CytoSorbents™

CRITICAL CARE PUBLICATIONS and SELECT ABSTRACTS

(Click on Hyperlinked Titles for Article Download**)**

CytoSorb® Articles and Posters

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

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

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

Intermittent use of cytokine adsorption in combination with CRRT in a patient with necrotising pancreatitis, septic shock and MOF
Emmerich M, Zietlow S, Tiesmeier J. Infection. 2015 Aug;43 Suppl 1:1-73. Abstract No. 72

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 Mar 18. pii: dkv068. (Epub ahead of print)*

First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: a case report
Bruenger, F., Kizner, L., Weile, J., Morshuis, M., and Gummert, J.F. Int J Artif Organs 2015 EPub ahead of print

CytoSorb in a patient with Legionella-Pneumonia Associated Rhabdomyolysis: a case report
Wiegele, M. and Krenn, C.G. ASAIO J 2015 61(3):e14-16.

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 of Crit Care Med 2014, 18(12):822-824

First description of single-pass albumin dialysis combined with cytokine adsorption in fulminant liver failure and hemophagocytic syndrome resulting from generalized herpes simplex virus 1 infection. (see poster)
Frimmel S, Schipper J, Henschel J, Yu TT, Mitzner SR, Koball S. Liver Transplantaton 2014, 20(12): 1523-1524.

First use of a hemoadsorption device (CytoSorb®) during continuous venovenous hemofiltration (CVVH) in a patient undergoing retransplantation with ABO incompatible graft for Acute Graft Dysfunction.
Tomescu D, Popescu M, Tănase CP, Năstase A, Dima SO. Liver Transplantation 2014, 20:221.

Effects of a novel cytokine haemoadsorbtion 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 J of Anaesthesia and Intensive Care 2014, 21(2):134-138.

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):422-426.

Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model.
Peng ZY, Bishop JV, Wen XY, Elder MM, Zhou F, Chuasuwan A, Carter MJ, Devlin JE, Kaynar AM, Singbartl K, Pike F, Parker RS, Clermont G, Federspiel WJ, Kellum JA Crit Care 2014, 18(4):R141

Leukocyte capture and modulation of cell-mediated immunity during human sepsis: an ex vivo study.
Rimmelé T, Kaynar AM, McLaughlin JN, Bishop JV, Fedorchak MV, Chuasuwan A, Peng Z, Singbartl K, Frederick DR, Zhu L, Carter M, Federspiel WJ, Zeevi A, Kellum JA. Crit Care 2013, 17:R59

A multicenter randomized controlled study of an extracorporeal cytokine hemoadsorption device in septic patients.
Schädler D**,** Porzelius C**,** Jörres A**,** Marx G**,** Meier-Hellmann A**,** Putensen C**,** Quintel M**,** Spies C**,** Engel C**,** Weiler N, and Kuhlmann M. Crit Care 2013, 17 (Suppl 2):P62

Hemoperfusion using CytoSorb® in a cirrhotic patient with sepsis and multiple organ failure – A case report.
Gruber, A, Firlinger F, Clodi, M. DIVI 2013 Congress, Leipzig, Germany, Dec 2013. Oral Presentation.

Pattern of cytokine removal using an adsorption column CytoSorb® during severe candida albicans induced septic shock.
Bracht H, Schneider M, Weiss M, Georgieff M, Barth E. DIVI 2013 Congress, Leipzig, Germany, Dec 2013. Poster

In situ removal of antibodies, free hemoglobin, cytokines and bioactive lipids from packed red blood cells using hemoadsorbent polymer beads.
Capponi V, Golobish T, Ali H, Gilliland M, Reynolds R, Chiappetta A, Ali S, and Chan P
Oral Presentation, Military Health System Research Symposium, August 12-15, 2013, Fort Lauderdale, Florida

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 Purification 2013; 35:314-315.

Effect of cytokine hemoadsorption on brain death-induced ventricular dysfunction in a porcine model.
Mikhova KM, Don CW, Laflamme M, Kellum JA, Mulligan MS, Verrier ED, Rabkin DG. J Thorac Cardiovasc Surg 2013 Jan; 145(1):215-223

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; 18:1366-74.

Moving from a Cytotoxic to a cytokinetic 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 Jouke, and Spapen HD.
Mol Med 2012; 18:1363-65.

Acute removal of common sepsis mediators does not explain the effects of extracorporeal blood purificiation in experimental sepsis
Peng Z, Wang HW, Carter MJ, Dileo MV, Bishop JV, Zhou F, Wen X, Rimmelé T, Singbartl K, Federspiel WJ, Clermont G, and Kellum JA. Kidney Int. 2012; 81(4):363-9.

In-vitro myoglobin clearance by a novel sorbent system.
Kuntsevich VI, Feinfeld DA, Audia PF, Young W, Capponi V, Markella M, Winchester JF; Artif Cells Blood Substit Immobil Biotechnol. 2009; 37(1):45-7.

Hemoadsorption improves long-term survival after sepsis in the rat.
Peng ZY, Wang H, Carter MJ, DiLeo M, Kellum JA; Crit Care Med. 2008 Mar;36(12 suppl):A1.

Effects of hemoadsorption on cytokine removal and short-term survival in septic rats.
Peng, ZY, Carter MJ, Kellum JA; Crit Care Med. 2008 Mar;36(5):1573-77.

The potential application of sorbents in peritoneal dialysis
Winchester JF, Amerling R, Harbord N, Capponi V, Ronco C.; Contrib Nephrol. 2006;150:336-43.

Extracorporeal strategies for the removal of middle molecules
Winchester JF, Audia PF; Semin Dial. 2006 Mar-Apr;19(2):110-4.

Novel Changes in Beta-2-Microglobulin in Dialysis Patients
Winchester JF, Clinical Chemistry. 2005;51:1089-1090

Absence of NF- B Activation by a New Polystyrene-Type Adsorbent Designed for Hemoperfusion
Elisa Menegatti, Claudio Ronco, James F. Winchester, Antonella Dragonetti, Debora Di Simone, Annalisa Davit, Giulio Mengozzi, Giorgio Marietti, Giuseppina Loduca, Morteza Mansouri, Gian Piero Sancipriano, Luigi M. Sena, Dario Roccatello, Blood Purification 2005, Vol. 23, No. 1

Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia.
Kellum JA, Song M, Venkataraman R.; Crit Care Med. 2004 Mar;32(3):801-5.

Cytokine Removal with a Novel Adsorbent Polymer
Mingchen Song, James Winchester, Robert L. Albright, Vincent J. Capponi, Michael D. Choquette, John A. Kellum, Blood Purification 2004, Vol. 22, No. 5.

Hemoadsorption to Improve Organ Recovery from Brain-Dead Organ Donors: A Novel Therapy for a Novel Indication
Ramesh Venkataraman, Mingchen Song, Rachel Lynas, John A. Kellum, Blood Purification 2004, Vol. 22, No. 1.

Sorbents in Acute Renal Failure and End-Stage Renal Disease: Middle Molecule and Cytokine Removal
James F. Winchester, Jeffrey Silberzweig, Claudio Ronco, Viktoria Kuntsevich, Daniel Levine, Tom Parker, John A. Kellum, Jamie A. Salsberg, Peter Quartararo, Nathan W. Levin, Blood Purification 2004, Vol. 22, No. 1

Sorbents in Acute Renal Failure and the Systemic Inflammatory Response Syndrome
Winchester JF, Kellum JA, Ronco C, Brady JA, Quartararo P, Salsberg J, Levin NW. Blood Purification, 2003;21:79-84.

Beta-2 Microglobulin and ESRD: An In-Depth Review
Winchester JF, Salsberg J. Advances in Renal Replacement Therapy, 2003 Oct;10(4): 279-309.

Middle molecules and small-molecular-weight proteins in ESRD: properties and strategies for their removal
Clark WR, Winchester JF. Advances in Renal Replacement Therapy, 2003 Oct;10(4):270-8.

Effect of a novel adsorbent on cytokine responsiveness to uremic plasma.
Morena MD, Guo D, Balakrishnan VS, Brady JA, Winchester JF, Jaber BL. Kidney International 2003 Mar;63(3):1150-4.

Removal of Middle Molecules with Sorbents
Winchester JF, Salsberg J, Yousha E. Artificial Cells, Blood Substitutes and Biotechnology, 2002;30:547-554

Extracorporeal Removal of Toxic Substances, in Critical Care Toxicology
JF Winchester (in press)

Hemoperfusion, in Replacement of Renal Function by Dialysis (5th Edition)
JF Winchester; editors Horl W, Koch KM, Lindsay RM, Ronco C, Winchester JF (Editor in Chief). Kluwer Academic Publishers, Dordrecht, Boston (in press)

Bleeding Disorders in Renal Failure, in Replacement of Renal Function by Dialysis (5th Edition)
JF Winchester; editors Horl W, Koch KM, Lindsay RM, Ronco C, Winchester JF (Editor in Chief). Kluwer Academic Publishers, Dordrecht, Boston (in press)

Peritoneal Dialysis Program Management, in Replacement of Renal Function by Dialysis (5th Edition)
JF Winchester; editors Horl W, Koch KM, Lindsay RM, Ronco C, Winchester JF (Editor in Chief). Kluwer Academic Publishers, Dordrecht, Boston (in press)

Dialysis and Hemoperfusion in Poisoning, in Therapy in Nephrology and Hypertension
JF Winchester; editors HR Brady, CS Wilcox. WB Saunders Co, Philadelphia 2003:947-953

Special Issue: Sorbent-Based Extracorporeal Blood Treatments
SR Ash and JF Winchester (Guest Editors). Advances in Renal Replacement Therapy, 2002; Vol 9, No 1.

Sorbent Hemoperfusion in End Stage Renal Disease: An In-Depth Review
JF Winchester, C Ronco. Advances in Renal Replacement Therapy, 2002; 9:19-25.

The Next Step From High Flux Dialysis: Application Of Sorbent Technology
James F. Winchester, Claudio Ronco, James A. Brady, Larry D Cowgill, Jamie Salsberg, Eric Yousha, Mike Choquette, Robert Albright, Jonathan Clemmer, Vadim Davankov, Maria Tsyurupa, Ludmila Pavlova, Mikhail Pavlov, Gerald Cohen, Walter Horl, Frank Gotch, Nathan Levin. Blood Purification, 2002; 20: 81-86.

Sorbents in Extracorporeal Blood Therapy
SR Ash, JF Winchester. Advances in Renal Replacement Therapy, 2002; 9:1-2.

Effect of the Betasorb(TM) Perfusion Column On The Bioreactivity Of Uremic Plasma
Marion D. Morena, Daqing Guo, V. S. Balakrishnan, James A. Brady, James F. Winchester, Bertrand L. Jaber. Abstr ASAIO Journal 2002; 48: 178.

Sorbent Augmented Dialysis Systems, in Contributions to Nephrology
James F. Winchester, Ronco C, Salsberg J, Yousha E, Brady JA, Cowgill LD, Choquette M, Albright R, Clemmer J, Davankov V, Tsyurupa M, Pavlova L, Pavlov M, Cohen G, Horl W, Gotch F, Levin NW; eds Ronco C, LaGreca G. 2002;137: 181-188.

Select Company Abstracts

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

INTRODUCTION:
Hemoadsorption using CytoSorb has gained attention as a potential immunotherapy to control systemic inflammation and sepsis. We report on a patient with septic shock, successfully treated with CytoSorb therapy.

METHODS:
A 72-year-old male with periodically recurring infectious episodes 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.

RESULTS:
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.

CONCLUSIONS:
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 this patient, further studies are necessary to elucidate to what extent these favorable consequences are attributable to the adsorber itself.

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 Mar 18. pii: dkv068. (Epub ahead of print)*

This case study reports on a male patient with septic shock and multiple organ failure who was admitted to the ICU. The patient‘s condition was characterized by an excessive inflammatory response. Initial laparotomy revealed an ischemic bowel with peritonitis with jejunum and colon segmental resection and ileotransverse colostomy being performed. Immediate antibiotic treatment with meropenem was started and linezolid was added 5 hours after admission. Due to persisting excessive cytokine storm, adjuvant therapy with a CytoSorb adsorber was initiated with a total of 4 treatments in the further course. Over the following days, the patient‘s condition substantially improved. The use of CytoSorb in this patient with severe septic shock proved to be effective (decay of IL-6) and safe (antibiotic levels well above the lower of therapeutic range). This is the first time an in vivo pharmacokinetic monitoring of Linezolid and Meropenem during treatment with CytoSorb is described. In case therapeutic drug monitoring is not available, high loading doses or shorter intervals between antibiotic administrations could be used to achieve adequate antibiotic levels.

First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: a case report
Bruenger, F., Kizner, L., Weile, J., Morshuis, M., and Gummert, J.F. Int J Artif Organs 2015 EPub ahead of print

PURPOSE: A new hemoadsorption device intended as adjunctive treatment for patients with elevated cytokine levels in the setting of SIRS and sepsis has shown promising results. We report on the beneficial application of the device in a patient with cardiogenic septic shock receiving combined extracorporeal life support with rECMO, LVAD, and CVVH despite his highly septic condition.

METHODS: A 39-year-old patient presented with fulminant ARDS and cardiogenic septic shock. A veno-arterial ECMO was implanted for circulatory support. During the course of illness, the patient developed acute renal failure in addition to his chronic renal insufficiency, 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 IL-6 levels and vasopressor dosages increased drastically. A CytoSorb hemoadsorption device was therefore installed in the CVVH circuit and 3 sessions were run during the following 4 days.

RESULTS: During CytoSorb treatment, inflammatory markers IL-6, procalcitonin, and C-reactive protein decreased concomitant with significantly reduced vasopressor support. No adverse device-related side effects were documented during or after the treatment sessions.

CONCLUSIONS: 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. This combination represents a reasonable approach to improve survival in patients with multiple organ dysfunction necessitating several organ supportive techniques.

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 of Crit Care Med 2014, 18(12):822-824

CytoSorb ® (CytoSorbents Corporation, USA) is a novel sorbent hemoadsorption device for cytokine removal. The aim of this study was to examine the clinical use of CytoSorb ® in the management of patient with septic shock. We used this device as an adjuvant to stabilize a young patient with multi-organ failure and severe sepsis with septic shock. A 36-year-old female patient was hospitalized with the complaints of malaise, general body ache, and breathing difficulty and had a medical history of diabetes mellitus type II, hypertension, obstructive sleep apnea, hypothyroidism and morbid obesity. She was diagnosed to have septic shock with multi-organ dysfunction (MODS) and a low perfusion state. CytoSorb ® hemoadsorption column was used as an attempt at blood purification. Acute physiology and chronic health evaluation score, MODS score, and sequential organ failure assessment score were measured before and after the device application. CytoSorb application as an adjuvant therapy could be considered in septic shock.

First description of single-pass albumin dialysis combined with cytokine adsorption in fulminant liver failure and hemophagocytic syndrome resulting from generalized herpes simplex virus 1 infection.
Frimmel S, Schipper J, Henschel J, Yu TT, Mitzner SR, Koball S. Liver Transplantaton 2014, 20(12): 1523-1524.

Acute liver failure (ALF) is a rare, life-threatening complication of herpes simplex virus (HSV) infection that can occur in immunocompetent patients. Liver transplantation (LT) is the ultima ratio in cases of ALF that progress despite antiviral treatment. To bridge the time until LT, extracorporeal liver support with the Molecular Adsorbent Recirculating System (MARS; Gambro, Lund, Sweden) has been shown to be a therapeutic option in ALF. Data concerning the use of single-pass albumin dialysis (SPAD) in such cases, however, are scarce. Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome that can occur in many underlying conditions. Animal studies, case reports, and preliminary data from a clinical trial in septic patients have demonstrated that a reduction in blood cytokine levels achieved with an extracorporeal cytokine adsorption cartridge that contains blood-compatible porous polymer beads (CytoSorb, Monmouth Junction, NJ) can effectively attenuate the inflammatory response during sepsis and possibly improve outcomes.

First use of a hemoadsorption device (CytoSorb®) during continuous venovenous hemofiltration (CVVH) in a patient undergoing retransplantation with ABO incompatible graft for Acute Graft Dysfunction.
Tomescu D, Popescu M, Tănase CP, Năstase A, Dima SO. Liver Transplantation 2014, 20:221.

Acute graft dysfunction (AGD) after liver transplantation (LT) represents a life-threatening event, with fatal outcome without retransplantation (rLT). The systemic inflammatory response syndrome (SIRS) accompanying AGD is mainly responsible for severe systemic complications and death.

Methods: We report the case of a 46 years old man undergoing emergency rLT with an ABO incompatible graft for AGD. During surgery CVVH was used with a hemoadsorption device (CytoSorb®). A second CVVH session with CytoSorb® was necessary 24 hours after rLT, because of a hyperdynamic hemodynamic status interpreted as SIRS. Cytokine levels were measured at the beginning of rLT (T0), after graft reperfusion (T1), at the end of rLT (T2) and before (T3) and after (T4) the second CVVH session. Hemodynamic parameters and laboratory data were assessed.

Results: During the first session of CVVH with CytoSorb®, proinflammatory cytokines IL-1b, TNF-alfa, IL-6 and IL-8 levels decreased and IL-4, IL-13 remained constant and within the normal range.

Also, IL-10 and MCP-1 levels decreased 10-fold to near normal levels. The patient had an improvement in hemodynamics with a continuous decrease of vasopressor support during surgery. A further decrease was observed in IL-6 and MCP-1 levels during the use of the second CytoSorb® while the level of other cytokines remained constant. An improvement in cardiac output (CO) was observed after the second CVVH session with CytoSorb®: cardiac index decreased from 7.2 to 4.1 l/min/m2 systemic vascular resistance index increased from 823 to 1438 dyn*s*cm-5*m2.

Conclusion. The use of CytoSorb® during a non-infectious SIRS was associated with an improvement in both CO and hemodynamics during surgery. Hemoadsorption devices may be usefull in bridging patients with AGD to LT.

Effects of a novel cytokine haemoadsorbtion 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 J of Anaesthesia and Intensive Care 2014, 21(2):134-138.

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):422-426.

INTRODUCTION: Numerous animal studies and preliminary data from a clinical trial in septic patients demonstrated that a decrease in blood cytokine levels using an extracorporeal cytokine filter (CytoSorb) can effectively attenuate the inflammatory response during sepsis and possibly improve outcomes.

METHODS: A 60-year-old female was admitted to hospital due to a forearm fracture. After surgical wound care by osteosynthesis the patient developed surgical wound infection which progressed to necrotizing fasciitis. All diagnostic criteria for SIRS were evident with additional proven infection from β-hemolytic streptococcus. On admission to the ICU, the patient presented a full picture of multiple organ dysfunction syndrome due to septic shock including kidney failure, lung failure as well as thrombocytopenia, metabolic acidosis, and arterial hypotension.
RESULTS: After one day on mechanical ventilation and an IL-6 level of 70,000 pg/ml the patient was treated with CytoSorb therapy over a period of four days, resulting in a significant reduction of IL-6 to 66 pg/ml and an overall improvement of the patient's condition. Despite the necessity of enucleation, the patient was successfully stabilized until control of the surgical infectious source was achieved. Importantly, treatment was safe and well-tolerated, without any adverse events.
CONCLUSIONS: This is the first report of the clinical application of CytoSorb hemoadsorption in combination with a CRRT in a patient with septic shock. CytoSorb as described was able to significantly reduce IL-6 plasma levels and decrease vasopressor need while no adverse and device-related events occurred. CytoSorb seems to be an interesting and safe extracorporeal therapy to stabilize and bridge septic patients to surgery or recovery.

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

Peng ZY, Bishop JV, Wen XY, Elder MM, Zhou F, Chuasuwan A, Carter MJ, Devlin JE, Kaynar AM, Singbartl K, Pike F, Parker RS, Clermont G, Federspiel WJ, Kellum JA Crit Care 2014, 18(4):R141

INTRODUCTION: Prior work suggests that leukocyte trafficking is determined by local chemokine gradients between the nidus of infection and the plasma. We recently demonstrated that therapeutic apheresis can alter immune mediator concentrations in the plasma, protect against organ injury, and improve survival. Here we aimed to determine whether the removal of chemokines from the plasma by apheresis in experimental peritonitis changes chemokine gradients and subsequently enhances leukocyte localization into the infected compartment, and away from healthy tissues.

METHODS: In total, 76 male adult Sprague-Dawley rats weighing 400 g to 600 g were included in this study. Eighteen hours after inducing sepsis by cecal ligation and puncture, we randomized these rats to apheresis or sham treatment for 4 hours. Cytokines, chemokines, and leukocyte counts from blood, peritoneal cavity, and lung were measured. In a separate experiment, we labeled neutrophils from septic donor animals and injected them into either apheresis or sham-treated animals. All numeric data with normal distributions were compared

with one-way analysis of variance, and numeric data not normally distributed were compared with the Mann-Whitney U test.
RESULTS:
Apheresis significantly removed plasma cytokines and chemokines, increased peritoneal fluid-to-blood chemokine (C-X-C motif ligand 1, ligand 2, and C-C motif ligand 2) ratios, and decreased bronchoalveolar lavage fluid-to-blood chemokine ratios, resulting in enhanced leukocyte recruitment into the peritoneal cavity and improved bacterial clearance, but decreased recruitment into the lung. Apheresis also reduced myeloperoxidase activity and histologic injury in the lung, liver, and kidney. These Labeled donor neutrophils exhibited decreased localization in the lung when infused into apheresis-treated animals.

CONCLUSIONS: Our results support the concept of chemokine gradient control of leukocyte trafficking and demonstrate the efficacy of apheresis to target this mechanism and reduce leukocyte infiltration into the lung.

A multicenter randomized controlled study of an extracorporeal cytokine hemoadsorption device in septic patients

Schädler D**,** Porzelius C**,** Jörres A**,** Marx G**,** Meier-Hellmann A**,** Putensen C**,** Quintel M**,** Spies C**,** Engel C**,** Weiler N, and Kuhlmann M. Crit Care 2013, 17 (Suppl 2):P62

Introduction: A novel sorbent hemoadsorption device for cytokine removal (CytoSorbents, USA) was developed and successfully tested in animal models of sepsis. The experience in the clinical setting is still limited to case reports. In this first clinical trial, we tested the hypothesis that treatment with sorbent hemoadsorption could safely and effectively reduce cytokines in septic patients with acute lung injury (ALI).

Methods: Ventilated patients fulfilling the criteria for severe sepsis and ALI were enrolled in this multicenter randomized, controlled, open-label study comparing standard of care with or without hemoperfusion treatment. Primary endpoints were safety and IL-6 reduction. Treated patients underwent hemoperfusion at flow rates of ~200 to 3003ml/ minute for 6 hours per day for 7 consecutive days. The overall mean reduction in individual plasma cytokines for the control and treatment groups during the treatment period was calculated using a generalized linear model.

Results: Forty-three patients (18 treated, 25 control) completed the study and were further analyzed. Incidence of organ dysfunction at enrollment (treatment vs. control) was: septic shock (94% vs. 100%, P = 0.42), acute respiratory distress syndrome (67% vs. 56%, P = 0.33), and renal failure (39% vs. 24%, P = 0.54). During 115 treatments no serious device-related adverse events occurred. On average, there were no changes in hematology and other blood parameters except for a modest reduction in platelet count (<10%) and albumin (<5%) with treatment. Hemoperfusion decreased IL-6 blood concentration significantly (-49.1%, P = 0.01), with similar reductions of MCP-1 (-49.5%, P = 0.002), IL-1ra (-36.5%, P = 0.001), and IL-8 (-30.2%, P = 0.002). The 28-day mortality (28% vs. 24% control, P = 0.84) and 60-day mortality (39% vs. 32% control, P = 0.75) did not differ significantly between the two studied groups.

Conclusion: In this first clinical study of a novel sorbent hemoadsorption device in patients with severe sepsis and ALI, the device appeared to be safe and decreased the blood concentration of several cytokines. Further research is needed to study the effect of the device on the clinical outcome of septic patients.

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

Mikhova KM, Don CW, Laflamme M, Kellum JA, Mulligan MS, Verrier ED, Rabkin DG
J Thorac Cardiovasc Surg 2013 Jan; 145(1):215-223

Objective: In an effort to expand the cardiac donor pool, we tested the hypothesis that hemoadsorption of cytokines with CytoSorb® attenuates brain death-induced ventricular dysfunction.

Methods: Eighteen Yorkshire pigs (50-60 kg) were instrumented with a left ventricular conductance catheter. Cytokine expression, preload recruitable stroke work, and the diastolic relaxation constant tau were measured at baseline and at hourly intervals for 6 hours after induction of brain death by intracranial balloon inflation (brain death, n = 6) or sham operation (control, n = 6). In a third group (brain death + hemoadsorption,

n = 6), 3 hours after induction of brain death, animals were placed on an extracorporeal circuit containing a cytokine-hemoadsorption device for the remaining 3 hours of the experiment. Myocardial water content was measured after the animals were killed.

Results: Six hours after induction of brain death, tumor necrosis factor and interleukin-6 were highest in the brain death group (106 ± 13.1 pg/mL and 301 ± 181 pg/mL, respectively), lowest in controls (68.3 ± 8.55 pg/mL and 37.8 ± 11 pg/mL, respectively), and intermediate in the brain death + hemoadsorption group (81.2 ± 35.2 pg/mL and 94.6 ± 20 pg/mL, respectively). Compared with controls, preload recruitable stroke work was significantly reduced in the brain death group 4 hours after the induction of brain death and was 50% of baseline by 5 hours. In the brain death + hemoadsorption group, preload recruitable stroke work was relatively preserved at 80% of baseline at similar time points. Tau remained unchanged in the control and brain death + hemoadsorption groups, whereas in the brain death group it was significantly elevated versus baseline 5 (139.3% ± 21.5%) and 6 (172% ± 16.1%) hours after induction of brain death. Myocardial water content was significantly greater in the brain death group than in the other 2 groups.

Conclusions: Hemoadsorption of cytokines using an extracorporeal circuit attenuates brain death-induced ventricular dysfunction in a porcine model. Improvement in function generally correlates with trends in cytokine expression, but this relationship requires further investigation.

In situ removal of antibodies, free hemoglobin, cytokines and bioactive lipids from packed red blood cells using hemoadsorbent polymer beads

Capponi V, Golobish T, Ali H, Gilliland M, Reynolds R, Chiappetta A, Ali S, and Chan P
Military Health System Research Symposium, August 12-15, 2013, Fort Lauderdale, Florida

Blood transfusions carry risks of adverse reactions due to contaminants present from the donor or that accumulate during storage. Examples include free hemoglobin, cytokines, bioactive lipids, anti-HLA and other antibodies, toxins, foreign antigens and others. CytoSorbents Corp. has developed a novel, proprietary blood purification technology using hemocompatible, porous polymer beads to remove these contaminants from pRBCs. Each bead contains millions of pores and channels designed to capture contaminants based on pore size and surface adsorption. Beads were incubated with non-leukoreduced pRBCs at 1:15 v/v ratio in standard PVC blood storage bags for 41 days at 4°C. Free hemoglobin from pRBCs (on a rocking shaker to exacerbate hemolysis) using porous beads increased less (57 mg/dL, Day 0; 648 mg/dL, Day 41) than the 37.5-fold increase in no-bead controls (57 mg/dL, Day 0; 2,135 mg/dL, Day 41). With no rocking, concentrations of IgG antibodies and LysoPC were decreased by 73% (vs. 10% increase control) and 86% (vs. 5% decrease control), respectively, by day 41. Cytokine levels of TNF-α, IL-8 and IL-7 were reduced by 97, 52 and 100%, respectively, at 41 days vs. increases in control (81%, 468% and 222%, respectively). These data demonstrate that porous hemoadsorbent beads can efficiently remove a broad range of contaminants from pRBC during blood storage. This may have significant clinical relevance in improving the safety and quality of blood products.

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

Peng Z, Wang HW, Carter MJ, Dileo MV, Bishop JV, Zhou F, Wen X, Rimmelé T, Singbartl K, Federspiel WJ, Clermont G, and Kellum JA
Kidney Int. 2012; 81(4):363-9.

The effect of extracorporeal blood purification on clinical outcomes in sepsis is assumed to be related to modulation of plasma cytokine concentrations. To test this hypothesis directly, we treated rats that had a cecal ligation followed by puncture (a standard model of sepsis) with a modest dose of extracorporeal blood purification that did not result in acute changes in a panel of common cytokines associated with inflammation (TNF-α, IL-1β, IL-6, and IL-10). Pre- and immediate post-treatment levels of these cytokines were unchanged compared to the sham therapy of extracorporeal circulation without blood purifying sorbent. The overall survival to 7 days, however, was significantly better in animals that received extracorporeal blood purification compared to those with a sham procedure. This panel of common plasma cytokines along with alanine aminotransferase and creatinine was significantly lower 72 h following extracorporeal blood purification compared to sham-treated rats. Thus, the effects of this procedure on organ function and survival do not appear to be due solely to immediate changes in the usual measured circulating cytokines. These results may have important implications

for the design and conduct of future trials in sepsis including defining alternative targets for extracorporeal blood purification and other therapies.

Note: CytoSorb® is concentration dependent, removing cytokines very aggressively at high concentrations, and less aggressively at lower concentrations. The levels of cytokines in this sub-acute model of sepsis are much lower than seen in the fulminant sepsis model reported in the Crit Care Med 2008 paper below, and this helps to explain why they were not removed effectively. Also, the size of the cartridge used here was 1/10 the size of the one used in the Crit Care Med 2008 paper below. In addition, researchers only looked at 4 cytokines, but did not look at the reduction of other cytokines. Because CytoSorb® is a broad spectrum filter, it has the ability to remove many different toxic substances besides cytokines.

Hemoadsorption improves long-term survival after sepsis in the rat.
Peng ZY, Wang H, Carter MJ, DiLeo M, Kellum JA; Crit Care Med. 2008 Mar;36(12 suppl):A1.

Introduction: The over-production of inflammatory mediators is associated with the multi-organ failure and death in sepsis. We have previously shown that hemoadsorption could remove inflammatorv cytokines and improve short-term survival in rats using a lethal model of cecal ligation and puncture. With the current studv, we sought to determine if this treatment can also be effective to improve the long-term survival in a less lethal modeL Hypothesis: Hemoadsorption could eliminate cytokines and improve long-term survival after sepsis in the rat. Methods: 18 h after cecal ligation and puncture (ClP), ligating 25% of the cecum and using two punctures, we randomized 46 adult Sprague Dawley rats to receive hemoadsorption (HA) or sham HA for four hours. HA was performed using a venous-venous circuit with a cartridge containing 1g of CytoSorb beads (MedaSorb Technologies, Princeton NJ) using a blood flow of l-l.5 ml/min. We measured plasma bv ELISA and analyzed changes using ANOVA for repeated measures. Survival time was assessed for one week and analyzed by Kaplan-Meier and overall survival in each group was compared using Fisher's exact. Results: Baseline concentrations of IL-6 were similar between HA and sham groups (385.69 pg/ml vs 336.16 pg/ml). IL-6 continued to increase in the sham-treated animals with time, while the increase in IL-6 was significantly inhibited in the HA group (219.41 pg/ml vs 522.66 pg/ml after treatment; 259.70 pg/ml vs 677.40 pg/ml after day3, p<O.O5). The survival time was also significantly longer in the HA group (5.65 days vs 4.52 days, p<O.O5). The seven-day survival rate was 52% vs 28%, (hazard ratio: O.5O. 0.17-0.96, p<O.O5) in favor of HA. Conclusions: Hemoadsorption begun 18 hours after onset of experimental sepsis in the rat resulted in reduced plasma IL-6 concentrations and improved the long-term survival

Effects of hemoadsorption on cytokine removal and short-term survival in septic rats.
Peng, ZY, Carter MJ, Kellum JA; Crit Care Med. 2008 Mar;36(5):1573-77.

OBJECTIVE: A broad-spectrum immune-regulating therapy could be beneficial in the treatment of sepsis. Our previous studies have shown that a hemoadsorption device (CytoSorb) removes both pro- and anti-inflammatory cytokines and improves survival in experimental endotoxemia. We sought to determine whether hemoadsorption can also be effective in the treatment of sepsis. DESIGN: Randomized controlled laboratory experiment. SETTING: University laboratory. INTERVENTIONS: Rats were subjected to cecal ligation and puncture (CLP) and 20 hrs later were randomized to receive either hemoadsorption or sham treatment using an arterial-venous circuit. Hemoadsorption was accomplished using a cartridge containing Cytosorb beads. Blood was drawn for cytokine measurements and mean arterial pressure (MAP) was continuously monitored. Cytokines were measured via multiplex bead immunoassays. Survival time was observed for 9 hours after the intervention and assessed by Kaplan-Meier statistics. The overall survival in each group was compared using Fisher's exact test. Finally, we used a Cox proportional-hazards model to examine the effects of cytokine removal on survival time. MEASUREMENTS AND MAIN RESULTS: Baseline plasma cytokine concentrations and MAP were similar between hemoadsorption and sham-treated groups. However, the concentrations of tumor necrosis factor, interleukin (IL)-1beta, IL-6, and IL-10 were significantly lower after hemoadsorption compared to the sham group. Six hours after treatment ended, IL-6 and IL-10 concentrations were still lower in hemoadsorption group. MAP was significantly better in hemoadsorption compared to sham-treated animals ($p < .05$). Finally, mean survival time was significantly longer (720 vs. 381 min, $p < .05$, Mann-Whitney test), and overall survival was significantly better (11/17 vs. 2/16, $p < .01$) with hemoadsorption compared to sham. Combined reduction in both IL-6 and IL-10 was associated with a significantly decreased risk of death (hazard

ratio, .11, p = .005). CONCLUSION: Hemoadsorption reduced circulating cytokines, improved MAP, and resulted in better short-term survival in CLP-induced septic rats.

Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia.
Kellum JA, Song M, Venkataraman R.; Crit Care Med. 2004 Mar;32(3):801-5.

OBJECTIVES: Previous studies have shown that inflammatory mediators can be removed from the circulation with hemofiltration and that adsorption plays an important role. Because adsorptive capacity of hollow-fiber dialyzers is limited, we sought to determine whether hemoadsorption using high surface area beads would result in greater mediator removal and improved survival in experimental sepsis. DESIGN: Randomized controlled laboratory experiment. SETTING: University laboratory. SUBJECTS: Sixty-six adult Sprague-Dawley rats. INTERVENTIONS: We conducted two ex vivo and two in vivo experiments. For in vivo experiments, we administered Escherichia coli endotoxin (20 mg/kg) by intravenous infusion and then randomized each animal to receive either hemoadsorption or a sham circuit for 4 hrs. Hemoadsorption was performed for 4 hrs using an arterial-venous circuit and a CytoSorb cartridge containing 10 g of polystyrene divinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone coating. Survival time was measured to a maximum of 12 hrs. In a separate set of experiments, we studied 12 animals using the same protocol except that we killed all animals at 4 hrs and removed standardized sections of liver for analysis of nuclear factor-kappaB DNA binding. MEASUREMENTS AND MAIN RESULTS: Mean survival time among hemoadsorption-treated animals was 629+/-114 vs. 518+/-120 mins for sham-treated animals ($p < .01$). Overall survival (defined at 12 hrs) was also significantly better in the hemoadsorption group, seven of 20 vs. one of 20 ($p < .05$). Plasma interleukin-6 and interleukin-10 concentrations and liver nuclear factor-kappaB DNA binding were significantly reduced by hemoadsorption. Ex vivo experiments showed no endotoxin adsorption but strengthened our in vivo observations by showing rapid adsorption of tumor necrosis factor, interleukin-6, and interleukin-10. CONCLUSIONS: Hemoadsorption was associated with reduced inflammation and improved survival in this murine model of septic shock.

Cytokine Removal with a Novel Adsorbent Polymer
Mingchen Song, James Winchester, Robert L. Albright, Vincent J. Capponi, Michael D. Choquette, John A. Kellum, Blood Purification 2004, Vol. 22, No. 5.

BACKGROUND/AIMS: We sought to characterize a novel adsorbent polymer in terms of cytokine removal. METHODS: We challenged 50 rats with lipopolysaccharide to obtain cytokine-rich blood and circulated this through cartridges containing polymer. In separate experiments, cell-free supernatants were passed through cartridges containing polymer. We measured tumor necrosis factor alpha, interleukin 10 and interleukin 6 concentrations under a variety of conditions to evaluate adsorption kinetics. RESULTS: 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. There was no significant difference in the effect across a range of blood flows and Ca2+ concentrations. Adsorption was decreased somewhat by extremely low temperature (4 degrees C). CONCLUSION: The adsorbent polymer removes cytokines with high efficiency, and binding is relatively unaffected by a variety of physical conditions.

Sorbents in Acute Renal Failure and the Systemic Inflammatory Response Syndrome
Winchester JF, Kellum JA, Ronco C, Brady JA, Quartararo P, Salsberg J, Levin NW. Blood Purification, 2003;21:79-84.

Renal replacement therapy in acute renal failure is currently focused on the use of modifications of dialysis (continuous arteriovenous hemofiltration and hemodiafiltration) to remove middle molecular weight toxins, consisting of small proteins, and cytokines involved in the systemic inflammatory response syndrome (SIRS). Conventional high-flux dialyzers are not efficient at removing these molecules, prompting the investigation of sorbents to augment or replace dialysis. Sorbents have been developed to modulate SIRS by targeting cytokines such as IL-1, IL-6, IL-10, IL-18 and TNF, among others. Extensive pre-clinical studies are underway to demonstrate the clinical utility and safety of either adding sorbent hemoadsorption devices to hemodialysis, or the use of such devices alone in SIRS, sepsis, acute renal failure, cardiopulmonary bypass and end-stage renal disease.

In-vitro myoglobin clearance by a novel sorbent system.

Kuntsevich VI, Feinfeld DA, Audia PF, Young W, Capponi V, Markella M, Winchester JF; Artif Cells Blood Substit Immobil Biotechnol. 2009; 37(1):45-7.

Rhabdomyolysis may lead to acute kidney injury following deposition of myoglobin in renal tubules. Although high-flux dialysis membranes may remove a substantial amount of myoglobin from plasma, this may still not be sufficient to prevent renal damage. We tested a new polymer sorbent, X-Sorb, in vitro to determine its potential to clear myoglobin from solutions. Normal saline or human serum in which myoglobin was dissolved was perfused by a peristaltic pump through a column packed with the sorbent. After a 4-hour perfusion, the myoglobin level in normal saline fell from 200,000 ng/ml to virtually undetectable (<780 ng/ml). Perfusion through the sorbent was then found to lower concentrations of dissolved myoglobin in 3 different 110-ml samples of human serum consistently by > 90% over 4 hours. X-Sorb appears to be an effective sorbent for myoglobin and warrants a trial in vivo to determine whether it is equally effective and safe.

Non-Company External Articles of Interest

The effect of age on the development and outcome of adult sepsis
Martin GS, Mannino DM, Moss M. Crit Care Med. 2006 Jan;34(1):15-21.
OBJECTIVE: Sepsis is an increasingly common and lethal medical condition that occurs in people of all ages. The influence of age on sepsis risk and outcome is incompletely understood. We sought to determine the independent effect of age on the incidence, severity, and outcome of adult sepsis.
DESIGN: Longitudinal observational study using national hospital discharge data.
SETTING: Approximately 500 geographically separated nonfederal acute care hospitals in the United States.
PATIENTS: Patients were 10,422,301 adult sepsis patients hospitalized over 24 yrs, from 1979 to 2002.
INTERVENTIONS: None.
MEASUREMENTS AND MAIN RESULTS: Incident sepsis cases were age adjusted and characterized by demographics, sources and types of infection, comorbid medical conditions, and hospital discharge status. Elderly patients (> or = 65 yrs of age) accounted for 12% of the U.S. population and 64.9% of sepsis cases, yielding a relative risk of 13.1 compared with younger patients (95% confidence interval, 12.6-13.6). Elderly patients were more likely to have Gram-negative infections, particularly in association with pneumonia (relative risk, 1.66; 95% confidence interval, 1.63-1.69) and to have comorbid medical conditions (relative risk, 1.99; 95% confidence interval, 1.92-2.06). Case-fatality rates increased linearly by age; age was an independent predictor of mortality in an adjusted multivariable regression (odds ratio, 2.26; 95% confidence interval, 2.17-2.36). Elderly sepsis patients died earlier during hospitalization, and elderly survivors were more likely to be discharged to a nonacute health care facility. CONCLUSIONS: The incidence of sepsis is disproportionately increased in elderly adults, and age is an independent predictor of mortality. Compared with younger sepsis patients, elderly nonsurvivors of sepsis die earlier during hospitalization and elderly survivors more frequently require skilled nursing or rehabilitative care after hospitalization. These findings have implications for patient care and health care resource prioritization and provide insights for expanded scientific investigations and potential patient interventions.

Relationship between interleukin-6 plasma concentration in patients with sepsis, monocyte phenotype, monocyte phagocytic properties, and cytokine production.
Spittler A, Razenberger M, Kupper H, Kaul M, Hackl W, Boltz-Nitulescu G, Függer R, Roth E., Clin Infect Dis. 2000 Dec;31(6):1338-42. Epub 2000 Nov 22.

Monocyte phenotype, their phagocytic capacity as well as the cytokine production from 10 patients with sepsis with low interleukin-6 (IL-6) serum concentrations (<1000 pg/mL) and 8 patients with sepsis with high IL-6 (> or = 1000 pg/mL) plasma concentrations were investigated within 24 hours of fulfilling the criteria for sepsis. Monocytes from patients with high IL-6 levels had higher levels of human leukocyte antigen (HLA)-DR, HLA-ABC, CD64, and CD71, and the production of tumor necrosis factor-alpha (TNF-alpha) and IL-8, as well as the capacity of monocytes to phagocytose, was significantly elevated. Of 8 patients with high levels of plasma IL-6, 4 patients died. In contrast, all 10 patients with low plasma IL-6 concentrations survived until day 28. Patients who died had constant high IL-6 concentrations during the first 3 days, whereas IL-6 levels in patients who survived decreased by 88%. Our data indicate that IL-6 levels are a better prognostic parameter in the early phase of sepsis than the monocyte HLA-DR expression.

Mortality in patients with septic shock correlates with anti-inflammatory but not proinflammatory immunomodulatory molecules.
de Pablo R, Monserrat J, Reyes E, Diaz-Martin D, Rodriguez Zapata M, Carballo F, de la Hera A, Prieto A, Alvarez-Mon M., J Intensive Care Med. 2011 Mar-Apr;26(2):125-32.

BACKGROUND: Mortality in patients with septic shock remains unacceptably high and the attempts to antagonize certain proinflammatory cytokines based on the results of animal model studies have failed to improve survival rates. The objective of this article is to examine the pro-/anti-inflammatory cytokine balance in patients with septic shock and its connection with mortality.
METHODS: Serum levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin 1β [IL-1β], interferonγ [IFN-γ], and IL-6) and soluble cytokine antagonists (soluble TNF receptor I [sTNF-RI], sTNF-RII, and IL-1Ra) were determined on admission to the intensive care unit (ICU) and 3, 7, 14, and 28 days later in

52 patients with septic shock and in 36 healthy controls. Specific sandwich enzyme-linked immunosorbent assay (ELISA) was used for all determinations.
RESULTS: Serum levels of most of the pro- and anti-inflammatory molecules examined (TNF-α, IL-6, sTNF-RI, sTNF-RII, and IL-1 receptor agonist [IL-1Ra]) were significantly elevated on admission and during the 28-day observation period in patients when compared to controls. Notably, the anti-inflammatory mediators sTNF-RI, sTNF-RII, and IL-1Ra were better predictors of mortality. Receiver-operating characteristic (ROC) analysis revealed that sTNF-RI or sTNF-RII concentrations over 2767 or 4619 pg/mL, respectively, determined a high risk of death (sensitivity: 100%-100%, specificity: 57.1%-71.4%, area under the curve [AUC] 0.759-0.841, respectively), whereas IL-1Ra concentrations below 7033 pg/mL determined a high probability of survival (sensitivity: 60%, specificity: 100%, AUC 0.724). In addition, IFN-γ levels were significantly higher in survivors than in controls during the initial 2 weeks of observation.
CONCLUSIONS: Our data show that serum cytokine disturbance patterns have prognostic significance in patients with septic shock admitted to the ICU. The pattern, defined by an early response to continuously elevated anti-inflammatory cytokine serum levels, is associated with an enhanced risk of a fatal outcome for patients.

Note: This JAMA paper is important because it demonstrates, in a randomized controlled prospective trial, the benefit of blood purification as a strategy to treat sepsis, albeit in a highly selective population.

Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial
Cruz, DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. JAMA 2009 Jun 17; 301(23):2445-52.

Polymyxin B fiber column is a medical device designed to reduce blood endotoxin levels in sepsis. Gram-negative-induced abdominal sepsis is likely associated with high circulating endotoxin. Reducing circulating endotoxin levels with polymyxin B hemoperfusion could potentially improve patient clinical outcomes. OBJECTIVE: To determine whether polymyxin B hemoperfusion added to conventional medical therapy improves clinical outcomes (mean arterial pressure [MAP], vasopressor requirement, oxygenation, organ dysfunction) and mortality compared with conventional therapy alone. DESIGN, SETTING, AND PATIENTS: A prospective, multicenter, randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) conducted at 10 Italian tertiary care intensive care units between December 2004 and December 2007. Sixty-four patients were enrolled with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection. INTERVENTION: Patients were randomized to either conventional therapy (n=30) or conventional therapy plus 2 sessions of polymyxin B hemoperfusion (n=34). MAIN OUTCOME MEASURES: Primary outcome was change in MAP and vasopressor requirement, and secondary outcomes were PaO(2)/FIO(2) (fraction of inspired oxygen) ratio, change in organ dysfunction measured using Sequential Organ Failure Assessment (SOFA) scores, and 28-day mortality. RESULTS: MAP increased (76 to 84 mm Hg; P = .001) and vasopressor requirement decreased (inotropic score, 29.9 to 6.8; P < .001) at 72 hours in the polymyxin B group but not in the conventional therapy group (MAP, 74 to 77 mm Hg; P = .37; inotropic score, 28.6 to 22.4; P = .14). The PaO(2)/FIO(2) ratio increased slightly (235 to 264; P = .049) in the polymyxin B group but not in the conventional therapy group (217 to 228; P = .79). SOFA scores improved in the polymyxin B group but not in the conventional therapy group (change in SOFA, -3.4 vs -0.1; P < .001), and 28-day mortality was 32% (11/34 patients) in the polymyxin B group and 53% (16/30 patients) in the conventional therapy group (unadjusted hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.20-0.94; adjusted HR, 0.36; 95% CI, 0.16-0.80). CONCLUSION: In this preliminary study, polymyxin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intra-abdominal gram-negative infections.

Note: The following NEJM paper is important because it documents the direct role of non-infectious cytokine storm in causing severe sepsis/systemic inflammatory response syndrome in 6 otherwise healthy young men. This is in the absence of an infection or endotoxin.

Cytokine storm in a phase I trial of the anti-CD28 monoclonal antibody TGN1412
Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N.
NEJM 2006 Sep 7; 355(10):1018-28

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti-interleukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all six patients survived. Documentation of the clinical course occurring over the 30 days after infusion offers insight into the systemic inflammatory response syndrome in the absence of contaminating pathogens, endotoxin, or underlying disease.

Blood purification for hypercytokinemia.
Nakada T, Hirasawa H, Oda S, Shiga H, Matsuda K. Transf Apher Science 2006; 35:253-264

Blood purification has been steadily improved in the field of critical care, supported by advances in related biomedical technologies as well as efforts to develop better operating procedures. As it has become clear that hypercytokinemia plays a key role in the pathophysiology of critical pathological conditions, use of various blood purification techniques to control hypercytokinemia has been investigated. Answers to questions concerning the optimal cytokine-removing device (dialyzer/ hemofilter/adsorber) as well as operating procedures and conditions of such devices in particular clinical conditions have been obtained in the course of such investigations. The recent success in real-time monitoring of cytokine levels in clinical practice to assess the extent of cytokine network activation may improve the precision and efficacy of blood purification in the treatment of hypercytokinemia. In addition, the recently documented effects of genetic factors on hypercytokinemia suggest that the introduction of tailor-made medicine considering the differences in genetic background among individual patients may improve the efficacy of blood purification as a countermeasure to hypercytokinemia.

Clinical review: extracorporeal blood purification in severe sepsis
Venkataraman R, Subramanian S, Kellum JA

Sepsis and septic shock are the leading causes of acute renal failure, multiple organ system dysfunction, and death in the intensive care unit. The pathogenesis of sepsis is complex and comprises a mosaic of interconnected pathways. Several attempts to improve patient outcomes by targeting specific components of this network have been unsuccessful. For these reasons, the ideal immunomodulating strategy would be one that restores immunologic stability rather than blindly inhibiting or stimulating one or another component of this complex network. Hence, the recent focus of immunomodulatory therapy in sepsis has shifted to nonspecific methods of influencing the entire inflammatory response without suppressing it. Here, we discuss the various modalities of extracorporeal blood purification, the existing evidence, and future prospects.

Endotoxin and cytokine removal in sepsis.
Tetta C, Bellomo R, Inquaqqiato, Wratten ML, Ronco C. Ther Apher 2002 Apr; 6(2): 109-15.

Sepsis, the leading cause of mortality in intensive care units, is a complex series of interrelated effects caused by the overproduction of multiple mediators and their unrestrained biological activity. Both proinflammatory and antiinflammatory mediators participate in the high complexity of sepsis and explain the failure of specific therapies to improve survival. Continuous extracorporeal therapies have been proposed as therapeutic options and as tools for blood purification in sepsis. Along these lines and in order to achieve higher clearances and mass removal rates, we studied the effects of plasmafiltration coupled with adsorption and provided in vitro and in vivo evidence that adsoprtion of multiple cytokines, activated complement components, and lipid mediators

such as the platelet-activating factor occurs. We also showed that such treatment may lead to improved survival in a rabbit model of sepsis and to improved hemodynamics, reduced norepinephrine dose, and restoration of near-to-normal responsiveness of blood leukocytes to endotoxin in humans. It is anticipated that treatment of plasma, as a modular device to conventional hemofiltration, may pave the way to innovative approaches in the extracorporeal treatment of septic patients.

Blood purification in sepsis: a reasonable scientific hypothesis or pipe dream?
Bellomo, R. Crit Care Resuscitation 2001; 3:202-5.

Hemofiltration-absorption systems for the treatment of experimental sepsis: Is it possible to remove the "evil humors" responsible for septic shock?
Opal, SM. Crit Care Med 2000 May; 28(5):1681-1682

Immunosuppression in sepsis
Lyn-Kew K, Standiford TJ. Curr Pharm Des 2008; 14(19)1870-81

The often fatal sepsis syndrome is characterized by the systemic release of inflammatory mediators, which is regulated and counterbalanced by the coordinated expression of anti-inflammatory molecules. The magnitude of sepsis-induced tissue injury and subsequent risk of infectious complications is dictated by the balance between the expression of pro- and anti-inflammatory mediators. As our understanding of the pathophysiology of sepsis continues to evolve, we have gained a greater appreciation for the profound effects that sepsis and similar states of overwhelming stress have on host innate and adaptive immunity. Impaired leukocyte function in sepsis has important clinical consequences, as high mortality rates have been observed in patients who display evidence of sepsis-induced immune dysregulation. Functional defects in leukocytes isolated from patients with sepsis include diminished expression of important cell surface molecules, dysregulated cytokine production, alterations in antigen-presenting ability, and accelerated apoptosis. In this article, we review the current literature supporting the notion that dysregulation of host immunity occurs during sepsis syndrome, and describe novel therapeutic interventions directed at augmenting host immunity during sepsis.

The inflammatory balance in human sepsis
Adrie C, Pinsky MR. Intensive Care Med 2000; 26:364-75.

Cytokine signaling-regulation of the immune response in normal and critically ill states.
Oberholzer, A; Oberholzer, C; Moldawer, LL. Crit Care Med 2000; 28(Suppl):N3-N12

Cytokines are produced during the activation of innate and acquired immunity, and are the principal means for intercellular communication of a microbial invasion. Cytokines serve to initiate the inflammatory response and to define the magnitude and the nature of the acquired immune response. The response of critically ill patients to their injury and/or invading pathogens is dependent, in large part, on the pattern of cytokines which are produced. The immunologic response of critically ill patients can vary from a strongly proinflammatory response, characterized by increased production of tumor necrosis factor-[alpha], interleukin (IL)-1, interferon (IFN)-[gamma], and IL-12 to one predominantly of anergy, characterized by increased production of TH2 cytokines, like IL-10 and to IL-4. Therapeutic efforts to modify the host immune response in critical illness will require a more thorough understanding of the cytokine milieu and the factors that determine their production.

The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome (Review)
Wang H, Ma S. American J of Emer Med 2008;26:711-715

Multiple organ dysfunction syndrome (MODS) is a major cause of morbidity and mortality in intensive care units. It is being encountered frequently in critically ill patients owing to advancements in organ-specific supportive technologies to survive the acute phase of severe sepsis and shock. It is now believed that MODS is the result of an inappropriate generalized inflammatory response of the host to a variety of acute insults. The pathologic mechanisms of MODS were reviewed, and factors determining the sequence and severity of organ

dysfunction were discussed in depth. In the early phase of MODS, circulating cytokines cause universal endothelium injury in organs. In the later phase of MODS, overexpression of inflammatory mediators in the interstitial space of various organs is considered a main mechanism of parenchyma injury. The difference in constitutive expression and the upregulation of adhesion molecules in vascular beds and the density and potency of intrinsic inflammatory cells in different organs are the key factors determining the sequence and severity of organ dysfunction. By activating the intrinsic inflammatory cell in a distant organ, organ dysfunctions are linked in a positive feedback loop through circulating inflammatory mediators. Antagonists targeted at adhesion molecules may alleviate the severity of endothelial damage. And nonsteroidial anti-inflammatory drugs or steroids administered judiciously in the early phase of MODS may retard the progress of multiple organ failure.

Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia
De Jong MD, Simmons CP, Thanh TT, Hien VM, Smith GJ, et al. Nature Medicine 2006 Oct; 12(10): 1203-7.

Avian influenza A (H5N1) viruses cause severe disease in humans, but the basis for their virulence remains unclear. In vitro and animal studies indicate that high and disseminated viral replication is important for disease pathogenesis. Laboratory experiments suggest that virus-induced cytokine dysregulation may contribute to disease severity. To assess the relevance of these findings for human disease, we performed virological and immunological studies in 18 individuals with H5N1 and 8 individuals infected with human influenza virus subtypes. Influenza H5N1 infection in humans is characterized by high pharyngeal virus loads and frequent detection of viral RNA in rectum and blood. Viral RNA in blood was present only in fatal H5N1 cases and was associated with higher pharyngeal viral loads. We observed low peripheral blood T-lymphocyte counts and high chemokine and cytokine levels in H5N1-infected individuals, particularly in those who died, and these correlated with pharyngeal viral loads. Genetic characterization of H5N1 viruses revealed mutations in the viral polymerase complex associated with mammalian adaptation and virulence. Our observations indicate that high viral load, and the resulting intense inflammatory responses, are central to influenza H5N1 pathogenesis. The focus of clinical management should be on preventing this intense cytokine response, by early diagnosis and effective antiviral treatment

Abberant innate immune response in lethal infection of macaques with the 1918 influenza virus
Kobasa D, Jones SM, Shinya K, Kash JC, Copps J, Ebihara H, et al. Nature 2007 Jan 18; 445:319-323.

The 1918 influenza pandemic was unusually severe, resulting in about 50 million deaths worldwide. The 1918 virus is also highly pathogenic in mice, and studies have identified a multigenic origin of this virulent phenotype in mice. However, these initial characterizations of the 1918 virus did not address the question of its pathogenic potential in primates. Here we demonstrate that the 1918 virus caused a highly pathogenic respiratory infection in a cynomolgus macaque model that culminated in acute respiratory distress and a fatal outcome. Furthermore, infected animals mounted an immune response, characterized by dysregulation of the antiviral response, that was insufficient for protection, indicating that atypical host innate immune responses may contribute to lethality. The ability of influenza viruses to modulate host immune responses, such as that demonstrated for the avian H5N1 influenza viruses, may be a feature shared by the virulent influenza viruses.

Pathology of fatal human infection associated with avian influenza A H5N1 virus
To KF, Chan PK, Chan KF, Lee WK, et al. J Med Virol 2001 Mar; 63(3):242-6.

Eighteen cases of human influenza A H5N1 infection were identified in Hong Kong from May to December 1997. Two of the six fatal cases had undergone a full post-mortem which showed reactive hemophagocytic syndrome as the most prominent feature. Other findings included organizing diffuse alveolar damage with interstitial fibrosis, extensive hepatic central lobular necrosis, acute renal tubular necrosis and lymphoid depletion. Elevation of soluble interleukin-2 receptor, interleukin-6 and interferon-gamma was demonstrated in both patients, whereas secondary bacterial pneumonia was not observed. Virus detection using isolation, reverse transcription-polymerase chain reaction and immunostaining were all negative. It is postulated that in fatal human infections with this avian subtype, initial virus replication in the respiratory tract triggers hypercytokinemia complicated by the reactive hemophagocytic syndrome. These findings suggest that the pathogenesis of influenza A H5N1 infection might be different from that of the usual human subtypes H1-H3.

Cytokine storm in avian influenza (Review)
Us D. Mikrobiyol Bul 2008 Apr; 42(2):365-80.

The most dramatic example of defining the pathogenicity of influenza virus A/H5N1 strains is the higher fatality rate of avian influenza epidemic (>50%) occured in Southeast Asia in 1997 comparing to the pandemic caused by influenza virus A/H1N1 in 1918 (5-10%) which was recorded as the most destructive pandemic in the world. When considering the fatal/total case numbers (208/340) reported by World Health Organization in respect of December 14th, 2007, the mortality rate has now reached to 61 percent. Recent studies have shown that the high fatality rate of avian influenza virus infections is a consequence of an overactive inflammatory response and the severity of infection is closely related with virus-induced cytokine dysregulation. The most important feature of A/H5N1 immunopathogenesis is the appearence of hypercytokinemia ("cytokine storm") which is characterized by the extreme (exaggerated) production and secretion of large numbers and excessive levels of pro-inflammatory cytokines. This phenomenon is blamed on the emergence of lethal clinical symptoms such as extensive pulmonary oedema, acute bronchopneumoniae, alveolar haemorrhage, reactive haemophagocytosis, and acute respiratory distress syndrome, associated with necrosis and tissue destruction. Numerous in vitro, in vivo and clinical studies have pointed out that A/H5N1 viruses are very strong inducers of various cytokines and chemokines [Tumor Necrosis Factor (TNF)-alpha, Interferon (IFN)-gamma, IFN-alpha/beta, Interleukin (IL)-6, IL-1, MIP-1 (Macrophage Inflammatory Protein), MIG (Monokine Induced by IFN-gamma), IP-10 (Interferon-gamma-Inducible Protein), MCP-1 (Monocyte Chemoattractant Protein), RANTES (Regulated on Activation Normal T-cell Expressed and Secreted), IL-8], in both humans and animals. The privileged cells of cytokine storm are macrophages and CD8+ T-lymphocytes, while the primary contributor cytokines are TNF-alpha, IL-6 and IFN-gamma. It has been detected that, mutations of some viral genes (NS1, PB2, HA and NA) are responsible for the cytokine storm, by increasing the viral replication rate, expending the tissue tropism, facilitating the systemic invasion and emerging of resistance against the host antiviral response. It has been shown that Glu92 and Ala149 mutations, and carboxyl-terminal ESEV/EPEV motif of NS1 protein have been implicated as determinants of virulence for A/H5N1 strains. In addition, Lys627 mutation in PB2 protein, polybasic aminoacid mutations in the cleavage region of hemagglutinin (HA) polyprotein, and glycosylation and sialylation mutations in HA and neuraminidase (NA) proteins were found to enhance the immune-mediated patology of highly virulent A/H5N1 strains. In this review article, the immunopathogenesis of influenza infection and the mechanisms of cytokine storm caused by influenza A/H5N1 viruses have been discussed under the light of recent literature.

A probable role for IFN-gamma in the development of a lung immunopathology in SARS
Theron, M, Huang K-J, Chen Y-W, Liu, C-C, Lei H-Y Cytokine 2005 Oct 7; 32(1):30-38.

Recent work carried out in our laboratory showed the existence of a cytokine storm in SARS patients, dominated by Th1-type mediators. We thus hypothesized that IFN-gamma may play a major role in the pathology by triggering immune-mediated alveolar damage. As we assessed or re-assessed some effects of IFN-gamma on a number of human lung epithelial and fibroblast cell lines, chosen for their wide use in the literature, we found that alveolar epithelial cells were more sensitive to IFN-gamma, in terms of proliferation inhibition and enhancement of Fas-mediated apoptosis. While similar effects were obtained on fibroblasts, concentrations of IFN-gamma 4--8-fold greater were required. In addition, both epithelial and fibroblastic cell lines were able to secrete large quantities of T cell-targeting chemokines, similar to the ones detected in SARS patients. Based on the clinical data collected previously, the available literature and our in vitro experimentation, we propose that IFN-gamma may be responsible for acute lung injury in the late phase of the SARS pathology.

Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells.
Chan MC, Cheung CY, Chui WH, Tsao SW, et al. Respiratory Research 2005 Nov 11; 6(1):30-38.

Fatal human respiratory disease associated with influenza A subtype H5N1 has been documented in Hong Kong, and more recently in Vietnam, Thailand and Cambodia. We previously demonstrated that patients with H5N1 disease had unusually high serum levels of IP-10 (interferon-gamma-inducible protein-10). Furthermore, when compared with human influenza virus subtype H1N1, the H5N1 viruses in 1997 (A/Hong Kong/483/97) (H5N1/97) were more potent inducers of pro-inflammatory cytokines (e.g. tumor necrosis factor-a) and chemokines (e.g. IP-10) from primary human macrophages in vitro, which suggests that cytokines dysregulation may play a role in pathogenesis of H5N1 disease. Since respiratory epithelial cells are the primary target cell for replication of influenza viruses, it is pertinent to investigate the cytokine induction profile of H5N1 viruses in these cells. METHODS: We used quantitative RT-PCR and ELISA to compare the profile of cytokine

and chemokine gene expression induced by H5N1 viruses A/HK/483/97 (H5N1/97), A/Vietnam/1194/04 and A/Vietnam/3046/04 (both H5N1/04) with that of human H1N1 virus in human primary alveolar and bronchial epithelial cells in vitro. RESULTS: We demonstrated that in comparison to human H1N1 viruses, H5N1/97 and H5N1/04 viruses were more potent inducers of IP-10, interferon beta, RANTES (regulated on activation, normal T cell expressed and secreted) and interleukin 6 (IL-6) in primary human alveolar and bronchial epithelial cells in vitro. Recent H5N1 viruses from Vietnam (H5N1/04) appeared to be even more potent at inducing IP-10 than H5N1/97 virus. CONCLUSION: The H5N1/97 and H5N1/04 subtype influenza A viruses are more potent inducers of proinflammatory cytokines and chemokines in primary human respiratory epithelial cells than subtype H1N1 virus. We suggest that this hyper-induction of cytokines may be relevant to the pathogenesis of human H5N1 disease.