropped from 3 pre to 0.6 ng/ml post adsorber use. Sequential Organ Failure Assessment (SOFA) score reduced significantly from 12 pre-adsorber to 1 so that twelve hours after CytoSorb was stopped he was discharged to the normal ward, and from the hospital 3 days later completely recovered.

[Link to Article](#)

### **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; 1905871

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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.ncbi.nlm.nih.gov/pubmed/31428479>

## 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; 42(11): 658 - 64

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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; 42(9): 516 - 20

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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.

[Link to Article](#)

## **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.  
*IJA* 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.

<https://www.ncbi.nlm.nih.gov/pubmed/29198456>

### First application of CVVHDF, plasmapheresis and "CytoSorb absorber" to solve a pediatric haemophagocytic Histiocytosis 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.

[Link to Article](#)

### 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.

[Link to Article](#)

## 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 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.

[Link to Article](#)

## 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 hemoadsorption 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 hemoadsorption 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 lymphohistiocytosis (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 9<sup>th</sup> - 17<sup>th</sup> 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 52<sup>nd</sup> 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- $\alpha$ , interleukins and interferon gamma - IFN- $\gamma$ ) 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.

[Link to Article](#)

### 1.3.6 COVID-19

#### **NEW; Successful Treatment of Suspected Donor-derived Human Herpesvirus-8 Infection in a Liver Transplant Patient With Coronavirus Disease-19**

Peri AM, Magro B, van den Bogaart L, Dalla Pria A, Giuffrida P, Gianatti A, Fabretti F, Maria Barbui A, Tebaldi A, Rizzi M, Fagioli AS.

*Transplantation 2021; 105(6): e65-e67*

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#### **Summary**

This letter to the editor describes the case of a 62 yr old liver transplant recipient infected with the coronavirus (COVID-19), who developed life threatening organ dysfunction due to the onset of human herpes virus-8 (HHV8) and who was successfully treated with rituximab and CytoSorb. The patient was admitted two months after the initial liver transplant with COVID-19 associated pneumonia. Despite maximum therapy his condition rapidly deteriorated so rituximab (an anti-lymphocyte (CD20) monoclonal antibody) and continuous veno-venous hemodialysis (CVVHD) plus CytoSorb were started. The patient responded quickly with a significant clinical improvement over the following days. He soon regained full consciousness, and his acute kidney injury and thrombocytopenia resolved. The patient was discharged after a full recovery and was found to be doing well with no adverse events observed at 1 year follow-up. Finally, the authors discuss extracorporeal cytokine adsorption as a promising alternative to pharmacological inhibition of IL-6 in severe cases of COVID-19. They describe as an advantage the fact that CytoSorb non-selectively blocks the immune cascade, and in particular that it is possible to terminate CytoSorb at any time without long term effects that might harm immunocompromised hosts.

<https://www.ncbi.nlm.nih.gov/pubmed/34048423>

#### **NEW; Hemadsorption as a Treatment Option for Multisystem Inflammatory Syndrome in Children Associated With COVID-19. A Case Report.**

Ruiz-Rodríguez JC, Chiscano-Camón L, Palmada C, Ruiz-Sanmartin A, García-de-Acilu M, Plata-Menchaca E, Perurena-Prieto J, Hernandez-Gonzalez M, Pérez-Carrasco M Soler-Palacin P, Ferrer R.

*Frontiers in Immunology 2021; 12: 665824*

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#### **Summary**

In this case report a 17 year old with a history of COVID-19 was admitted to intensive care unit (ICU) eventually diagnosed with acute myocarditis secondary to multisystem inflammatory syndrome in children (MIS-C). On the first day in ICU he was started on standard pharmacological treatments along with CytoSorb (for 24 hours). Pre and post CytoSorb use showed inflammatory parameters such as interleukin (IL)-6 and IL-10 decreased from 3457 – 47.8 pg/mL and 90.3 – 9.24 pg/mL respectively. His respiratory function improved with an increase in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio from 60 – 400 mmHg. With CytoSorb use the amount of noradrenaline required also decreased by more than 80% (0.8 – 0.08 µg/kg/min). Despite the severity of his condition, the patient was able to be discharged from ICU on day 5 and from hospital on day 20 with no chronic sequelae detected. The authors consider hemoadsorption responsible for the rapid improvement in respiratory, hemodynamic, and organ dysfunction and therefore is a potential adjunctive therapy in patients with MIS-C severe multiorgan dysfunction.

<https://www.ncbi.nlm.nih.gov/pubmed/34140949>

#### **Successful use of CytoSorb in a Covid-19 patient with secondary septic shock due to a sacral decubitus infection**

Pancani F, Pavani R, Quacquarelli A, Feri M.

*Int J Artif Organs 2021; epub*

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## Summary

This is a case of a 75-year-old man with respiratory failure due to Sars-CoV-2 infection and secondary septic shock due to a sacral decubitus ulcer. He was admitted to the Intensive Care Unit five days after his initial admission to hospital with a Glasgow Coma Scale of 5, hypotension (systolic pressure 65 mmHg), and dyspnoeic (35 breaths per min). The patient presented with a clinical picture of mixed acidosis with high levels of lactate (7.57 mmol/L) and inflammatory indexes (procalcitonin – PCT 10.23 ng/ml, C-Reactive Protein – CRP 14.3 mg/L). Along with intubation and protective mechanical ventilation, and antibiotic therapy, a norepinephrine infusion was started (0.6 – 1.4 µg/kg/min) along with terlipressin in the later course. After 24 hrs, the inflammatory parameters remained high (interleukin – IL-6 6768 pg/mL) so hemoadsorption treatment with CytoSorb was started for the septic clinical picture, first in hemoperfusion mode and later in combination with continuous venous-venous hemodiafiltration (CVVHDF). Three consecutive cycles of 24 hrs each were performed. After the three days of treatment, PCT decreased to 1.1 ng/ml, CRP 9.4 mg/L, lactate 1.91 mmol/L and IL-6 to 1731 pg/mL. Norepinephrine and Terlipressin doses were progressively decreased as the hemodynamics stabilized. Due to an obvious deterioration in the decubitus lesion, curettage and vacuum assisted therapy (VAC) was performed. At the end of the treatment the patient had recovered his vital functions and the infection was successfully treated. Use of the CytoSorb device in this COVID-19 positive patient was safe and well-tolerated. Early use of CytoSorb within 24h from ICU admission decreased IL-6 plasma levels and inflammatory indexes, resulting in earlier stabilization of homeostasis. The authors conclude that this case suggests that the use of CytoSorb could be a possible adjuvant therapy in patients with septic shock even when affected by COVID-19.

<https://pubmed.ncbi.nlm.nih.gov/33998306/>

## Cytosorb treatment in severe COVID-19 cardiac and pulmonary disease

Ciabatti M, Martinese L, Quacquarelli A, Pieroni M, Feri M, Bolognese L.

*Eur Heart J Case Rep* 2021; 5(4): ytab123

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## Summary

A 75-year-old man was admitted for COVID-19-related pulmonary disease. He was initially treated with intravenous dexamethasone, enoxaparin and non-invasive ventilation. Levels of cardiac damage and inflammatory biomarkers were significantly elevated (including interleukin-IL-6 6768 ng/L). He received two cycles of tocilizumab therapy over the following 2 days, but over the next 3 days his clinical condition deteriorated with severe respiratory failure, severe hypoxaemia, hypotension, and hypoperfusion. He was intubated and mechanically ventilated before being transferred to the COVID-19 intensive care unit. Computed tomography showed bilateral ground-glass lesions, sub-pleural consolidations, pleural effusions, and subsegmental pulmonary embolism. Despite treatment with high-dose vasoactive drugs, unfractionated heparin and antibiotics, he developed refractory shock with anuria so was started on continuous renal replacement therapy (CRRT) with Cytosorb on day 6. After 72 hrs, a significant hemodynamic improvement together with an important decline in inflammatory (IL-6 decreased from 7100 to 2500 ng/L, Ferritin from 1250 µg/l to 450 µg/l), and cardiac damage markers levels (e.g. high sensitivity troponin T reduced from 55 – 35 pg/mL during treatment) was observed, and, due to the presence of spontaneous diuresis with negative fluid balance, CRRT and CytoSorb therapy were stopped. The patient was extubated 3 days later and on day 14 transferred to a respiratory rehabilitation centre with stable hemodynamics and no need for CRRT. After 6 months, the patient has completely recovered with normal right ventricular function.

<https://www.ncbi.nlm.nih.gov/pubmed/33870079>

## The Combined Use of Tocilizumab and Hemoadsorption in a Patient with SARS-COV-2-19-Associated Pneumonia: A Case Report

Berlot G, Tomasini A, Roman Pognuz E, Randino A, Chiella F, La Fata C, Piva M, Amato P, di Maso V, Bianco F, Gerini U, Tomietto P, Trenti T.

*Nephron* 2020; 144(9):459-462

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## Summary

In this case report a 40 year old previously well man was admitted to Intensive Care with severe respiratory failure caused by SARS-CoV-2 (COVID-19). Due to the high interleukin (IL)-6 and C-Reactive Protein (CRP) levels the anti-IL-6 drug, tocilizumab plus hemoperfusion with CytoSorb was started. Tocilizumab was given for 2 days, and CytoSorb, given in hemoperfusion mode - due to the lack of a need for renal replacement therapy (RRT) - for 3 days (exchanged every 24 hrs). Notably, tocilizumab was not removed by the CytoSorb due to its elevated molecular weight. Levels of IL-6 decreased from 1,040 to 415 pg/mL and CRP from 229 to 59 mg/L, respectively. The gas exchange

and the chest imaging rapidly improved (PaO<sub>2</sub>/FiO<sub>2</sub> ratio from 132 – 220), and the patient was extubated 10 days later, and eventually discharged home. The authors suggest considering the use of the combined approach of CytoSorb and tocilizumab in patients with SARS-CoV-2 induced pneumonia, Acute Respiratory Distress Syndrome (ARDS), and/or multiple organ dysfunction syndrome with elevated levels of CRP.

<https://pubmed.ncbi.nlm.nih.gov/32694244>

### **COVID-19 presenting as acute abdomen and sepsis: a rare case-report**

Alharthy A, Balhamar A, Faqihi F, Nasim N, Noor A, Alqahtani SA, Memish ZA, Karakitsos D.

*New Microbes and New Infections* 2020; 38: 100818

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#### **Summary**

In this case report a 45 year old man with severe COVID-19 pneumonia with associated pulmonary embolism, presented with an acute abdomen (bowel ischemia). He underwent emergency laparotomy, where he was found to have a small intestinal perforation with peritonitis, so he underwent resection of an ischemic area of the jejunum. Postoperatively, he had septic shock, acute-respiratory-distress syndrome, and acute kidney injury (AKI) necessitating continuous-renal-replacement-therapy (CRRT). He was given therapeutic anticoagulation along with two sessions of hemoadsorption by CytoSorb (24 hrs each), in conjunction with the CRRT. After 2 days his inflammatory biomarkers and lactate levels normalised, and vasopressors could be weaned off by day 3 of ICU stay. His renal function and oxygenation progressively improved, too and he was able to be extubated on day 7 of his ICU stay. The authors conclude that extracorporeal blood purification may be useful in managing perioperative sepsis, AKI and cytokine storm which are all poor prognostic factors in critically ill patients with COVID-19. Presumably, the early application of hemoadsorption mitigated a full blown picture of COVID-19 related hyperinflammation and/or the development of refractory septic shock.

<https://pubmed.ncbi.nlm.nih.gov/33224507/>

### **SARS-CoV-2 infection in kidney transplant recipients: experience of the Italian Marche region.**

Maritati F, Cerutti E., Zuccatosta L, Fiorentini A, Finale C, Ficosecco M, Cristiano F, Capestro A, Balestra E, Taruscia D, Vivarelli M, Donati A, Perna GP, Giacometti A, Tavio M, Onesta M, Di Sante L, Ranghino A.

*Transpl Infect Dis* 2020; 22(5); e13377

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#### **Summary**

This case series included 5 patients who were kidney transplant recipients (KTR) and also SARS-CoV-2 (COVID-19) positive. One of the patients developed acute kidney injury with the need for continuous renal replacement therapy (CRRT) where CytoSorb was also used for 3 x 24hr treatments. The authors speculate that use of CytoSorb in this patient for removal of the initially very high interleukin 6 levels, could potentiate the effect of tocilizumab, an IL6 receptor agonist. Indeed, during CRRT treatment plus CytoSorb, the patient's hemodynamic and hypoxemic conditions improved. Finally, it is suggested that the use of CytoSorb in combination with tocilizumab might be considered in patients with severe SARS-CoV-2 with need of CRRT.

<https://www.ncbi.nlm.nih.gov/pubmed/32573895>

### **Cytosorb filter: An adjunct for survival in the COVID-19 patient in cytokine storm? a case report.**

Rizvi S, Danic M, Silver M, LaBond V

*Heart & Lung* 2021; 50(1): 44 - 50

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#### **Summary**

This report describes the case of a 51 yr old male patient with COVID-19 admitted to hospital with dyspnea, lethargy, myalgias and fever. He initially responded well to treatment on the respiratory ward, but on day 4 he had to be intubated and ventilated due to his hypoxemia and developing acute respiratory distress syndrome (ARDS) so was transferred to intensive care. Here he continued to deteriorate however, and so on day 6 his antibiotics and ventilator settings were reviewed and adjusted accordingly (including prone positioning). After an initial positive response, it was noted that his creatinine was starting to increase and his oxygenation to worsen again so it was decided to start continuous renal replacement therapy (CRRT). After having received IRB approval for compassionate

use the decision was then made to insert the CytoSorb adsorber into the CRRT before his developing cytokine storm became insurmountable. The adsorber was changed 12hrly for the first 48 hrs, and thereafter every 24 hrs. Eight adsorbers were used over a 12 day period with a temporary halt of four days into the treatment. Once the CytoSorb adsorber was placed in the pre-filter position his hemodynamic status improved and stabilized. Having survived the cytokine storm and sepsis associated COVID-19, the patient was able to tolerate further novel treatments including tocilizumab and convalescent plasma. The patient's clinical course was then complicated further by a hypoxic cardiopulmonary arrest, upper GI bleed and severe depression and anxiety, before he was finally discharged to subacute rehab after 60 days in hospital. The authors believe that in this severely ill patient the use of CytoSorb seemed to stabilize the patient (better oxygen requirements, pressor support and inflammatory markers), and that the use of CytoSorb successfully completed the goal of prolonging the patient's life to bridge to definitive therapies during the cytokine storm.

<https://pubmed.ncbi.nlm.nih.gov/33041058/>

### **Cytokine adsorption in a patient with severe coronavirus disease 2019 related acute respiratory distress syndrome requiring extracorporeal membrane oxygenation therapy: A case report**

Rieder M, Zahn T, Benk C, Lothar A, Bode C, Staudacher D, Duerschmied D, Supady A.

*Artif Organs 2020; epub*

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#### **Summary**

In this letter to the editor the case of a 59 year old female with COVID-19 related ARDS is described. After 8 days of various symptoms she was finally admitted to hospital with severe respiratory insufficiency requiring immediate non-invasive ventilation. Over the following days, and despite maximum therapeutic measures including progression to invasive ventilation and prone positioning, her hypoxemia deteriorated further so that the decision was made to put her on veno-venous extracorporeal membrane oxygenation (vv ECMO) on day 5 of her hospital stay. Because of her elevated inflammatory parameters (interleukin – IL 6 540 pg/ml, C-Reactive Protein – CRP 482.3 mg/L) a CytoSorb adsorber was included directly into the ECMO circuit. CytoSorb therapy was continued for 72 hours. No adjustments to the antibiotic doses appeared to be necessary during this time. Very quickly after the start of ECMO / CytoSorb, the patient stabilized clinically allowing lung protective ventilation strategies according to the ARDS treatment guidelines. The need for vasopressors also decreased significantly as did the CRP and IL-6 levels. The authors noted abnormal clotting of the ECMO circuit despite PTT monitored anticoagulation (D-dimers increased while platelets decreased) which they attributed to the effects of the hypercoagulability with COVID-19 infection. During the further course of treatment the patient developed a septic shock with multi-organ failure, most likely due to bacterial superinfection of the lung and, based on the presumed will of the patient, the therapy was therefore terminated 17 days after the initial hospital admission. According to the authors this case suggests that cytokine adsorption may help with the initial stabilization of patients with severe COVID-19 disease requiring vv ECMO support.

<https://www.ncbi.nlm.nih.gov/pubmed/32929761>

### **Cytokine Hemoadsorption in the Management of a Pregnant Woman with COVID-19 Pneumonia: Case Report.**

Karabulut Keklik ES, Dal H, Bozok Ş

*SN Comprehensive Clinical Medicine 2020; epub*

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#### **Summary**

This case report describes a 22-year-old pregnant woman (gestational age: 32 weeks) infected with COVID-19 who presented with fever (39.1 °C) and respiratory symptoms. The patient was admitted for supportive care and anti-viral and anti-inflammatory agents, however, her general health status deteriorated and she had to be transferred to the intensive care unit (ICU) on day 3 of her hospital admission. In ICU she deteriorated further with the development of respiratory failure and acute respiratory distress syndrome (ARDS). Thus, extracorporeal cytokine hemoadsorption with CytoSorb was performed every other day (3 sessions in total) in order to remove inflammatory cytokines from the circulation and to relieve the systemic inflammatory response. On day 7 of ICU admission, it was decided to terminate her pregnancy due to worsening hypoxemia and a healthy, premature infant was born. On day 2 after the cesarean section, the patient needed to be intubated and mechanical ventilation was initiated due to a worsening of her respiratory system. She continued to show an increasingly complicated clinical course (including acinetobacter sepsis and deep vein thrombosis)

and died on day 22 after ICU admission. The authors describe the use of CytoSorb in this patient for controlling fever, improving hypoxemia and reducing the inflammatory status (reduction in C-Reactive Protein levels) and buying extra time for hemodynamic and metabolic stabilization. According to the authors there may be a “window of opportunity” for patients with severe COVID-19, where early application of blood purification therapies should be considered.

<https://pubmed.ncbi.nlm.nih.gov/32954212/>

## 2. Pre-Clinical data

### 2.1. Animal models

#### **Pharmacokinetics of anti-infective agents during CytoSorb hemoadsorption**

Schneider AG, Andre P, Scheier J, Schmitt M, Ziervogel H, Buclin T, Kindgen-Milles D.

*Scientific Reports 2021; 10493*

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#### **Summary**

In this experimental study, 24 pigs were randomly allocated to either CytoSorb hemoadsorption or sham extracorporeal circuits (controls) and to different drug combinations. Seventeen different drugs were evaluated including; clindamycin, fluconazole, linezolid, meropenem, piperacillin, anidulafungin, ganciclovir, clarithromycin, posaconazole, teicoplanin, tobramycin, ceftriaxone, ciprofloxacin, metronidazole, liposomal amphotericin B, flucloxacillin and cefepime. Repeated blood measurements were taken from the extracorporeal circulation (pre and post adsorber) over six hours and total - and adsorber specific - clearance computed. Hemoadsorption was associated with increased clearance of all study drugs, except ganciclovir. However, CytoSorb impact on total body clearance was considered as moderate for fluconazole (282%) and linezolid (115%), mild for liposomal amphotericin B (75%), posaconazole (32%) and teicoplanin (31%) and negligible for all other drugs. This classification is based on the classification proposed by the WHO Committee for Proprietary Medicinal Products (CPMP) for drug inhibitors and inducers according to potency. Hemoadsorber clearance declined over time, with even delayed desorption for beta-lactams. In conclusion, hemoadsorption with CytoSorb appears to have a limited effect on the pharmacokinetics of the majority of drugs tested. However, the clearance of fluconazole, linezolid and liposomal amphotericin B appears to be increased by the procedure. Studies in humans are required to confirm the need for dosage adjustments for these agents.

<https://www.ncbi.nlm.nih.gov/pubmed/34006946>

#### **Pumpless Extracorporeal Hemoadsorption Technique: A New Method for Early Cytokine Elimination?**

Fiedler MO, Reyher C, Kalenka A, Rolfes C, Lotz C, Muellenbach RM.

*Blood Purif 2021; epub*

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#### **Summary**

In this proof of principle experimental study on two pigs, a femoral arteriovenous shunt was established with a CytoSorb adsorber inserted into the shunt circulation. A small 10 Fr arterial cannula was placed as the arterial line and a 14 French venous cannula was utilized as the venous return. As a major determinant for flow through the adsorber, the mean arterial pressure (MAP) was varied between 45 and 85 mmHg using norepinephrine or urapidil. Pre and post adsorber pressures, cardiac output and shunt blood flows were continuously recorded. Blood flows were observed between 206 and 393 mL/min through the CytoSorb adsorber, thus ranging between 3 and 6% of the cardiac output. This is the first experimental study to show the feasibility of using CytoSorb without the need for an additional pump (such as a renal replacement machine). Knowing that treatment with CytoSorb seems to be most effective when started within the first 24 hrs, this pumpless technique might be a valuable option in order to expedite the commencement of cytokine elimination in critically ill patients. Potential ischemia of the arterially cannulated limb is noted as one of the possible main complications which would need continuous monitoring, as would monitoring of flow. At the present time this remains an experimental application.

<https://www.ncbi.nlm.nih.gov/pubmed/33503608>

#### **Perfusate-adsorption during ex vivo lung perfusion improves early post-transplant lung function**

Iskender I, Arni S, Maeyashiki T, Citak N, Sauer M, Monné Rodriguez J, Frauenfelder T, Opitz I, Weder W, Inci I.

*Journal of Thoracic and Cardiovascular Surgery* 2021; 161(2): e109 - 21

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### Summary

In this ex vivo lung perfusion study (EVLP), the effect of ischemia-reperfusion injury after lung transplantation was studied in donor pig lungs. In the treatment group, the perfusate was also adsorbed through a CytoSorb adsorber, whereas the control lungs were perfused according to the standard protocol (n = 5, each). Variables of EVLP physiology and biochemistry were monitored. Cytokine concentrations in the perfusate were markedly lower with Cytosorb, resulting in improved EVLP physiology and biochemistry during the 6-hour ex-vivo perfusion period. After the subsequent transplant, dynamic lung compliance was markedly better during the 4-hour reperfusion period in the treatment group, as was isolated allograft oxygenation function and dynamic compliance at the end of reperfusion which was accompanied by a markedly decreased local inflammatory response. The authors conclude that the implementation of CytoSorb has refined the standard EVLP protocol. Furthermore, cytokine removal during EVLP improved immediate post-transplant graft function together with a less intense inflammatory response as a consequence of reperfusion in this pig model. <https://www.ncbi.nlm.nih.gov/pubmed/32201002>

### Hemoadsorption Improves Survival of Rats Exposed to an Acutely Lethal Dose of Aflatoxin B1

Ruggeberg KG, O'Sullivan P, Kovacs TJ, Dawson K, Capponi VJ, Chan PP, Golobish TD, Gruda MC  
*Scientific Reports* 2020; 10(1): 799

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### Summary

Mycotoxins, including aflatoxin B1 (AFB1), are highly toxic, causing a severe inflammatory reaction, and pose a serious threat as biological weapons due to their easy accessibility and lack of effective therapeutics. This study investigated whether CytoSorb (CS) could improve survival in rats after a lethal aflatoxin dose. The rats received a lethal dose of AFB1 intravenously and hemoperfusion with CytoSorb or a control device was initiated immediately, or after 30, 90, or 240-minute delays, and then conducted for 4 hours. It was found that CytoSorb removes AFB1 from the circulation and significantly improves survival when initiated within 90 minutes of toxin administration. It is known that CytoSorb also removes damage associated molecular patterns (DAMPs), which, together with the reduction in inflammatory mediators, may be an additional aspect that helps to explain the reduction of associated tissue damage, and the observed survival benefit. The authors suggest that CytoSorb could be a viable countermeasure against acute mycotoxin exposure. <https://www.ncbi.nlm.nih.gov/pubmed/31964964>

### Midkine Is Elevated After Multiple Trauma and Acts Directly on Human Cardiomyocytes by Altering Their Functionality and Metabolism.

Lackner I, Weber B, Baur M, Haffner-Luntzer M, Eiseler T, Fois G, Gebhard F, Relja B, Marzi I, Pfeifer R, Halvachizadeh S, Lipiski M, Cesarovic N, Pape H-C, Kalbitz M  
*Frontiers in Immunology* 2019; 10: 1910

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### Summary

Midkine is an inflammatory marker which is elevated in humans after fractures, burns and traumatic spinal cord injuries and appears to be associated with cardiac pathologies in these patients. In this experimental model, midkine levels were investigated in the blood plasma of 11 multiply injured humans admitted to an Emergency Dept, and 20 pigs treated according to a trauma model. Human cardiomyocytes were also cultured in the presence/absence of midkine and analysed. Finally, the ability of CytoSorb to adsorb midkine was tested with recombinant midkine or plasma from these multiply injured patients. Results showed that midkine levels were significantly increased in the blood plasma of multiply injured humans and pigs, and that it acted on human cardiomyocytes by altering their mitochondrial respiration and calcium metabolism in vitro, affecting both the function and metabolism of the cardiomyocytes, depressing cardiac function. Adsorption with CytoSorb reduced midkine concentrations both ex vivo and in vitro in a concentration dependent manner (by up to 95% when the midkine levels were 10,000 pg/ml). The use of CytoSorb may be a very promising therapeutic approach for the treatment and prevention of post-traumatic cardiac dysfunction. As noted, one huge benefit of using CytoSorb is that it is able to adsorb a high amount of many miscellaneous damage-associated and inflammatory molecules after trauma. Furthermore, adsorption of midkine by



CytoSorb might limit other negative effects of midkine in polytrauma patients, as it has been previously shown that midkine inhibits fracture healing and is associated with poor outcome in septic patients.

<https://www.ncbi.nlm.nih.gov/pubmed/31552013>

## **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* 2018; 37(2): 283 - 91

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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 hemoadsorptive 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 $\alpha$ , IL-1 $\beta$ , IL-6 und IL-10), organ injury/dysfunction (HMGB-1, ALT, and creatinine), production of cytokines (via NF $\kappa$ B 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 $\alpha$ , IL-1 $\beta$ , 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- $\kappa$ 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**

### **Hemoadsorption eliminates remdesivir from the circulation: Implications for the treatment of COVID-19**

Biever P, Staudacher D, Sommer M, Triebel H, Neukamm MA, Bode C, Supady A, Lothar A.

*Pharmacol Res Perspect* 2021; 9(2): e00743

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### **Summary**

This in-vitro study tested whether the antiviral drug, remdesivir - and its main active metabolite GS-441524, was adsorbed by CytoSorb, as both can be used for the treatment of severe COVID-19 patients. Fetal calf serum containing remdesivir or GS-441524 was circulated in a custom-made system containing a CytoSorb device. Concentrations of remdesivir and GS-441524 before and after the adsorber were analyzed. Measurements of remdesivir post adsorber indicated almost complete removal by the device, with concentrations showing an exponential decay which were no longer detectable after 60 mins. GS-441524 showed a similar exponential decay but reached an adsorption-desorption equilibrium at ~48 microg/L. In conclusion, remdesivir and GS-441524 are rapidly eliminated from the perfusate by the CytoSorb adsorber device in vitro. This should be considered in patients for whom both therapies are indicated, and so simultaneous application should maybe avoided. While benefit from the use of remdesivir in later stages of the COVID-19 disease remains questionable at this time, hemoadsorption therapy may be limited to critical cases of COVID-19 that are associated with a significant increase in cytokine levels. In general, however, and as also recommended by the company, plasma levels of therapeutic drugs should be closely monitored in patients who are also on concurrent CytoSorb therapy.

<https://www.ncbi.nlm.nih.gov/pubmed/33710753>

### **Cytokine absorption during human kidney perfusion reduces delayed graft function-associated inflammatory gene signature**

Ferdinand, JR, Hosgood SA, Moore T, Ferro A, Ward CJ, Castro-Dopico T, Nicholson ML, Clatworthy MR.

*Am J Transplant* 2021; 21(6):2188-2199

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### **Summary**

Transplantation is the optimal treatment for most patients with end stage kidney disease but organ shortage is a major challenge. A new technique, normothermic machine perfusion (NMP) has been used to re-condition

marginal organs however mechanisms by which NMP might benefit organs are not well understood. Using pairs of human kidneys obtained from the same donor, the authors compared the effect of NMP with that of cold storage on global kidney transcriptome. Cold storage led to the global reduction in gene expression, including inflammatory pathway genes. In contrast NMP, led to upregulation of the OXPHOS genes (required for energy generation processes), but also of a number of immune and inflammatory pathway genes. Using biopsies from kidneys undergoing NMP that were subsequently transplanted, the authors found that higher inflammatory gene expression occurred in organs with prolonged delayed graft function (DGF). Therefore, CytoSorb was used to remove pro-inflammatory cytokines for a period of 4 hours. Use of CytoSorb attenuated the negative effects of immune gene induction, and increased OXPHOS pathway genes. There were no effects on renal blood flow, urine output or composition, oxygen consumption or acid-base homeostasis. The authors suggest that their data shows that adsorption of pro-inflammatory mediators from the perfusate represents a potential intervention which may improve organ viability, including also liver and lung transplantation.

<https://www.ncbi.nlm.nih.gov/pubmed/33098231>

### **Similarities, Differences, and Potential Synergies in the Mechanism of Action of Albumin Dialysis Using the MARS Albumin Dialysis Device and the CytoSorb Hemoperfusion Device in the Treatment of Liver Failure.**

Dominik A & Stange J

*Blood Purif* 2021; 50(1): 119 - 28

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#### **Summary**

In this in vitro two-compartment model the molecular adsorption recirculating system (MARS) albumin dialysis was compared to CytoSorb for effects on marker molecule removal. Ammonia removal was increased using CytoSorb. CytoSorb also lead to a statistically significant reduction of albumin-bound toxins, total bilirubin and subfractions. Bile acid removal was comparable. MARS did not appear to remove the cytokines interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-alpha), whereas CytoSorb allowed for near complete removal. Notably, CytoSorb displayed 50% of lipophilic substance and cytokine removal during the first hour of treatment. Compared to MARS, CytoSorb hemoperfusion lead to an initially fast removal of cytokines, TNF-alpha and IL-6, as well as reduction of albumin-bound toxins such as indirect bilirubin and bile acids in this model. Whether the observed reduction of albumin is specific for more oxidized forms of albumin should be investigated in further studies.

<https://www.ncbi.nlm.nih.gov/pubmed/32615564>

### **Increased Cell-Free DNA Plasma Concentration Following Liver Transplantation Is Linked to Portal Hepatitis and Inferior Survival.**

Krenzien F, Katou S, Papa A, Sinn B, Benzing C, Feldbrugge L, Kamali C, Brunnbauer P, Splith K, Lorenz RR, Ritschl P, Wiering L, Ollinger R, Schoning W, Pratschke J, Schmelzle M.

*J Clin Med* 2020; 9(5); 1543

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#### **Summary**

Donor organ quality is crucial for transplant survival and long-term survival of patients after liver transplantation. Besides bacterial and viral infections, endogenous damage-associated molecular patterns (DAMPs) can stimulate immune responses. Cell-free DNA (cfDNA) is one such DAMP that exhibits highly proinflammatory effects via DNA sensors. This study measured cfDNA after liver transplantation and found elevated levels when organs from resuscitated donors were transplanted. High levels of cfDNA were associated with high C-reactive protein, leukocytosis as well as granulocytosis in the recipient. In addition to increased systemic immune responses, portal hepatitis was observed, which was associated with increased interface activity and a higher numbers of infiltrating neutrophils and eosinophils in the graft. In fact, the cfDNA was an independent significant factor in multivariate analysis and increased concentration of cfDNA was associated with inferior 1-year survival. Moreover, cfDNA levels were found to be decreased significantly during the postoperative course when patients underwent continuous veno-venous haemofiltration. In conclusion, patients receiving livers from resuscitated donors were characterised by high postoperative cfDNA levels. Those patients showed pronounced portal hepatitis and systemic inflammatory responses in the short term leading to a high mortality.

<https://www.ncbi.nlm.nih.gov/pubmed/32443763>

### **Effects of Circulating HMGB-1 and Histones on Cardiomyocytes-Hemadsorption of These DAMPs as Therapeutic Strategy after Multiple Trauma.**

Weber B, Lackner I, Baur M, Fois G, Gebhard F, Marzi I, Schrezenmeier H, Relja B, Kalbitz M.  
*J Clin Med* 2020; 9(5): 1421

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## Summary

The aim of the study was to determine the effects of post-traumatically released nuclear proteins (High Mobility Group Box-1 protein (HMGB1)) and extracellular histones on cardiomyocytes (CM). The authors also evaluated a therapeutic option to capture circulating histones after trauma, using CytoSorb hemadsorption to treat CM dysfunction. The results of the *in-vitro* study show clearly that both HMGB-1 and extracellular histones altered the calcium handling and reduced the cell viability as well as the mitochondrial respiration of human cardiomyocytes. A specially adapted CytoSorb adsorber was applied either directly to eliminate exogenous extracellular histones *in-vitro* or to remove endogenous circulating histones from blood samples obtained from the trauma patients. CytoSorb significantly reduced the histone concentrations *in-vitro*, depending on the dosage, as well as *ex-vivo* in plasma samples from injured patients. In summary, damage associated molecular patterns (DAMPs) such as HMGB-1 and extracellular histones impair human CM *in-vitro*. Hemadsorption as with CytoSorb could be a therapeutic option to reduce high concentrations of these DAMPs thereby lessen the early myocardial damage post trauma.

<https://www.ncbi.nlm.nih.gov/pubmed/32403440>

## In-Vitro Sorbent-Mediated Removal of Edoxaban from Human Plasma and Albumin Solution

Angheloiu AA, Tan Y, Ruse C, Shaffer SA, Angheloiu GO.

*Drugs R D* 2020; 20(3): 217 - 23

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## Summary

Based on previous experience of sorbent-mediated ticagrelor, dabigatran, and radiocontrast agent removal, the authors tested the effect of two 40-ml sorbent columns (containing either CytoSorb or Porapak Q – a non-clinically available polymer) on the removal of edoxaban, a direct oral anticoagulant acting reversibly on factor Xa and being widely used in patients with atrial fibrillation. 100 mL of edoxaban solution was circulated during six (3 for each adsorber) first-pass cycles using human plasma (2 samples) and 4% bovine serum albumin solution (4 samples) as drug vehicles. Drug concentration was measured by liquid chromatography-tandem mass spectrometry. The average edoxaban concentration decreased from 407 ng/mL to 3.3 ng/mL ( $p = 0.017$ ), for a removal rate of 99% across all six samples. The drug concentrations with CytoSorb were undetectable if the cycle time was 60 mins. The authors conclude that sorbent-mediated technologies (including CytoSorb) may represent a viable pathway for edoxaban removal from human plasma or albumin solution.

<https://www.ncbi.nlm.nih.gov/pubmed/32415538>

## Bioassay for Endothelial Damage Mediators Retrieved by Hemoadsorption

Denzinger M, Staendker L, Ehlers K, Schneider JM, Schulz T, Hein T, Wiese S, Roecker A, Gross R, Munch J, Bracht H, Barth E, Weiss M, Georgieff M, Schneider EM.

*Sci Rep* 2019; 9(1): 14522

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## Summary

Microvascular endothelial cells form the innermost layer of vessels in the cardio-vasculature, serving protective and barrier functions, and interacting with factors in the blood to mediate wound healing and the inflammatory response. When the immune system attempts to combat invading pathogens, such as in septic conditions, substantial collateral damage leads to impaired barrier function in the endothelium. This scientific *in-vitro* study was aimed at the proof of concept that endothelial-specific damage mediators are adsorbed by the CytoSorb adsorber, which could explain immediate recovery of microvascular endothelial cells' (mEC) function and rapid recovery from catecholamine-dependency and septic shock in patients. The study results demonstrated that CytoSorb is able to eliminate circulating nucleic acids (bound to an as yet undefined protein), which are considered to have a significant deleterious effect on endothelial integrity and may constitute a major danger-associated molecular pattern (DAMP) in the exacerbation of inflammation when patients experience septic shock. Hemoadsorption with CytoSorb may therefore limit endothelial damage, through the binding of these nucleic acid-bearing aggregates and thus contribute to improved endothelial barrier function in septic shock patients.

<https://www.ncbi.nlm.nih.gov/pubmed/31601835>

## **Cytokine Removal in Extracorporeal Blood Purification: An in vitro Study.**

Harm S, Schildbock C, Hartmann J.

*Blood Purif* 2020; 49(1): 33 - 43

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### **Summary**

The aim of this in-vitro study was to compare three different medical devices (CytoSorb, the high cut-off filter EMiC2 - Fresenius Medical Care, Bad Homburg, Germany - and the hemofilter HemofeelCH 1.8 - Toray, Tokio, Japan) with respect to their clearance for the cytokines interleukin-6 (IL-6), IL-8, IL-1beta, and tumor necrosis factor alpha (TNF $\alpha$ ) using a multiFiltrate machine with 1 litre human plasma for 8 hrs with samples for cytokine quantification taken at defined time points from the plasma pool. Each experiment was conducted in triplicate, and clearance was calculated for all tested cytokines. Cytosorb showed the best adsorption kinetics and highest clearance for all cytokines. The authors describe a level of protein and albumin loss with CytoSorb in this in-vitro setup, and call for further in-vitro experiments to specify the adsorptive removal of important plasma components such as hormones, coagulation factors, and immunoglobulins by membranes and adsorbents.

<https://www.ncbi.nlm.nih.gov/pubmed/31509822>

## **Removal of dabigatran using sorbent hemadsorption.**

Angheloiu AA, Angheloiu GO

*Int J Cardiol.* 2019; 293: 73 - 75

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### **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  $0.0000002$ ). In conclusion, dabigatran is robustly removed by CytoSorb, a method already proven successful for the P2Y<sub>12</sub> 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

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### **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% (1<sup>st</sup> experiment) or human albumin 5% (2<sup>nd</sup> 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 (3<sup>rd</sup> 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  $1.22 \pm 0.07$  L/h and in human albumin,  $1.29 \pm 0.08$  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, Rugeberg 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 (SIRS), and tissue damage. The released damage-associated molecular pattern 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 Purif* 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>

## **Hemoadsorption 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.

<https://www.ncbi.nlm.nih.gov/pubmed/30167561>

## **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 adsorbents. 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.

[Link to Article](#)

## **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).

[Link to Article](#)

## **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 removal rate of individual cytokines only depends on a single cytokine-polymer specific parameter ( $\Gamma_i$ ). 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  $\beta_2$ -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; Sepsis-Pathophysiology and Therapeutic Concepts**

Jarczak D, Kluge S, Nierhaus A.

*Front Med (Lausanne)* 2021; 2021: 8: 628302

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#### **Summary**

Sepsis is a life-threatening condition and a global disease burden. Despite all efforts of experimental and clinical research during the last three decades, the ability to positively influence course and outcome of the syndrome remains limited. This review provides an overview of sepsis immune pathophysiology, including acute respiratory distress syndrome, sepsis-induced acute kidney injury and cardiac dysfunction. Various therapeutic concepts covering causal therapy as well as supportive therapy are then discussed with a section on the role of adsorption techniques and in particular CytoSorb. Immunotherapies and immunoglobulins are also described before, finally, the role of artificial intelligence in sepsis is briefly explored. In the summary the authors note that the previous approach of using exclusively anti-inflammatory therapies has been disappointing, and that the

investigation of strategies that aim to re-balance the profound immune dysregulation during sepsis and septic shock seems to be a promising goal.

<https://www.ncbi.nlm.nih.gov/pubmed/34055825>

## **Extracorporeal Cytokine Adsorption Therapy As a Preventive Measure in Cardiac Surgery and As a Therapeutic Add-On Treatment in Sepsis: An Update Systematic Review of Comparative Efficacy and Safety**

Goetz G, Hawlik K, Wild C.  
*Crit Care Med 2021; epub*

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### **Summary**

In this systematic review of cytokine adsorption, four databases (Medline, Embase, Cochrane Library, and the European Network for Health Technology Assessment) were searched on December 2019, and any randomized controlled trials and prospective studies with a concurrent control in patients with sepsis or undergoing cardiac surgery were included. Results showed for the preventive treatment of extracorporeal cytokine adsorption therapy in cardiac surgery, very low-quality inconclusive evidence for mortality, length of intensive care stay, and length of hospitalization. Very low-quality inconclusive evidence was found for (serious) adverse events. For the therapeutic treatment of extracorporeal cytokine adsorption therapy in patients with sepsis/septic shock, the authors found very low-quality inconclusive evidence for mortality up to 60-day follow-up, organ function and length of stay in the ICU. Very low-quality inconclusive evidence was again found for (serious) adverse events. The authors strongly recommend that well-powered studies with patient-relevant endpoints be encouraged. They note that it is also potentially a wrong interpretation of the evidence to discredit the additive measure fully, as absence of evidence of effect should not be confused with evidence of absence, so evidence of no effect.

<https://www.ncbi.nlm.nih.gov/pubmed/33935160>

## **Effect of Extracorporeal Blood Purification on Mortality in Sepsis: A Meta-Analysis and Trial Sequential Analysis**

Snow TAC, Littlewood S, Corredor C, Singer M, Arulkumaran N  
*Blood Purif 2020; epub*

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### **Summary**

The objective of this study was to conduct a meta-analysis and trial sequential analysis (TSA) of published randomized controlled trials (RCTs) to determine whether mortality benefit exists for extracorporeal blood purification techniques in sepsis. Thirty-nine RCTs were identified, including 2,729 patients. Fourteen studies used hemofiltration (n = 789), 17 used endotoxin adsorption devices (n = 1,363), 3 used nonspecific adsorption (n = 110), 2 used cytokine removal (CytoSorb) (n = 117), 2 used coupled plasma filtration adsorption (CPFA) (n = 207), 2 combined hemofiltration and perfusion (n = 40), and 1 used plasma exchange (n = 106). Using conventional meta-analysis, hemofiltration, endotoxin removal devices and nonspecific adsorption devices were associated with mortality benefit, however, the use of TSA revealed that, based on the number of existing patients recruited for RCTs, neither hemofiltration, endotoxin removal devices, nor nonspecific adsorption devices were associated with mortality benefit. Due to the low number of studies/patients, TSA was not performed for the two CytoSorb studies. The authors conclude that there are inadequate data for any technique at present to conclude that the use of extracorporeal blood purification techniques in sepsis is beneficial. Further adequately powered RCTs are required to confirm any potential mortality benefit, which may be most evident in patients at greatest risk of death.

<https://www.ncbi.nlm.nih.gov/pubmed/33113533>

## **(Hemoadsorption for blood purification - incomparability of the clinically offered methods) Original Article in German. English or Spanish translations available on request**

Krenn CG and Steltzer H  
*Med Klin Intensivmed Notfmed 2021; 16(5):449-453*

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### **Summary**

In this review article, the authors highlight the different aspects between hemoadsorption products on the market and take a critical look at the available evidence. Technical features, applications specific characteristics and existing evidence of the adsorption technologies including CytoSorb® (CytoSorbents

TM Inc., Monmouth Junction, NJ, USA), Jafron® HA series (Jafron Biomedical Co., Guangdong, China) and the Biosky® MG series (Biosun® Medical Technology Co., Foshan City, Guangdong Province, China) were analysed. A comprehensive analysis of these criteria showed that there are significant differences between the available technologies in terms of materials used, adsorption characteristics, application and available data on safety and clinical experience. Furthermore, it became clear that for blood purification technologies not only their efficacy should be considered in the light of an effect price/performance ratio, but also, and in particular, the clinical safety of the individual processes is of crucial importance. Among the technologies analyzed, CytoSorb currently represents, according to the authors, the best investigated and clinically most established procedure. In addition, it should be noted that not only clinical results, but especially also safety-relevant aspects are not transferable between the products due to the technically different procedures.

<https://www.ncbi.nlm.nih.gov/pubmed/32583037>

### **Hemoadsorption efficacy for uncomplicated high-risk cardiac surgery.**

Redant S, Legrand M, Langman Y, Aguilar AG, Angoulvant F, Kaefer K, De Bels D, Attou R, Kashani K, Honore PM.

Crit Care 2019; 23(1): 343

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#### **Summary**

In this letter the authors comment on the paper by Poli et al., Crit Care 2019; 23(1): 108 which, whilst it didn't show a clinical or laboratory benefit, states that there was no association with any complications of intraoperative CytoSorb use either. They note that the perioperative peak levels of interleukins in the patients were low, which may explain why there was no obvious benefit. They then list a number of publications from various CytoSorb application fields in patients with higher levels of interleukins, which showed a positive clinical course with an improvement in hemodynamic parameters such as mean arterial pressure, cardiac index, and need for catecholamines. Finally they state that the patients who will most likely benefit most from CytoSorb are those with a significant systemic inflammatory response, and agree with the authors that the device should be tested in patient populations with high levels of circulating cytokines, such as IL-6.

<https://www.ncbi.nlm.nih.gov/pubmed/31684994>

### **Ticagrelor Removal by CytoSorb® in Patients Requiring Emergent or Urgent Cardiac Surgery: A UK-Based Cost-Utility Analysis**

Javanbakht M, Trevor M, Rezaei Hemami M, Rahimi K, Branagan-Harris M, Degener F, Adam D, Preissing F, Scheier J, Cook SF, Mortensen E.

*PharmacoEconomics - Open* 2020; 43(2): 307 - 19

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#### **Summary**

Acute coronary syndrome patients receiving dual antiplatelet therapy who need emergent or urgent cardiac surgery are at high risk of major bleeding, which can impair postoperative outcomes. CytoSorb has been demonstrated to remove ticagrelor, one of these antiplatelet therapies, from blood during on-pump cardiac surgery. The aim of this study was to evaluate the cost utility of intraoperative removal of ticagrelor (using CytoSorb) versus usual care among patients requiring emergent or urgent cardiac surgery in the UK. A de novo decision analytic model was developed to estimate the short- and long-term costs and outcomes. Results from randomised clinical trials and national standard sources such as National Health Service (NHS) reference costs were used to inform the model. Results of the model calculations showed that in emergent cardiac surgery, intraoperative removal of ticagrelor using CytoSorb was less costly (£12,933 vs. £16,874) and more effective (0.06201 vs. 0.06091 quality-adjusted life-years) over a 30-day time horizon than cardiac surgery without prior natural washout of ticagrelor. For urgent cardiac surgery, the use of CytoSorb was less costly than any of the three comparators (delaying surgery for natural washout without adjunctive therapy, adjunctive therapy with short-acting antiplatelet agents, or adjunctive therapy with low-molecular-weight heparin). Results showed that CytoSorb has a high probability of being cost saving (99% in emergent cardiac surgery and 53–77% in urgent cardiac surgery, depending on the comparators). Cost savings derive from fewer transfusions of blood products and re-thoracotomies, and shorter stay in the hospital/intensive care unit. Therefore the implementation of CytoSorb as an intraoperative intervention for patients receiving ticagrelor undergoing emergent or urgent cardiac surgery is a cost-saving strategy, yielding improvement in perioperative and postoperative outcomes and decreased health resource use.

<https://www.ncbi.nlm.nih.gov/pubmed/31620999>

## **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; 48(3):203-214

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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 adsorbents, 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; 48(3):196 - 202

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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

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### 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 Friessecke 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.

[Link to Article](#)

## **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 glycocalyx, 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.

<https://www.ncbi.nlm.nih.gov/pubmed/29732183>

## **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- $\alpha$ ) and interleukin-1beta (IL-1 $\beta$ ), 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 $\beta$ , IL-6, IL-8, IL-10, and TNF- $\alpha$ . 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 Anesthesiol 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, hemoadsorption, 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>