

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

1.1. Studies

1.1.2. Cardiac surgery

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 Apr 9;20(1):96.

1.2. Case series

1.2.1. Sepsis

Observations in early vs. late use of CytoSorb® haemadsorption therapy in critically ill patients

Kogelmann K, Druener M, Jarczak D
Critical Care 2016, 20(Suppl 2):P195

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

Laddomada T, Doronzio A, Balicco B
Critical Care 2016, 20(Suppl 2):P193

1.2.2. Cardiac surgery

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; 00(00): 000-000

1.3. Case reports

1.3.3. Liver

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

2. Pre-clinical data

2.2. In vitro data

In vitro adsorption of a broad spectrum of inflammatory mediators with CytoSorb® hemoadsorbent polymer beads

Gruda et al.
Critical Care 2016, 20(Suppl 2):P194

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
Critical Care 2016, 20(Suppl 2):P192

1. Clinical data

1.1. Studies

1.1.1. Sepsis

1.1.2. Cardiac surgery

NEW: 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 Apr 9;20(1):96.

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Summary:

Objective of this first blinded, randomized and controlled single-center trial in 46 adult patients undergoing elective open heart surgery (coronary artery bypass graft [CABG], valve surgery, 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) on changes of pro- and anti-inflammatory cytokines levels, inflammation markers, and differences in patients' perioperative course. The authors did not find any reduction of the pro-inflammatory response in 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 also in the control group. The use and installation of the CytoSorb adsorber in a CPB circuit were technically feasible, and no adverse device-related side effects occurred. The results also show that albumin and platelet levels are not significantly affected by CytoSorb. There is 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 Mar 12;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 and CytoSorb promises to attenuate this inflammatory response. Aim of the single-centrerandomised, two-arm, patient-blinded RECCAS trial is to assess the efficacy of intraoperative CytoSorb usage during cardiopulmonary bypass (CPB) to reduce the proinflammatory 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 patients at high risk. 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

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 2/2014

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Summary:

In this **retrospective observational study** in **40 patients** undergoing a major cardiosurgical procedure with the application of a Cardio-Pulmonary-Bypass (CPB) (n=20 with CPB, n=20 with CPB and additionally implemented CytoSorb-adsorber into the circulation) the hypothesis was tested, whether the intraoperative treatment with CytoSorb has a positive effect on the developing post-operative SIRS. Results show, that CytoSorb contributes to a significant reduction of post-operative SIRS in those patients. This study further emphasizes the reliability and safety of CytoSorb also in the setting of cardio surgery.

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

1.1.3. Other indications

International registry on the use of the CytoSorb-Adsorber in ICU patients (NCT02312024)

Schein M, Bahr V, Reißner F, Jakob M, Schumacher U, Brunkhorst FM
Infection. 2015 Aug;43Suppl 1:1-73. Abstract No. 125

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Summary:

This article gives an overview on the objectives and methods of the currently implemented international CytoSorb registry.

<http://link.springer.com/article/10.1007%2Fs15010-015-0827-1>

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 Jan;36(1):268-72

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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 brain-dead humans (**n=8**).

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

1.2. Case series

1.2.1. Sepsis

NEW: Observations in early vs. late use of CytoSorb® haemadsorption therapy in critically ill patients

Kogelmann K, Druener M, Jarczak D
Critical Care 2016, 20(Suppl 2):P195

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Summary:

Aim of this case study conducted in 14 critically ill patients was to show the effectiveness of CytoSorb treatment used as adjunctive therapy. Increased survival occurred if treatment with the hemadsorption filter was started early (<48 h after diagnosis of septic shock) and patients who had a greater delay in start of therapy (>48 h after diagnosis of septic shock) had poor outcome. Start of CytoSorb therapy in nonsurvivors was by far later than in survivors. After CytoSorb therapy a pronounced decrease of catecholamine demand (Norepinephrine µg/h vs. thereby achieved MAP) was observed with catecholamine demand decreasing 10-fold. Blood lactate level was divided into halves. These observations implicate that a preferably early start of therapy not later than 24 hours after diagnosis of septic shock / severe SIRS is crucial for survival.

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

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

Laddomada T, Doronzio A, Balicco B
Critical Care 2016, 20(Suppl 2):P193

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Summary:

In this case series in 8 patients with severe sepsis and septic shock treated with CytoSorb the authors analyzed the influence of CytoSorb on clinical outcomes such as mean arterial pressure (MAP), vasopressors need and inflammatory markers, like procalcitonin (PCT). There was an overall improvement of MAP with a rapid reduction in vasopressors dosages. Moreover, CytoSorb treatment in combination with CRRT was associated with a marked decrease of PCT levels and an improvement in renal function. In non-survivors, MAP was hard to stabilize and decreased and there was an aggravation in overall patients' conditions. The authors conclude that a timely use of CytoSorb in combination with the standard therapy could have benefits in improving patients' hemodynamic and helping a more rapid stabilization. However, more in vivo studies are needed to confirm these results.

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

Case study of 8 Patients with multiple organ failure treated additionally with Cytosorbentshaemadsorption as adjunctive therapy in septic shock and severe SIRS in cardiac failure

Kogelmann K, Drüner M, Jarczak D

Infection. 2015 Aug;43Suppl 1:1-73. Abstract No. 58

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Summary:

In this **case series** the authors aimed to investigate the effectiveness of CytoSorb treatment **in 8 patients** with sepsis/SIRS and multiple organ failure. They found a pronounced decrease in catecholamine demand and distinct tendency in decrease of blood lactate levels during the treatment period and within 72 h after CytoSorb therapy. However, no significant changes for SOFA-Score nor SAPS II-Score were detected. Importantly, compared with overall survival of about 45 % in severe sepsis including septic shock the authors could find a survival of 62.5 % in these patients. Treatment with CytoSorb was safe and without any noticed side effects.

<http://link.springer.com/article/10.1007%2Fs15010-015-0827-1>

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

Morris C, Gray L, Giovannelli M

Journal of Intensive Care Society 0(0)

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Summary:

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

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

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

Sathe P, Sakhavalkar P, Kumar S, Choudhary S

Critical Care 2015, 19(Suppl 1): P130

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Summary:

In this **retrospective case series in 19 ICU patients** treated with standard of care plus CytoSorb as adjuvant therapy the authors intended to analyze clinical safety, selection of a subgroup of patients where CytoSorb could be used, selection of timing for initiation, number of CytoSorb devices required per patient, and selective markers to identify its initiation. All of the patients had a high predicted mortality (APACHE II >17, SOFA >11). Four patients could be saved 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 single application of CytoSorb therapy. Of those patients who died, the majority (n = 11) could be 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 well-designed studies are needed to clarify the role of CytoSorb in patients with MOF/septic shock.

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

1.2.2. Cardiac surgery

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; 00(00): 000-000

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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>

1.2.3. Other indications

1.3. Case reports 1.3.1. Sepsis

Hemoadsorption in Infection-Associated Rhabdomyolysis.

Suefke S, Sayk F, Nitschke M

TherApher Dial. 2016 Mar 17

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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. In the further course the patient developed fulminant manifest pneumogenic sepsis and acute respiratory distress syndrome (ARDS) with massive 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 massive 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. 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. The patient was discharged at day 13 with ongoing renal failure and need for renal replacement therapy. 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>

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

van der Linde GW, Grootendorst A

Neth J Crit Care. 24(2): 27-29

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Summary:

This **case study** reports on a 17-year-old male who reported to the pediatrician at 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 for 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 to 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 after the start, 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 diminished 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 the CytoSorb, but they feel that his stay in our ICU might have been shortened by the CytoSorbadsorber

http://njcc.nl/sites/default/files/pdf/case-report4_0.pdf

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

Traeger K, Schuetz C, Fischer G, Schroeder J, Skrabal C, Liebold A, Reinelt H
Case Reports in Critical Care, Volume 2016 (2016)

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Summary:

This case study reports on a 45-year-old male who was admitted to the hospital with a small bowel obstruction due to torsion and immediately scheduled for surgical intervention. At anesthesia induction, the patient aspirated and subsequently developed a severe SIRS with ARDS and multiple organ failure requiring the use of ECMO, CRRT, antibiotics, and low dose steroids. Due to a rapid deterioration in clinical status and a concurrent surge in inflammatory biomarkers, CytoSorb was added to the CRRT blood 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 patient could be discharged to a respiratory weaning unit where successful respiratory weaning could be achieved later on. The authors attribute the clinical improvement to the rapid control of the hyperinflammatory response and the reduction of inflammatory mediators using a combination of CytoSorb and these other therapies. CytoSorb treatment was safe and well tolerated, with no device-related adverse effects observed.

<http://www.hindawi.com/journals/cricc/2016/9852073/>

Combination ECMO and cytokine adsorption therapy for severe sepsis with cardiogenic shock and ARDS

Lees N, Rosenberg A, Popov A, Hurtado-Doce A, Jones J, Marczin N, Simon A
Crit Care Med. 2015 Dec;43(12 Suppl 1):311

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Summary:

In this report the authors describe the case of a 33-year-old previously fit female, 5 months postpartum, who presented with shock, ARDS, metabolic acidosis and neutropenia as well as a severely impaired, non-dilated left ventricle. Treatment for community-acquired pneumonia was initiated including mechanical ventilation and significant vasopressor support. Venoarterial ECMO was started due to respiratory and cardiac failure, lactic acidosis and worsening organ

function. Additionally, CytoSorb was added to the hemofilter circuit and antibiotics were administered. Treatment resulted in improved oxygenation, gradual resolution of lactic acidosis and most notably withdrawal of vasopressor support within 12 hours. The patient fully recovered and was asymptomatic two months later. This case demonstrates the novel and successful use of ECMO and cytokine removal in severe S.aureus sepsis with ARDS and cardiomyopathy and adds to the evidence showing cytokine adsorption as a compelling adjuvant therapy in severe sepsis.

<http://www.ncbi.nlm.nih.gov/pubmed/26570899>

Intermittent use of cytokine adsorption in combination with CRRT in a patient with necrotising pancreatitis, septic shock and MOF

Emmerich M, Zietlow S, Tiesmeier J

Infection. 2015 Aug;43Suppl 1:1-73. Abstract No. 72

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Summary:

This **case study** reports on a 60-year-old female patient with septic shock and MOF after cholecystectomy which was complicated by massive aspiration during emergency gastroscopy and necrotizing pancreatitis requiring necrosectomy. On admission to ITU, the patient was in respiratory and acute renal failure and exhibited high needs for vasopressors and fluids. Following initial stabilization, colonic perforation and renewed septic shock occurred on day 13 post-operation, necessitating colectomy and further necrosectomy on day 14. Lung-protective ventilation and hemodynamic stabilization, antibiotic therapy and CRRT were started in the further course with a first application of Cytosorb for 48 h on day 2 post-operation and a second session for 96 h from day 13 post-operation. During the first 48 h of hemoadsorption, norepinephrine requirements decreased from 0.13 to 0.00 mcg/kg/min. During the second use of CytoSorb the initial norepinephrine need was 0.13 mcg/kg/min and rose to a maximum of 0.43 mcg/kg/min twelve hours post-operatively, however infusion could be stopped later after 40 h. The general condition of the patient improved dramatically despite further multiple operations for intra-abdominal bleeds, necrosis and wound healing impairment. CRRT could be stopped 11 days after the second CytoSorb treatment and two days later the patient was successfully weaned from ventilation. The authors conclude that they could successfully use intermittent cytokine hemoadsorption to manage a patient with recurrent septic shock, necrotizing pancreatitis and MOF. Supplementing the standard treatment for sepsis with two applications of hemoadsorption facilitated rapid hemodynamic stabilization. Cytosorb was easy to use and no adverse effects were observed.

<http://link.springer.com/article/10.1007%2Fs15010-015-0827-1>

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 ArtifOrgans. 2015 Sep 18;38(8):461-4

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Summary:

This **case study** reports on 72-year-old male patient with periodically recurring infectious episodes who was admitted with the suspicion of urosepsis. In the following hours his hemodynamic situation deteriorated markedly, exhibiting respiratory-metabolic acidosis, elevated inflammatory marker plasma levels, a severely disturbed coagulation, increased retention parameters, liver dysfunction, and confirmation of bacteria and leucocytes in urine. After admission to the ICU in a state of septic shock the patient received renal support with additional hemoadsorption using CytoSorb. Three CytoSorb sessions were run during the following days. The first and consecutive second session resulted in a reduction of procalcitonin, C-reactive protein and bilirubin and a markedly reduced need for vasopressors while hemodynamics improved significantly (i.e., cardiac index, extravascular lung water). Due to a recurring inflammatory "second hit" episode, another session with CytoSorb was run, resulting in a marked decrease in leukocytosis and liver (dys)function parameters. The rapid hemodynamic stabilization with reduction of vasopressor needs within hours and reduction of the capillary leakage as well as a 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. Despite the promising results of CytoSorb application in his patient, 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 May;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 that 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 from 32 before to 8 after day 3 of therapy, while IL-6 levels were reduced from 1356.3 pg/ml before to 26.12 pg/ml after the last session. Since the patient started to deteriorate clinically on the 5th day onwards despite on-going supportive care, the authors bring up a possible immunosuppressive effect and express their concern whether CytoSorb therapy could be involved. They feel that randomized controlled trials are necessary to check the risk-benefit ratio of hemoadsorption therapy in severe 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 Jul;70(7):2169-71

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Summary:

This **case study** reports on a patient with an excessive inflammatory response, septic shock and MOF who was admitted to the ICU. Initial laparotomy revealed an ischemic bowel with peritonitis requiring immediate jejunum and colon segmental resection and ileotransverse colostomy. Antibiotic treatment with Meropenem was started immediately and with Linezolid 5 hours after admission, both administered intravenously with short infusion times (15-60 min). Due to persisting excessive cytokine storm, a CytoSorb adsorber was repeatedly used (4 times over 96 hours). Therapy of septic shock including surgery, antibiotic treatment and CytoSorb resulted in a substantial improvement of the patient's condition including improvement in 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 (decay of IL-6 from 563.000 pg/ml on day 1 to 19.400 pg/ml on day 4) and safe (levels of meropenem and linezolid well above the lower therapeutic range). 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 a potential adsorption, however also due to the effects of the critical illness itself. This is the first time an in vivo pharmacokinetic monitoring of Linezolid and Meropenem during treatment with CytoSorb is described. Applying this regimen of dosing for Linezolid and Meropenem no negative impact on the effectiveness of antibiotic therapy was detected.

The authors suggest therapeutic drug monitoring wherever possible and if not available, high loading doses or shorter intervals of administration should be used to achieve adequate antibiotic levels. However, further studies are needed to determine the effect of CytoSorb on antibiotic levels.

<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 Mar 6;38(2):113-6

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Summary:

This case study reports on a 39-year-old patient presenting at a hospital with fulminant ARDS 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 hemoadsorption device was therefore installed in the CVVH circuit resulting in a decrease of 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 to improve 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 to have septic (urosepsis) with multi-organ dysfunction (ARDS, AKI, arterial hypotension) and a low perfusion state. 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 in 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 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 haemodynamic profile with a stable cardiac output and normalization of systemic vascular resistance index and decreased vasopressor requirements. The technology was simple to use and could be easily added on conventional CVVH machines. The therapy was well tolerated with no adverse effects. The timing of CytoSorb whether early (after onset of SIRS) or late (after onset of organ dysfunction) use of this novel therapy, has still to be established.

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

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

Hetz H, Berger R, Recknagel P, Steltzer H.
Int J Artif Organs. 2014 May;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 forearm fracture. After surgical wound care by osteosynthesis the patient developed surgical wound infection progressing to necrotizing fasciitis with additional proven infection from β -hemolytic streptococcus. The patient went into septic shock exhibiting a full picture of a MODS. Therefore, the patient was treated with CytoSorb therapy over a period of four days, resulting in a significant reduction of IL-6 and an overall improvement of the patient's condition. In this case, CytoSorb seems to be an interesting and safe extracorporeal therapy to stabilize and bridge septic patients to surgery or recovery.

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

Hemoadsorption using Cytosorb beads (Cytosorbents) in acirrhotic patient with septic multiorgan failure

Gruber A, Firlinger F, Lenz K, Clodi M
Infection (2013) 41 (Suppl 1):S1–S90; Abstract No. 056

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Summary:

In this **case study** a 37 year old patient with alcoholic liver cirrhosis and occurring septic shock with multiorgan failure due to bilateral pneumonia (staphylococcus aureus) was successfully treated with CytoSorb. The authors found an immediate change in organ function with stabilization of hemodynamics, as well as pulmonary and renal function.

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

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

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Summary:

This **case study** reports on a 46 old female with hypodynamic septic shock and documented candidemia infection. CRRT was started in combination with CytoSorb therapy. Within 24 h of hemoadsorption, vasopressor and inotropic support could be withdrawn. Several inflammatory mediators (e.g. IL-6, 8, 10) could be reduced significantly. Interestingly, the authors also found an almost perfect immunological reconstitution of a variety of immune parameters including HLA-DR.

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

Mitzner SR, Gloger M, Henschel J, Koball S
Blood Purif. 2013;35(4):314-5.

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Summary:

This **case study** reports on an 80 year old male diagnosed of having 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 CytoSorbadsorber for 24 hours.

In the further course, plasmatic IL-6 and other markers of inflammation as well as need for vasopressors could be reduced drastically while treatment was safe and well tolerated.

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

1.3.2. Cardiac surgery

1.3.3. Liver

NEW: 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

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Summary:

In this report the authors present the case of a 46-year-old man with primary graft nonfunction after liver transplantation who underwent emergency retransplantation with an ABO-incompatible graft. A severe inflammatory response syndrome (SIRS) was noted in the perioperative period of retransplantation. The patient was successfully treated for this condition 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 of 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 nonfunction undergoing emergency retransplantation.

<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 Dec;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 MOF and was listed for highly urgent liver transplantation. Since existing liver support techniques (MARS treatment) for bridging while awaiting for liver transplantation had no effect, SPAD in

combination with CytoSorb was applied resulting in a marked decrease of IL-6, bilirubin as well as a reduction of vasopressor need. Orthotopic liver transplantation could be successfully performed on the 4th day on ICU. CytoSorb treatment was safe and well-tolerated, without any adverse events occurring. Therefore, 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

Cytosorb™ in a patient with legionella-pneumonia associated rhabdomyolysis

Wiegele M, Krenn CG.

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

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Summary:

This **case study** reports on a 44-year-old man presenting with ongoing fever and impaired general condition for more than 5 days. Respiratory insufficiency finally led to hospitalization and rapid admission to an ICU with intubation and ventilatory support. Chest x-ray and computed tomography confirmed the clinical diagnosis of ARDS. Investigation of patient's specimen further revealed infection with *Legionella pneumophila*. Despite administration of antibiotics, liver enzymes and parameters of renal function deteriorated in parallel within the following days, indicating a trend toward multiple organ failure. Creatine kinase and myoglobin sera levels increased in combination with reduced urine excretion. Therefore Cytosorb™ treatment was run in stand-alone application form on day 6 after admission. Within 8 hours, myoglobin levels decreased from 18,390 to 10,020 ng/ml and in a second cycle 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 have been observed. This is the first time that a decrease of myoglobin levels following application of Cytosorb™ could be demonstrated *in vivo*.

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

1.3.5. Other indications

Case report of 1 Patient with multiorgan failure due to severe SIRS in cardiac failure treated additional with Cytosorbentshaemadsorption as adjunctive therapy

Kogelmann K, Drüner M, Jarczak D

Infection. 2015 Aug;43Suppl 1:1-73. Abstract No. 126

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Summary:

This **case study** reports on a patient with severe SIRS and multiple organ failure in cardiogenic shock due to refractory cardiac arrhythmia, diffuse hypokinesia and an ejection fraction of ~45 % with a heart rate of 36 bpm. After 24 hours of conventional treatment, CytoSorb therapy and CRRT was initiated due to high and stable catecholamine support associated with a persistent renal

failure. During CytoSorb therapy the authors found a decrease in catecholamine demand of more than 95 % and 72 h after therapy the patient had been free of catecholamines. SOFA Score did not change while SAPS II-Score decreased to 50% of its initial value. Blood lactate, creatinine and liver enzymes decreased markedly and normalized after 2 weeks. Treatment using CytoSorb adsorption in this patient had shown great effect, been safe and without any noticed side effects. The authors note that CytoSorb therapy was helpful even in a patient with severe cardiac failure and thereby initiated severe SIRS.

<http://link.springer.com/article/10.1007%2Fs15010-015-0827-1>

2. Pre-Clinical data

2.1. Animal models

Evaluation of the CytoSorbhemoadsorptive 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 Nov;44(5):487-95

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Summary:

In this *in vivo* study in a porcine model of smoke inhalation and burn injury the authors aim 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 a 40% total body surface area deep burn and observed for 72 hours or death. The animals were randomized to hemoadsorption treatment (n=9) or a 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 bronchoalveolar lavage fluid and also in circulating blood before and after the adsorbing column resulting in a significant removal of IL-1b, IL-6, IL-10 and myoglobin across the device mainly during the first run, while systemic cytokine or myoglobin serum concentrations did not change.

The authors conclude that further investigations are needed to optimize the efficiency of mediator clearance to impact 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 Jul 3;18(4):R141

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Summary:

In this *in vivo* study in a rat model of polymicrobial abdominal sepsis the authors investigate whether the removal of chemokines from the plasma changes chemokine gradients and subsequently enhances leukocyte localization into the infected compartment, and away from healthy tissues.

The results of the study nicely demonstrate 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 Dec;45(4):220-7.

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Summary:

This *in vivo* study in a porcine model undergoing cardiopulmonary bypass investigates the role of hemoadsorption using CytoSorb on left ventricular function, cytokine removal, hemodynamics and noncardiac 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 Jan;145(1):215-24

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Summary:

This *in vivo* study investigates the effect of hemoadsorption (using 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 Med. 2012 Dec 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 investigates whether hemoadsorption (using CytoSorb) is able to reduce, relocalize 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 Feb;81(4):363-9

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Summary:

This *in vivo* study in a subacute rat model of intraabdominal sepsis (cecal ligation puncture) investigates the effect of hemoadsorption (using CytoSorb®) that does not exert its positive effect as a direct reduction of cytokine plasma concentrations. Levels of cytokines in this model are low, resulting in low

removal by CytoSorb® (a concentration-dependent technology). However, 7-day survival is significantly improved in the treatment group, with a reduction in latent organ injury. Cytokine removal (TNF α , IL-1 β , IL-6 and IL-10), organ injury/dysfunction (HMGB-1, ALT, and creatinine), production of cytokines (via NF κ B binding in neutrophils) and 7-day survival is analyzed. The effect of exchange blood transfusions (between CytoSorb-treated and sham animals) on IL-6 levels and 7-day mortality is 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 May;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 explore the effect of hemoadsorption (using CytoSorb) on cytokine adsorption (TNF α , IL-1 β , IL-6 and IL-10), on mean arterial pressure (MAP) and short-term survival.

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

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

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

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Summary:

This *in vivo* study in a lethal endotoxemic rat model (in septic shock) investigates 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 characterizes 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 is relatively unaffected by a variety of physical conditions.

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

2.2. In vitro data

NEW: In vitro adsorption of a broad spectrum of inflammatory mediators with CytoSorb® hemoadsorbent polymer beads

Gruda et al.

Critical Care 2016, 20(Suppl 2):P194

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Summary:

This study set out to quantify the ability of the CytoSorb polymer to adsorb a broad selection of inflammatory pathogen-associated molecular pattern molecules (PAMPs), damage-associated molecular pattern molecules (DAMPs) and cytokines from whole blood in a single compartment, in vitro recirculation system.

Hemoperfusion of whole blood through porous polymer bead devices for five hours removed substantial quantities of a broad spectrum of DAMPS, PAMPS and cytokines (S100A8, complement C5a, procalcitonin, HMGB-1, MIP1- α , IL-6, IFN- γ , TNF- α , Staph enterotoxin TSST-1 and aflatoxin B1). Levels of the inflammatory proteins were reduced by <20% during the five hour hemoperfusion through a control device.

This study demonstrates that the CytoSorb polymer is capable of reducing a broad range of toxic DAMPS and PAMPS from blood providing a means, in addition to cytokine reduction, of reducing the uncontrolled inflammatory cascade that contributes to a maladaptive SIRS response, organ injury, multiple organ dysfunction syndrome (MODS) and death in critically ill patients. Further study to elucidate the potential clinical impact is warranted.

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

NEW: 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

Critical 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 shows the effectiveness of CytoSorb removing bilirubin, any significant loss of albumin, the resin ability to break the albumin-bilirubin complex and to adsorb irreversibly bilirubin. CytoSorb might represent a valid and simple aid in organ dysfunctions, without need of plasma separation. In vivo studies are ongoing to confirm the in vitro results.

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

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

Rimmele T, Kaynar AM, McLaughlin JN, Bishop J, Fedorchak M, Chuasuwan A, Peng Z, Singbartl K, Frederick DR, Zhu L, Carter M, Federspiel WJ, Zeevi A, Kellum JA.

Crit Care. 2013 Mar 26;17(2):R59

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Summary:

In this *ex vivo* study using human whole blood the authors test 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 Nov 4;1218(44):8013-20

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Summary:

In this work, the authors investigate *in vitro* whether competitive adsorption of serum solutes affects cytokine removal dynamics (IL-6 as representative) within the CytoSorb beads and find 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 Jul;98(1):47-53.

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Summary:

In this work performed *in vitro* the authors examine the dynamics of TNF capture within the CytoSorb beads and quantify how perturbation of TNF oligomeric structure accelerates TNF removal within the device. The authors find that dissociation of TNF into its smaller monomeric constituents significantly accelerates TNF capture rates and therefore propose strategies to promote localized TNF deoligomerization at the sorbent surface.

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

Selective improvement of tumor necrosis factor capture in a cytokine hemoadsorption device using immobilized anti-tumor necrosis factor.

DiLeo MV, Fisher JD, Burton BM, Federspiel WJ.

J Biomed Mater Res B Appl Biomater. 2011 Jan;96(1):127-33

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Summary:

In this *in vitro* study the authors test several approaches of anti-TNF antibody immobilization onto CytoSorb beads to improve capture rates of TNF.

<http://www.ncbi.nlm.nih.gov/pubmed/21086427>

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 Feb;92(2):390-6

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Summary:

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

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

Experimental validation of a theoretical model of cytokine capture using a hemoadsorption device.

DiLeo MV, Fisher JD, Federspiel WJ.

Ann Biomed Eng. 2009 Nov;37(11):2310-6

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Summary:

Goal of this *in vitro* study is to show that a mathematical model which predicts the time course of cytokine removal by a CytoSorb device can experimentally predict the rate of cytokine capture associated with key design and operational parameters of the device (e.g. initial cytokine concentration, perfusion rate through the device, and the size of the device and of its adsorbing beads).

<http://www.ncbi.nlm.nih.gov/pubmed/19680812>

A simple mathematical model of cytokine capture using a hemoadsorption device.

DiLeo MV, Kellum JA, Federspiel WJ

Ann Biomed Eng. 2009 Jan;37(1):222-9. Epub 2008 Oct 24

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Summary:

In this *in silico* study the authors present 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 (Γ_i).

The model and the theoretically calculated removal dynamics correlated well with experimental data from an *in vivo*-performed reference study (rats with endotoxemia).

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

In-Vitro Myoglobin Clearance by a Novel Sorbent System

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

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

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Summary:

Rhabdomyolysis (excessive break-down of muscle tissue due to crush injury, infection, drugs etc.) can result in acute kidney injury from myoglobinuria when the myoglobin released into the blood from damaged muscle passes through the glomerular filter and accumulates in the renal tubules.

Aim of this *in vitro* study is to investigate, whether hemoadsorption (using CytoSorb) is 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 hemoadsorption (using CytoSorb) 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 are 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 + conventional high-flux dialysis in patients with chronic renal failure. Results confirm, that removal of β_2 -microglobulin, angiogenin, leptin and IL-18 is much more effective when using combined therapy (CytoSorb+ conventional high-flux dialysis). Levels of leucocytes, thrombocytes and albumin were hardly affected.

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

Sorbents in acute renal failure and the systemic inflammatory response syndrome.

Winchester JF, Kellum JA, Ronco C, Brady JA, Quartararo PJ, Salsberg JA, Levin NW
Blood Purif. 2003;21(1):79-84

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Summary:

This study discusses the use of hemoadsorption in acute renal failure and systemic inflammatory states to reduce cytokine- and middle molecule levels. CytoSorb is discussed in detail in the context of experiments with septic rats (endotoxin model, cecal ligation and puncture model, „Kellum-experiments“) while the known advantages of CytoSorb are discussed (reduction of cytokine levels, improvement of hemodynamics and survival)

<http://www.ncbi.nlm.nih.gov/pubmed/12566666>

***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 is 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

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

Forni LG, Ricci Z, Ronco C.
SeminNephrol. 2015 Jan;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 further discuss the evidence accumulated to date and suggest possibilities for the future treatment of this entity of patients. In this context, the 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 animals studies as well as in case reports and due to its beneficial effect on chemokine gradients, which may restore chemokine 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 Sep;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 Mar;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) showed relatively negative results, attention is now drawn to new membranes and sorbents that could better eliminate massive amounts of unbound mediators in wider spectrum and also in greater magnitude

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 Dec 20;18:1363-5. doi: 10.2119/molmed.2012.00300.

●●●

Summary:

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

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

New membranes for extracorporeal blood purification in septic conditions.

Bello G, Di Muzio F, Maviglia R, Antonelli M

Minerva Anestesiol. 2012 Nov;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. Epub 2011 Feb 16

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Summary:

This review informs about the latest advances in blood purification for sepsis and how they relate to current concepts of disease. The authors further 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 like hemodynamics and oxygenation), there is an urgent need for confirming largemulticentertrialevaluatingtheabilityofthese 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>

Extracorporeal Therapies in Sepsis

Panagiotou A, Gaião S, Cruz DN

J Intensive Care Med. 2013 Sep-Oct;28(5):281-95

●●

Summary:

In this article the authors provide a concise overview of selected extracorporeal modalities (influencing the circulating levels of inflammatory mediators like cytokines and chemokines etc.) currently in clinical use (hemofiltration-, adsorption- and cell-based therapies). They also briefly introduce some new promising techniques for sepsis.

CytoSorb is discussed to effectively reduce cytokine levels mainly focussing on the Kellum *in vivo* study using the cecal ligation and puncture rat model.

<http://www.ncbi.nlm.nih.gov/pubmed/2202776>

Blood purification in sepsis: a new paradigm.

Peng Z, Singbartl K, Simon P, Rimmelé T, Bishop J, Clermont G, Kellum JA

Contrib Nephrol. 2010;165:322-8. Epub 2010 Apr 20

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Summary:

This review gives a good overview on the effects of blood purification therapies at the immunologic and cellular level.

It is discussed how therapies like high-volume hemofiltration, hemoadsorption, coupled plasma filtration adsorption and high-cutoff membranes have been improved in the meantime and adapted to the “setting” of sepsis.

www.ncbi.nlm.nih.gov/pubmed/20427984

Clinical review: extracorporeal blood purification in severe sepsis.

Venkataraman R, Subramanian S, Kellum JA

Crit Care. 2003 Apr;7(2):139-45

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Summary:

This review discusses the various modalities of extracorporeal blood purification, the existing evidence and future prospects.

Regarding CytoSorb, the authors briefly refer to the known advantages (reduction of cytokine levels, improvement of hemodynamics and survival).

<http://www.ncbi.nlm.nih.gov/pubmed/12720560>