

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

3. Background and Reviews

NEW: 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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1. Clinical data

1.1. Studies

1.1.1. Sepsis

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; epub

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Summary:

Mortality from refractory septic shock may reach 90-100% despite optimum therapy. In this study extracorporeal cytokine adsorption using CytoSorb in addition to regular therapy was studied prospectively in 20 patients with refractory shock (defined as increasing vasopressor dose required to maintain mean arterial blood pressure above 65 mmHg or increasing lactate levels despite protocol-guided shock therapy for six hours). CytoSorb® treatment was started after 7.8 ± 3.7 hours of shock therapy. Following the initiation of adsorption therapy, 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

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

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

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Abstract and article in German, abstract only in English.

Summary:

Cardiac surgical interventions using a cardiopulmonary bypass (CPB) machine induce a systemic inflammatory reaction due to activation of multiple inflammatory cascades. In the postoperative phase this can result in systemic inflammatory response syndrome (SIRS). Activation of various mediators of inflammation, 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 during cardiac surgery is evaluated. The study is being conducted as a prospective, observational pilot study to determine the clinical impact of the use of an adsorption filter (CytoSorb®) on the serum levels of IL-6, IL-8 and TNF-alpha using a CPB machine. This pilot study includes 300 patients planned for elective surgical myocardial revascularization, partitioned into 3 groups each with 100 patients with on-pump myocardial revascularization with CytoSorb®, on-pump

myocardial revascularization without CytoSorb® and off- pump myocardial revascularization. Primary outcome measures are the inflammatory response serum parameters IL-6, IL-8, TNF- alpha, complement C3/C4, leucocyte counts and C-reactive protein. Secondary outcome measures are length of intensive care unit (ICU) 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 concluding 60 % of the planned patients revealed a well- balanced group allocation of patients. In the group with CytoSorb® the 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 the standard procedure and applicable without technical difficulties. CytoSorb® reduces the cytokine load and seems to attenuate the inflammatory response.

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

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

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

Crit Care. 2016 9;20(1):96.

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Summary:

Objective of this 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 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-centre randomised, two-arm, patient-blinded RECCAS trial is to assess the efficacy of intraoperative CytoSorb usage 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 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

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 43 Suppl 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 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

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 critically ill patients with septic shock and need for renal replacement therapy. Treatment of these septic shock patients was associated with hemodynamic stabilization and a reduction in blood lactate levels. Actual mortality was lower than that predicted by the APACHE II score. This effect was more pronounced in patients where therapy was started within 24 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>

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 non-survivors 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>

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 Cytosorbents haemadsorption as adjunctive therapy in septic shock and severe SIRS in cardiac failure

Kogelmann K, Drüner M, Jarczak D

Infection. 2015; 43 Suppl 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 Cytosorb haemabsorption column as an adjunct in managing severe sepsis: initial experiences, review and recommendations

Morris C, Gray L, Giovannelli M

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

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Summary:

In this article the authors describe the use of CytoSorb hemoabsorption device in **2 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 Cytosorb haemoabsorption is mechanistically distinct from other extracorporeal therapies in sepsis and appears effective in reducing inflammatory cytokines during sepsis, much of the basic science and clinical benefits remain unclear. Suggestions for future research and how Cytosorb could be incorporated into practice are provided.

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

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

Sathe P, Sakhavalkar P, Kumar S, Choudhary S

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

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

Träger 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 2/2014

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Summary:

In this **retrospective observational study** in **40 patients** undergoing a major cardio-surgical 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>

1.2.3. Other indications

1.3. Case reports

1.3.1. Sepsis

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 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 his 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>

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 to the ED 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 CtoSorb and Septex) was continued for 72 hours in total and the patient could be discharged after 10 days. No adverse events related to the blood purification 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, Zerriouh 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 vasopressor infusions.

<http://link.springer.com/article/10.1007%2Fs10047-016-0915-8>

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

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

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Summary:

This **case study** reports on a 17-year-old male who reported 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 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 CytoSorb adsorber

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

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

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

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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/>

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 43 Suppl 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 necrostomy. 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 necrostomy 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 Artif Organs. 2015 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 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 hemadsorption 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 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 anin vivo pharmacokinetic monitoring of Linezolid and MeropenemduringtreatmentwithCytoSorbis described. Applyingthis 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 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 aCytoSorbhemoadsorption 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 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 a cirrhotic 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 multi-organ failure due to bilateral pneumonie (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 CytoSorb adsorber 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

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; epub

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Summary:

Post-infarction ventricular septal defect (VSD) remains a serious and often lethal complication of percutaneous coronary intervention. It remains unclear whether

surgery to correct this should be done immediately or delayed until after the patient is stabilized. This is a case report on the use of veno-arterial extracorporeal membrane oxygenation (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 (norepinephrine, dobutamine) and vasopressin could be significantly reduced (or stopped in the case of vasopressin) within the first 36 hours of treatment. After 4 days of treatment with ECMO and CytoSorb® therapy 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

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

Faltlhauser A, Kullmann F

Blood purification 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 the CytoSorb. In this report a 36-year-old patient with chronic viral hepatitis C and long term 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. During this time, an evaluation as to whether the patient could be listed for a liver transplantation was rejected. As a „last resort“ therapy, 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 non-existent 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 with planned discharge to his home environment, the patient subsequently developed a nosocomial pneumonia, after which the patient went into another episode of fulminant pneumogenic sepsis and died three weeks after the last CytoSorb treatment. In this case report, the treatment with combination of CRRT and hemoadsorption using 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 the authors present the case of a 46-year-old man with primary graft non-function after liver transplantation who underwent emergency re-transplantation with an ABO-incompatible graft. A severe inflammatory response syndrome (SIRS) was noted in the perioperative period of re-transplantation. 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 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 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

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. 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>

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 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

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

Mekala N and Damera S

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

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Summary:

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

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

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

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

Nephrol Dial Transplant 2017; 32(Suppl_3): SP247

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Summary:

In this case series 2 patients with 3 episodes of severe hemophagocytic lymphohistiocytosis (HLH) are treated with Cytosorb. In the first case of 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 sent on to make a full recovery. In both cases a marked decrease in IL-6 plasma levels, and vasopressor needs were the major results. Importantly, treatment was safe and well- tolerated, without any adverse events.

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

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

Schroeder I, Zoller M, Angstwurm M, Kur F, Frey L.
Int J Artif Organs 2017; epub

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Summary:

This **case report** describes a 19 yr old female who ingested 18g of venlafaxine - 240 times the daily therapeutic dose (a treatment for affective disorders) - 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 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; epub

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Summary

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

<https://www.ncbi.nlm.nih.gov/pubmed/28370393>

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

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

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Summary:

In this letter to the editor the authors describe the use of a CytoSorb in a patient with secondary hemophagocytic lymphohistiocytes (HLH) caused by CTLA-4 deficiency. CTLA-4 deficiency is 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 SIRS and multi-organ failure. Despite aggressive intervention his clinical condition rapidly worsened so a CytoSorb adsorber was added into the circuit of the hemodiafiltration. In total 4 adsorbers were used, with columns being changed every 24 hrs. Cytokine adsorption resulted in an immediate decrease in inflammatory parameters, 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, Nietzsche 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 who was admitted to hospital immediately following an explosion in the home environment with 2b-3-degree burns of a total of 60% of the body surface area. On the day of admission, he was immediately given bath therapy while he was still hemodynamically stable, with surgical wound treatment of the burned areas. Because of the severity of his burns, multiple operations were performed, with Meek transplants 1: 6 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 to induce a reduction in these parameters. The CytoSorb adsorber was used daily from the 9th - 17th treatment days and from days 32 - 52. The interleukins IL-6 and IL-10 were significantly reduced during the treatment, the catecholamine requirement was significantly reduced and circulatory stabilization could be achieved. Due to cardiopulmonary insufficiency in the context of a multiorgan failure, the patient died on the 52nd postoperative day.

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

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

Khan ZA

J Evid. Based Med. Healthc., 3(87): 4779 - 81

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Summary:

This **case study** reports on a patient with Dengue fever, septic shock and multiple organ failure (MOF). Dengue is a mosquito-borne viral disease where it is thought that elevated cytokines (tumour necrosis factor alpha - TNF- α , interleukins and interferon gamma - IFN- γ) cause damage to the endothelial cells of the capillaries that results in fluid leakage. Here a 32 year old male patient was admitted to the intensive care unit and because of multiple organ failure, he was mechanically ventilated and put on renal replacement therapy. CytoSorb was used as an adjuvant supportive therapy on days 2, 4 and 6 of admission. The patient also received multiple transfusions to address thrombocytopenia and coagulopathy. The patient showed gradual improvement with a normalization of the central nervous system, improved oxygenation status, adequate renal function and normal platelet count (APACHE score 27 before and 12 at the end of CytoSorb treatment). Liver function also improved significantly. Serum Glutamic Oxaloacetic Transaminase – GOT (AST) fell from 15,690 U/L to 156 U/L, and Serum Glutamic Pyretic Transaminase - GPT (ALT) fell from 3910 to 84 after CytoSorb treatment). The patient was discharged from ICU on day 13 and subsequently discharged. The authors note that CytoSorb® seems to be a useful and safe extracorporeal therapy option to stabilize and help dengue shock patients with MODS to recover.

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

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

Kogelmann K, Drüner M, Jarczak D

Infection. 2015 43 Suppl 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 heartrate 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

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

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

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Summary:

This study tested the safety and efficacy of cytokine adsorption during ex vivo lung perfusion (EVLP) in an animal model. Pig donor lungs were preserved for 24 hours at 4°C (to induce lung injury) and then randomly divided into 2 groups, the filter and control group (n=5 each), for a 12 hour EVLP procedure. In the filter 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 the CytoSorb beads 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 sepsis 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 CytoSorb

may reduce serum levels of inflammatory cytokines and improve cardiac function of septic rats.

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

Evaluation of the CytoSorbhemoadsorbptive 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:

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 broncho-alveolar 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 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 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 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 ThoracCardiovasc Surg. 2013 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 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, 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) 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 und 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 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;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

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

Summary:

The authors devised a method for ticagrelor removal (platelet aggregation inhibitor) from blood using Cytosorbent hemadsorption in 2 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 90% and more already after 3 - 4 hours.. CytoSorb hemadsorption was found to robustly remove ticagrelor from both BSA solutions and human blood samples.

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

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

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

Inflammation 2016 39(5): 1737 - 46

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Summary:

Endothelial activation (endothelium - tissue that acts as a barrier between the blood stream and the surrounding tissues) with excessive recruitment and adhesion of immune cells plays a central role in the progression of sepsis. In this study the authors 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. Specifically, in septic patients, blood 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 also obtained from healthy volunteers. Blood from both sets of patients (normal and septic) was then 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 (average pore sizes 15 or 30 nm) 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. Researchers found that plasma samples from sepsis 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. In conclusion, pre-incubation of the plasma samples with a polystyrene-divinylbenzene-based adsorbent (30 nm average pore size) reduced endothelial intercellular adhesion molecule-1 expression to baseline levels, resulting in significantly diminished monocyte adhesion. 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>

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

Gruda M

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>

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 in 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 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 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 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 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 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 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 37(1):222-9

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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

NEW: Extracorporeal Sorbent Technologies: Basic Concepts and Clinical Application

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

Contrib Nephrol 2017; 190: 43-57

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Summary:

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

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

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

Houschyar KS, Pyles MN, Rein S, Nietzsche I, Dusche D, Maan ZN, Weissenberg K, Philipps HM, Strauss C, Reichelt B, Siemers F.

Int J Artif Organs 2017; 40(5): 205 - 11

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Summary

Sepsis is a well-recognized worldwide healthcare issue, ultimately resulting in significant mortality, morbidity and resource utilization. In its most severe form, sepsis causes multi-organ dysfunction. Sepsis induces the activation of complement factor and the release of inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-1beta (IL-1 β), resulting in a systemic inflammatory response. Several clinical and experimental studies have reported that treatment using adsorption of cytokines is beneficial during endotoxemia and sepsis. This review article analyzes the efficacy of CytoSorb adsorber in reducing the inflammatory response during sepsis. The CytoSorb adsorber is known to have excellent adsorption rates for inflammatory cytokines such as IL-1 β , IL-6, IL-8, IL-10, and TNF- α . Studies have demonstrated that treatment with cytokine adsorbing columns has beneficial effects on the survival rate and inflammatory responses in animal septic models. Several cases have been reported in which treatment with cytokine adsorbing columns is very effective in the stabilization of organ failure and hemodynamics in critically ill patients. Therefore, treatment with cytokine adsorbing columns may play an important role in the treatment of sepsis in the near 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 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 animal studies as well as in case reports and due to its beneficial effects 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 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) 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 20; 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 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 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>

Extracorporeal Therapies in Sepsis

Panagiotou A, Gaião S, Cruz DN

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

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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 focusing 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

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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 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>