CytoSorb®

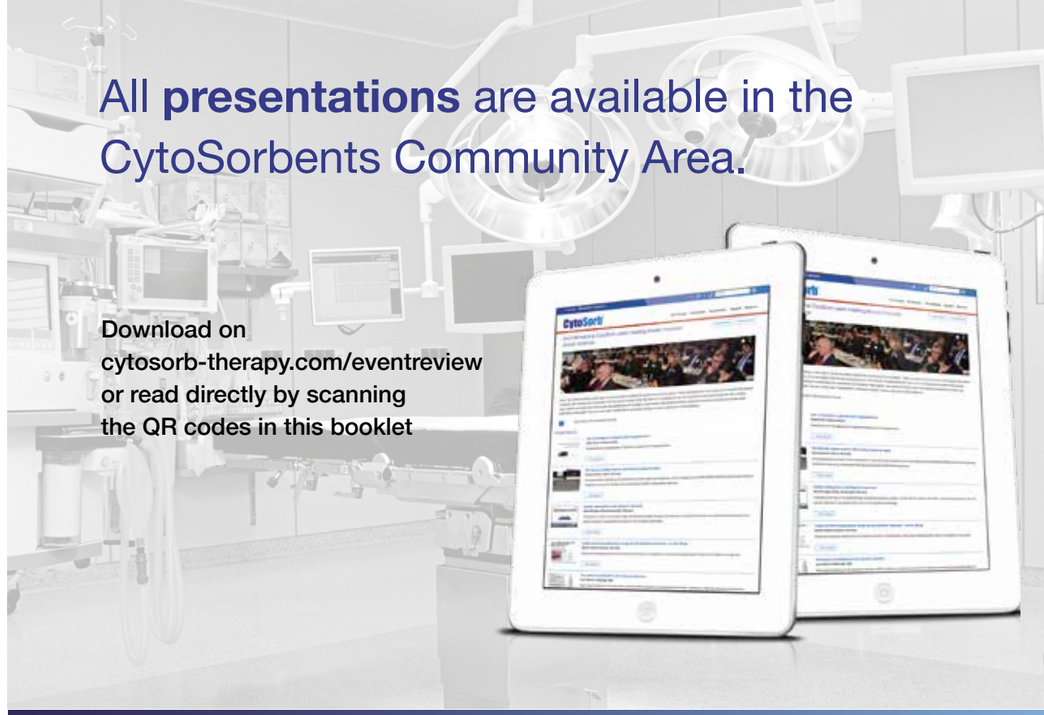
3rd International Users' Meeting

Proceedings

3rd International CytoSorb Users' Meeting
Brussels, Belgium, March 14th, 2016

CYTOSORB - THERAPY

REGAIN CONTROL



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3rd International CytoSorb Users‘ Meeting shows continuing experience of positive results

Held one day ahead of the International Symposium of Intensive Care and Emergency Medicine (ISICEM) the Users‘ Meeting brought together 107 members of the CytoSorb community from a total of 23 countries, to share data from many new pre-clinical and clinical studies. Up to now, data were migrating from single case reports studies to now case series and randomized clinical trials in a broad range of applications. We thank all participants having joined this platform that enabled users, partners and distributors to exchange their experiences with CytoSorb. The lessons learned will help how best to design large-scaled pivotal trials that will help to definitely answer outstanding issues and will ensure uniformity of treatment so that all users worldwide benefit from the latest information.

Key findings of the symposium include:

Safety

- To date, more than 11,000 CytoSorb human treatments have been safely performed in thousands of patients worldwide
- All of the presenters once again reiterated the safety of the device in all reported applications

Early use

- Several studies have suggested that early intervention with aggressive treatment is superior to late intervention in terms of clinical outcomes

Broadened removal and indication range

- In addition to cytokines, CytoSorb has been shown to remove a broad range of other inflammatory mediators called pathogen (PAMPs) and damage (DAMPs) associated molecular patterns, which play an important role in inducing systemic inflammation in a wide range of critical illnesses. PAMPs are toxins produced or released by bacteria, viruses and fungi that can cause tissue injury or inflammation. DAMPs originate from damaged or necrotic tissue, like HMGB-1, S100 protein, procalcitonin, and activated complement, and are also toxic in excessive quantities. DAMPs and PAMPs are a leading focus of international research on the uncontrolled systemic inflammatory response syndrome
- New systematic data, confirming previous observations, that CytoSorb can effectively remove liver toxins such as bilirubin, in some cases better than established liver support therapies
- Reiteration that CytoSorb is a useful therapy to reduce extensive myoglobinemia that occurs due to rhabdomyolysis due to trauma, burns, or infection
- An update on the start of the PACIFIC trial, using CytoSorb to treat severe acute pancreatitis

Reduction of post-operative complications in cardiac surgery

- The intra-operative application of CytoSorb in an ongoing three-arm controlled open heart surgery study in Cologne, Germany was associated with a statistically significant decrease in sternal wound infections, a major complication of cardiac surgery with a total of 165 patients enrolled to date
- In a cardiac surgery evaluation performed at Angers, France, CytoSorb was used intra-operatively on 10 patients undergoing a diverse set of complex cardiac surgery procedures. All ten patients did well, with CytoSorb credited with helping to stabilize two hemodynamically unstable patients going into extensive and complicated surgery, and reducing the need for vasopressors and extensive, costly, and risky extracorporeal life support that would normally be required in the post-operative period in these patients

Potential benefit in refractory septic shock

- Four different independent septic shock case series totaling more than 50 treated patients with severe or refractory shock, have all reported a consistent stabilization of the cardiovascular system following treatment, with a reduction in vasopressor support

On the following pages, you will have the opportunity to go through all the important information of a large part of the presentations at a glance. Enjoy your reading.

Introduction to the CytoSorb Therapy

John Kellum, Pittsburgh, USA

Setting the stage Professor Kellum gave a comprehensive introduction on blood purification in general and on the CytoSorb therapy in particular, the underlying operating principle derived from preclinical data and its potential benefit in fighting life-threatening infections.

Cytokine Patterns and Survival

- Association of different IL-6 and IL-10 levels with mortality in pneumonia and sepsis

Blood purification techniques and their association with mortality in patients with sepsis

- Blood purification techniques including hemoperfusion, plasma exchange, hemofiltration are associated with lower mortality in patients with sepsis compared to conventional treatment, with hemoperfusion having the strongest overall effect
- These results were mainly influenced by studies using polymyxin B hemoperfusion
- Studies using renal replacement therapy have not been as effective
- High-volume versus standard-volume hemofiltration for septic shock patients with acute kidney injury have not been terribly persuasive probably due to inadequate patient selection or due to the inability of whole fiber dialyzers to remove a substantial amount of cytokines

Hemoadsorption and CytoSorb technology has the potential to remove considerable amounts of cytokines

- Efficient in vitro elimination of key cytokines (TNFα, IL-6, IL-10) with CytoSorb
- Efficient removal of key cytokines (TNFα, IL-6, IL-10) and improved survival with CytoSorb in rat models of sepsis
- Even without acute reduction of plasma cytokine levels there are still late reductions in circulating cytokines associated with improvements in outcome pointing towards additional effects of the adsorber than just the removal of cytotoxic inflammatory mediators

Effects of CytoSorb beyond sole removal of cytotoxic inflammatory mediators

- Chemo-attractants
  - PMNs (e.g. IL-8)
  - T-Regs (e.g. CCL18)
  - Fibroblasts (e.g. MCP-1)
- DAMPs & PAMPs (Damage- and Pathogen-associated patterns)
  - Damage (e.g. HMGB1)
  - Pathogen (e.g. exotoxins, other bacterial or fungal products)

Usage of CytoSorb in an animal model of sepsis resulted in

- Decreased liver injury (ALT)
- Decreased kidney injury (creatinine)
- Decreased DAMPs (HMGB-1)

Underlying operating principle

- The ratio of local to systemic chemokine concentrations regulates neutrophil recruitment
- High systemic concentrations of cytokines “distract” the leukocytes from source of infection
- Hemoadsorption using CytoSorb modulates regulation of neutrophil recruitment via chemokine concentrations and results in retargeting and trafficking of neutrophils with enhanced neutrophil activity and bacterial clearance at the “true” site of infection

In summary, preclinical results with CytoSorb indicate:

- Broad spectrum removal of inflammatory mediators
- Reduced circulating concentration of inflammatory mediators
- Reprogramming of the innate immune response through modulation of chemokine gradients
- Protection of epithelium in the kidney and liver (presumably related to removal of DAMPs/PAMPs)
- Significant improvement in survival in high-lethality models

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Early cytokine adsorption in septic shock: The ACCES trial

Zsolt Molnar, Szeged, Hungary

Professor Molnar gave an overview on the evolution from a localized insult to life-threatening organ dysfunction caused by dysregulated host response, discussed the main conclusions from current CytoSorb evidence and presented data gained so far in the **ACESS** trial (**A**dsorption of **C**ytokines **E**arly in **S**eptic **S**hock) as well as data from two patients.

Preliminary results of ACESS

- In total 8 patients have been included in the treatment group so far
- Trend towards an improvement of SOFA score and oxygenation (PaO_2/FiO_2), as well as a considerable decrease of extravascular lung water (EVLW), need for norepinephrine and procalcitonin in the first 48 hours

Presentation of two cases demonstrating when to commence CytoSorb treatment and when not

Case history #1 – When to commence CytoSorb treatment

- Admitted with acute respiratory complaints
- Looked poorly on assessment, low SpO_2 despite on O_2, laboured breathing
- Transfer to the ICU with intubation and mechanical ventilation
- The following parameters were assessed
  - Tachycardia, dropping urine output, FiO_2 0.7, pyrexia, PCT (8.5 ng/ml)
  - High need for norepinephrine (25 µg/min) to keep MAP at 62 mmHg
  - A few hours later - unable to reduce norepinephrine and also deterioration of the other variables
- Recommendation to use CytoSorb in such a clinical picture due to massive (ongoing) inflammatory response with no improvement after resuscitation

Case history #2 - When not to commence CytoSorb treatment

- 46 year old woman admitted with cholangitis to medical ward via A&E
- Looked poorly, hypotensive, clammy, altered level of conciousness, however did not require mechanical ventilation at the time
- Transfer to the ICU
- The following parameters were assessed
  - High need for norepinephrine (25 µg/min) to keep MAP at 57 mmHg
  - Arterial blood gases looked poor (HCO_3 10 mmol/l, lactate 13 mmol/l)
  - Renal dysfunction
  - Increase of PCT to 173 nmol/L and CRP to 92 mmol/L
  - Still no need for mechanical ventilation
  - PiCCO measurement revealed hypovolemia followed by continued massive fluid resuscitation
  - Further, improvement of all parameters in the upcoming hours and full recovery in the next days without the need for CytoSorb

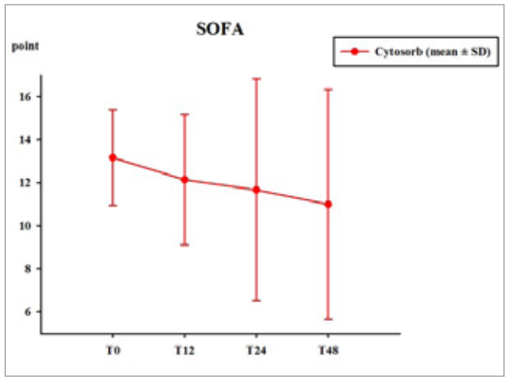

Fig 1: Course of SOFA score throughout the CytoSorb treatment in the ACESS trial

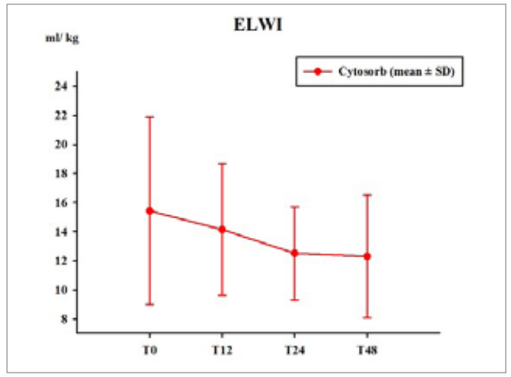

Fig 2: Course of extravascular lung water index (ELWI) throughout the CytoSorb treatment in the ACESS trial

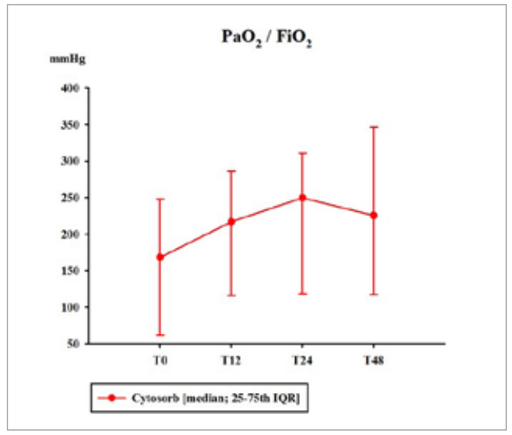

Fig 3: Course of PaO_2/FiO_2 ratio throughout the CytoSorb treatment in the ACESS trial

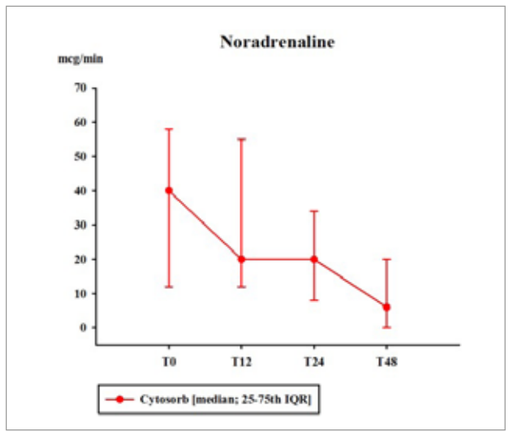

Fig 4: Course of norepinephrine throughout the CytoSorb treatment in the ACESS trial

view full presentation

CONCLUSIONS

- CytoSorb as an adjuvant therapy is safe and easy to apply, improves organ function and potentially attenuates the cytokine storm
- To get the most out of CytoSorb further knowledge is needed regarding:
  - In whom to treat and on which indications?
  - For how long to treat?
  - On what basis could treatment be individualised?

Outcome observations in early vs. late use in septic shock patients

M Drüner, Emden, Germany

In his talk Dr. Drüner described the clinical effects of CytoSorb therapy in his institution (Emden hospital, Germany) and presented outcome observations in early vs. late use.

Current status in Emden

- Start of using CytoSorb therapy in March 2014
- Up to now treatment of 21 patients with a mean of 3 CytoSorb adsorbers per patient

Setting

- Retrospective study and data analysis from 14 patients treated with Cytosorb
- All patients having septic shock due to pneumonia, pancreatitis or peritonitis
- Determination of SOFA and SAPS II score, evaluation of lactate, mean blood pressure and catecholamine demand before, during and after treatment with Cytosorb
- Indications for application of CytoSorb adapted to former Drotrecogin α trials

Results - Data pre/post CytoSorb treatment

- Increase of MAP of 30% while need for norepinephrine dropped by 76% at the same time
- To show these effects even better, the demand of norepinephrine in µg/h vs. the thereby achieved MAP was calculated showing a 90% decrease when comparing pre and post treatment ratios
- Decrease of lactate levels by 53%

Results - Comparison of Survivors and Non-Survivors

- No differences in SAPS, organ failure, lactate levels
- However, non-survivors showed the following differences compared to survivors:
  - Older, higher APACHE II, more norepinephrine
  - Greater delay of CytoSorb therapy start (61.3 hours vs. 28.8 hours in survivors)
- Dividing patients into 3 groups regarding initiation of CytoSorb therapy (> 48 hours, between 24 and 48 hours, < 24 hours after admission to ICU) showed that none of the patients receiving CytoSorb later than after 48 hours survived hospital stay while 50% of patients survived when therapy was started < 48 hours and even 66.7% of the patients survived if CytoSorb was commenced < 24 hours

		Minimum	Maximum	Mean	Std. Deviation
MAP (mmHg)	pre	35.00	70.00	54.21	12.03
	post	30.00	85.00	71.7 (+ 32%)	15.4
Norepinephrine (mg/h)	pre	1.90	18.00	4.03	4.17
	post	0	5.00	0.95 (- 76%)	1.41
SOFA-Score	pre	8.00	17.00	12.28	3.02
	post	4.00	18.00	10.85	3.91
Lactate (mg/dl)	pre	9.20	136.30	42.69	38.99
	post	4.70	55.1	20.19 (- 53%)	16.13
Norepinephrine (µg/h) vs. MAP (mmHg)	pre	31.66	428.60	84.81	104.47
	post	0	42.85	8.84 (- 90%)	11.76
SAPS-II score	pre	36	73	54.71	11.75
	post	22	73	42.21	15.89

Table 1: Data on hemodynamics, severity scores and lactate comparing values before CytoSorb initiation and after CytoSorb withdrawal

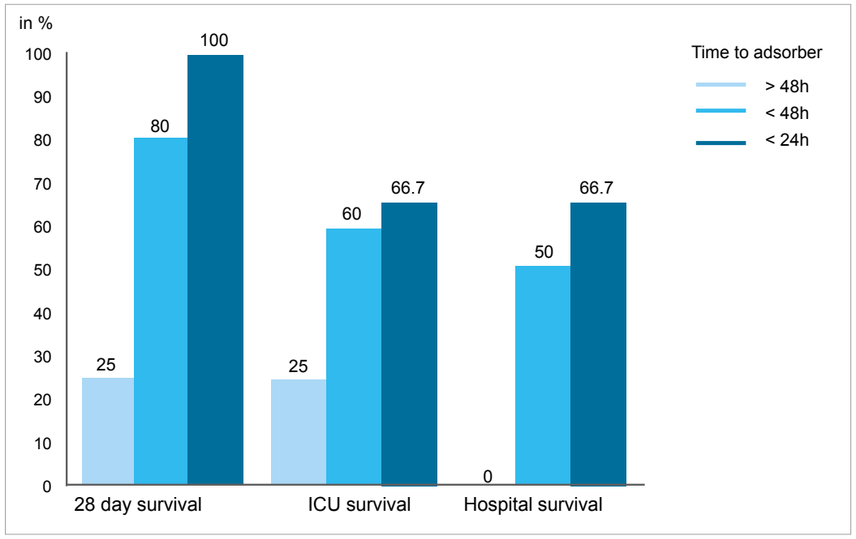

Fig 1: Impact of delay of therapy initiation (after admission to ICU) on survival

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CONCLUSIONS

- The main measurable effect seen in these patients is a drop of catecholamine-demand and a dramatic drop in lactate levels
- Therapy with CytoSorb seems to be safe and easy, with only one experience of filter-clotting during heparin anticoagulation and one case of severe lactate acidosis which was not likely to have been caused by the CytoSorb treatment
- Survival seems to be connected to an early start of therapy (within 24 hours)
  - Two-thirds of the patients with early treatment survived ICU (but only 25% of the patients with delayed treatment)
  - Nearly two-thirds of the early treated patients left hospital as survivors (but none of the delayed treated patients)
- Therefore, early start of CytoSorb therapy within 24 hours, latest within 48 hours seems to be favorable concerning survival.

Treatment experience in various types of septic shock

A Grootendorst, Rotterdam, Netherlands

Dr. Grootendorst outlined his history with blood purification presenting early experimental data in an animal model of endotoxic shock and shared his experience with the first 41 patients treated with CytoSorb in his department.

Patients (n=41) treated with CytoSorb comprise

- Abdominal septic shock (n=18)
- Pneumonia with septic shock (n=6)
- Septic arthritis with septic shock (n=3)
- Urinary tract infection with septic shock (n=3)
- Necrotizing fasciitis with septic shock (n=3)
- Rhabdomyolysis (n=2)
- Pancreatitis with shock (n=3)
- Other (n=3)

Results from 10 patients with abdominal septic shock

- Start of CytoSorb therapy in these patients at the moment when they need more than 3 mg/hour of norepinephrine (even before renal failure is evident by increased creatinine)
- Hemodynamic stabilization of the patients within hours
- CytoSorb therapy was stopped when septic shock stagnated and when norepinephrine was reduced to low levels resulting in a small number of CytoSorb treatments per patient (1-3) and modest time on renal replacement therapy
- 6 of 10 patients survived beyond the 3 month follow-up

However, to get the most out of CytoSorb further knowledge is needed regarding

- Is there a definite effect on mortality?
- What is the optimal duration of treatment?
- Is there an impact on levels of antibiotics, leading to a possible need for adjustment of dosage?

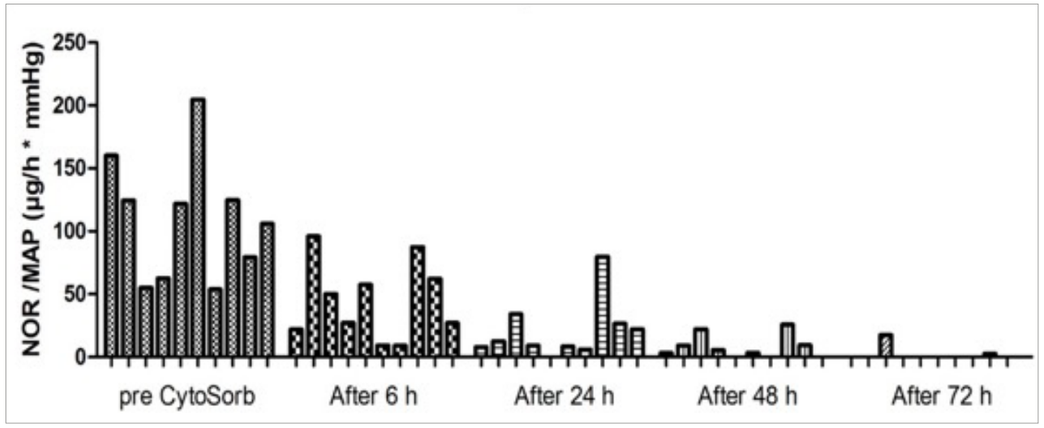


Fig 1: Demand of norepinephrine vs. the thereby achieved MAP in 10 septic shock patients treated with CytoSorb

Patient No.	Diagnosis	Age	Gender	BMI	APACHE IV (at admission)	APACHE IV predicted mortality (%)	Outcome ICU (alive/dead)
1	Abdominal Sepsis	59	F	54.7	119	77.7	alive
2	Abdominal Sepsis	79	M	29.4	79	17.9	dead
3	Abdominal Sepsis	52	F	25.4	123	80.5	dead
4	Abdominal Sepsis	66	F	43	92	48.9	dead
5	Abdominal Sepsis	54	M	25.5	113	56.6	alive
6	Abdominal Sepsis	72	M	23.5	48	10	alive
7	Abdominal Sepsis	38	M	18.8	80	29	alive
8	Abdominal Sepsis	80	F	29.1	117	64.8	dead
9	Abdominal Sepsis	57	F	23.9	112	67.4	alive
10	Abdominal Sepsis	42	F	30.1	99	69.2	alive

Fig. 2: Patient characteristics and outcome parameters

CONCLUSIONS

- Treatment with CytoSorb results in a significant stabilization of hemodynamics with declining needs for catecholamines
- RCT's are necessary to establish the true benefit of CytoSorb therapy
- Antibiotic therapy should be monitored
- CytoSorb treatment appears to be safe and well tolerated with no device-related adverse events

In vitro adsorption of a broad spectrum of sepsis inflammatory mediators with CytoSorb

M Gruda, CytoSorbents Corporation, New Jersey, USA

Dr. Gruda presented brand new in vitro data on the capability of CytoSorb to remove not only a broad spectrum of inflammatory mediators but also toxins from different microbiological sources using a whole blood single compartment model.

In vitro adsorption of cytokines and DAMPs from blood

- Human cytokines IFN-ɣ (25 kDa), IL-6 (26 kDa), MIP1-α (8 kDa) given at clinically relevant concentrations were all adsorbed well in comparison to a control device and were stable throughout the time course of the recirculation experiment
- Human TNF-α (52 kDa), IL-8, and HMGB-1 (25 kDa) were also all adsorbed well, however due to the molecular weight dependence TNF-α is not adsorbed as efficient as smaller molecules such as IL-8
- S100-A8 (20 kDa), procalcitonin (13 kDa) and C5a (8.2 kDa) are all rapidly adsorbed

In vitro adsorption of PAMPs (toxins) from blood

- Staph. aureus PAMPS
  - With Staph. aureus there is a number of pathogenic factors that are released depending on the different strains
  - Staph. aureus α–toxin (α–hemolysin; 28 kDa) which is a pore forming toxin is adsorbed very well by the adsorber
  - Staph. toxic shock syndrome toxin (TSST-1) representing a superantigen that dysregulates the immune response is also adsorbed well
- Streptococcus PAMPS
  - Strep pyrogenic exotoxin B (SPE B) involved in many septic infections is efficiently removed
- Fungal Toxins
  - Aspergillus flavus Aflatoxin B1 is very rapidly adsorbed

Examples of successful toxin removal with CytoSorb therapy

- MRSA sepsis
- S. aureus endocarditis
- Soft tissue infections (e.g. necrotizing fasciitis)
- Toxic shock syndrome

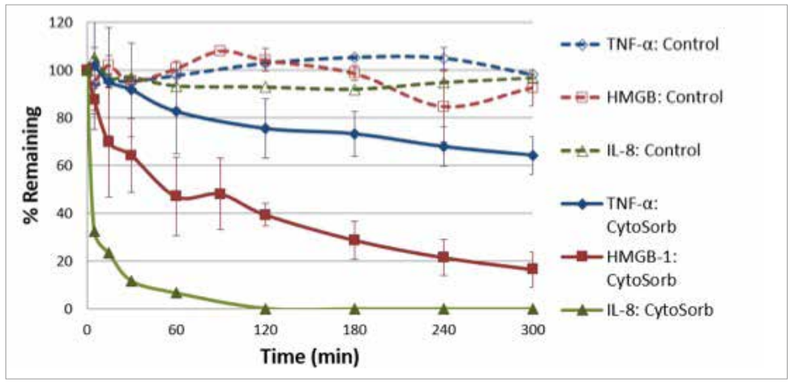


Fig 1: In vitro adsorption of TNF-α, HMGB-1 and IL-8 from blood with CytoSorb or control device

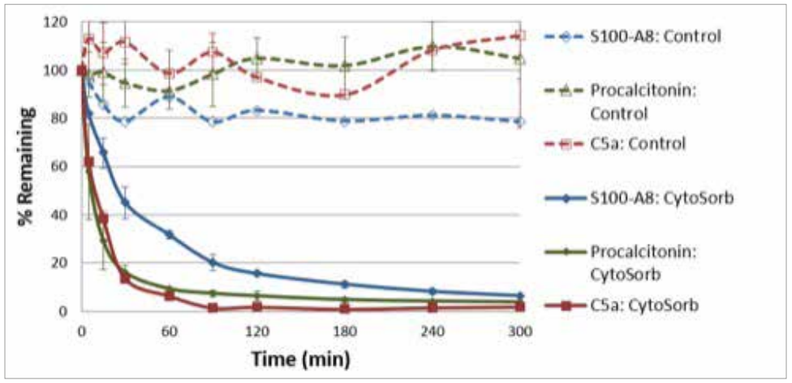


Fig 2: In vitro adsorption of S100-A8, procalcitonin and C5a from blood with CytoSorb or control device

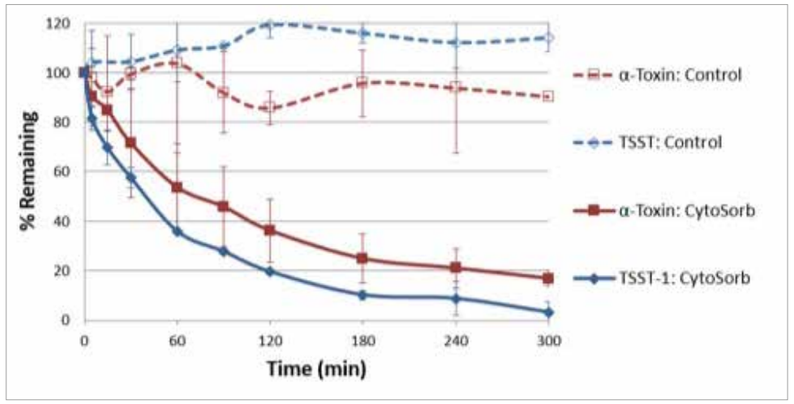


Fig 3: In vitro adsorption of Staph. aureus α-toxin (α-hemolysin) and Staph. aureus toxic shock syndrome toxin (TSST-1) from blood with CytoSorb or control device

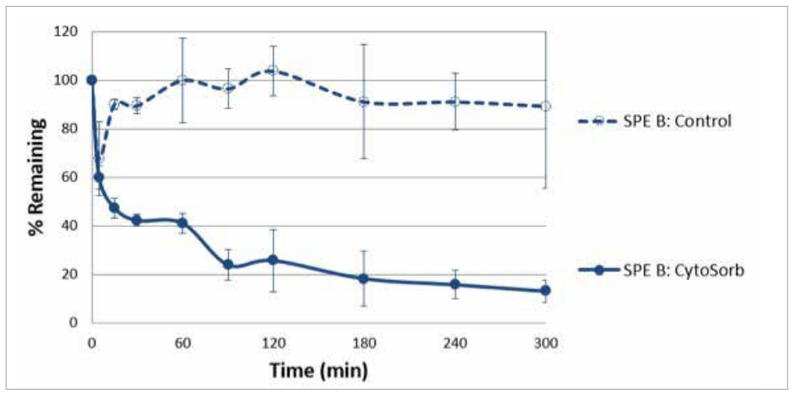


Fig 4: In vitro adsorption of Streptococcus pyrogenic exotoxin B (SPE) from blood with CytoSorb or control device

view full presentation

CONCLUSIONS

- Reduction of pro-inflammatory cytokines that drive inflammation, cell death and organ damage in sepsis
- Reduction of immunosuppressive cytokines & reestablishment of immune responsiveness
- Caution should be taken with procalcitonin as a biomarker when drawing clinical conclusions from it, as the compound is rapidly removed by the adsorber
- Adsorption of bacterial toxins that can cause tissue damage

CytoSorb in cardiac surgery: background, rationale and first data

AC Deppe, Cologne, Germany

Dr Deppe reported on the preliminary results of their large prospective pilot study in patients undergoing elective coronary artery bypass grafting (CABG).

Study type and patients

- Prospective, observational pilot study
- Elective surgical myocardial revascularization

Allocation

- 1 : 1 : 1 allocation to 3 groups (with 100 patients in each group)
  - On pump myocardial revascularization without CytoSorb = CPB group
  - On pump myocardial revascularization with CytoSorb = CytoSorb group
  - Off-pump myocardial revascularization = OPCAB group
- Only results comparing the two on-pump groups (CPB, CytoSorb) were presented

Interim results - Patient characteristics

- Up to this day inclusion of 64 patients in the CPB and 61 patients in the CytoSorb group
- Similar baseline characteristics and intraoperative data between both groups

Interim results - Laboratory

- IL-6 in CytoSorb group reduced without significance while levels of TNF-α and IL-8 are comparable in patients with CPB with and without CytoSorb, probably due to the short cardiopulmonary bypass time of ~80 minutes
- Hormone levels indicate a significantly reduced T3 in CytoSorb group, T4 and cortisol levels are comparable between the groups
- All other safety measurements (platelets, free hemoglobin, fibrinogen, etc.) with no differences between groups

Interim results - Clinical

- Slight trend towards quicker recovery of CytoSorb patients
  - Shorter stay at ICU and in hospital
  - Shorter time of hemodynamic support with catecholamines
  - Less need for antibiotics
- Significantly reduced amount of sternal wound infection

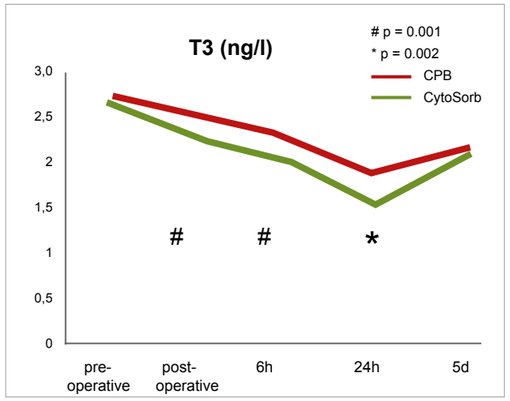


Fig 2: Course of T3 between patient groups

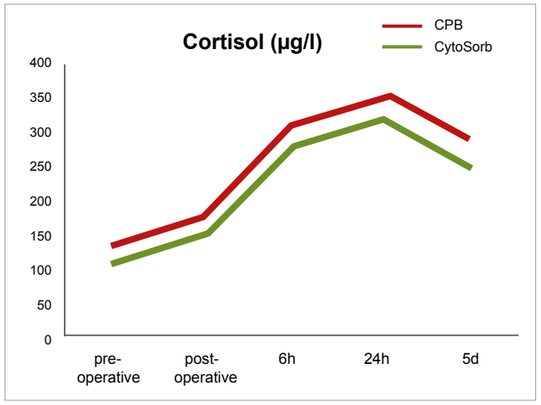


Fig 1: Course of cortisol between patient groups

	CPB (n=61) mean±SD or (N)	CytoSorb (n=61) mean±SD or (N)	p-value
Blood loss 24h (ml)	688 ± 280	712 ± 385	0.720
Transfusion			
- Erythrocyte concentrate 24h (units)	0.9 ± 1.8	1.2 ± 1.7	0.334
- FFP 24h (units)	0.6 ± 1.9	0.6 ± 1.9	0.924
- Platelets 24h (units)	0.1 ± 0.4	0.2 ± 0.5	0.367
Re-exploration	3.5	7.4	0.430
Length of stay (d)	10.4 ± 9.1	9.1 ± 3.0	0.172
ICU stay (d)	4.3 ± 5.0	3.9 ± 3.8	0.634
Noradrenaline (h)	32 ± 41	28 ± 30	0.553
Dobutamine (h)	21 ± 20	19 ± 14	0.513
Infection	36.8%	29%	0.546
Sternal wound infection	12.5%	1.8%	0.036
Hemodialysis	3.6	0	0.496
Cerebrovascular accident	3.6	0	0.496

Fig. 3: Clinical outcomes between patient groups

CONCLUSIONS

- The use of CytoSorb during CPB is safe and applicable without technical complicacy
- CytoSorb reduces cytokines and inflammatory response
- Hormone levels, especially T3, should be monitored after Cytosorb adsorption
- Trends in improved clinical recovery and reduced incidences of sternal wound infection need to be confirmed

Experiences with intraoperative CytoSorb treatment in cardiac surgery

G Peeters, Angers, France

Dr. Peeters reported his clinical experience with the use of CytoSorb during cardiopulmonary bypass (CPB) surgery.

Objective of the treatment series

- To test safety and feasibilty of the adsorber therapy in a CPB circuit
- To test efficacy of the adsorber
- To validate postoperative outcome

Results - Patient characteristics

- 10 patients (included from 1st of July - 20th of September 2015)
- Altered left ventricular function
- Patients for whom intraoperative hemofiltration is considered (i.e. renal function or impaired liver function, long surgical procedure)
- Active endocarditis (n=3), aortic valve replacements (n=4), aortic valve + mitral valve (n=2), coronary bypass surgery (n=1)

Results - Laboratory

- Moderately elevated levels of procalcitonin on post-operative day 1 with considerably decreasing values in the next days
- Leucocytosis on post-operative day 1 normalizing on post-operative day 3
- CRP levels increased with decreasing values from post-operative day 3

Results - Morbidity

- Time on ventilator (median 13 hours)
  - Two patients could be weaned from CPB much earlier than expected
- Very low total volume of blood loss within first 24 hours (median 60 ml)
- Pulmonary and renal failure (n=1), dialysis (n=1), transfusion (n=2)
- Flow rate and pressures with CytoSorb in the CPB circuit
  - No problems with the recommended flow rate of 400 ml/min
  - No problems with inflow and outflow pressures
- No adverse event nor clotting or thrombosis were seen

Criteria	Results (median 1st and 3rd quartile or number of patient)
Age	66 [54 ; 68]
BMI	23.4 [20.7 ; 25.2]
Body surface	1.87 [1.66 ; 1.98]
Gender (male)	8
Euroscore	1.34 [0.94 ; 2.51]
Ejection Fraction	40 [35 ; 53]

Table 1: Patient characteristics

Criteria	Results (median 1st and 3rd quartile)
Total volume of priming (mL)	1700 [1344 ; 1700]
Surgery procedure length time (min)	69 [35 ; 104]
Extracorporeal circulation length time (min)	119 [69 ; 152]
Aortic clamp length time (min)	79 [51 ; 116]

Table 2: Extracorporeal circulation data

Criteria	Results (median 1st and 3rd quartile)
Time of ventilator (hours)	13 [6.75 ; 30]
Total volume on blood loss in 24h (ml)	60 [30 ; 220]

Table 3: Comorbidity data

CONCLUSIONS

- CytoSorb was biocompatible considering the goal directed anticoagulation practice
- Pressure drop across CytoSorb remained stable (60-80 mmHg)
- Intraoperative hemofiltration can be used in series with CytoSorb, upstream of the adsorber
- Cytosorb can reduce the need for catecholamines in hemodynamically unstable patients which receive complicated cardiac surgery. As a result of that, there is probably less need for extracorporeal life support
- No mortality was observed

Quantification and kinetics of bilirubin removal with CytoSorb

S Faenza, Bologna, Italy

In his presentation Professor Faenza presented the results of his in vitro research on bilirubin removal with CytoSorb and outlined his experience in patients with liver transplantation and liver insufficiency.

Results

- In vitro study (to test kinetics of bilirubin/albumin removal)
  - In vitro experiments demonstrated the capability of CytoSorb to adsorb protein-bound solutes (i.e. bilirubin) breaking the albumin-bilirubin complex in an equimolar solution of albumin-bilirubin containing only unconjugated bilirubin which is strongly albumin-bound and is normally difficult to adsorb when attached to albumin
  - Removal of 90% of total bilirubin within 24 hours and a minimal loss of albumin in a setting reproducing clinical conditions with higher concentration of bilirubin and lower of albumin
  - Adsorption capacity remained intact for all the 24 hours with no release of bilirubin by CytoSorb
- In vivo study (to test congruence of in vivo data with in vitro results)
  - Clinical outcomes in 3 patients with gram-negative sepsis and cirrhosis post-transplantation
  - Bilirubin could be successfully reduced in two of the three patients to up to 64% removal within the treatment interval

Case report

- 66-years-old male patient with hepatitis C virus (HCV)-related cirrhosis, complicated by hepatocellular carcinoma (HCC), listed for liver transplantation (MELD 10)
- First liver transplantation from a non-heart-beating donor developing post-reperfusion injury with high need of noradrenaline and adrenaline, severe metabolic acidosis, hyperlactatemia, hypernatremia, and acute renal failure
- Second liver transplantation after rejection of the first graft resulting in acute renal failure, hyperbilirubinemia, severe sepsis
- Initiation of CVVHDF combined with 4 sessions of CytoSorb for 96 hours in total
- Results:
  - No more need of inotropes after the 2nd treatment
  - Dramatic reduction and normalization of bilirubin
  - Normalization of myoglobin levels
  - Functional recovery of the graft
  - Dismission of the patient from ICU

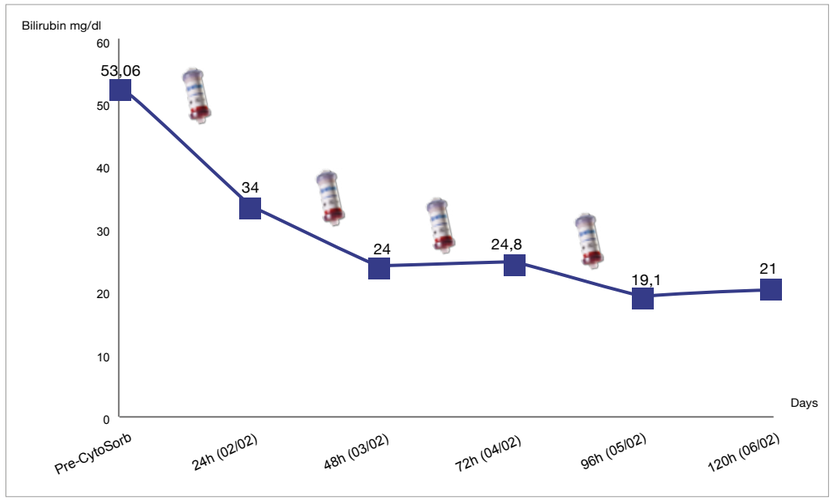
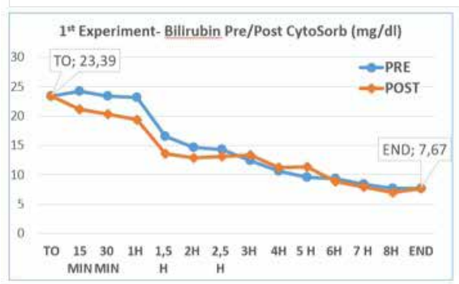


Fig 1: Course of bilirubin in a patient with hyperbilirubinemia post transplantation treated with CytoSorb

Experiment	Time (h)	Vol. Solution (lt)	Concent. mmol/lt	Bilibrubin Mass Balance
1st	8	6	0.4	944
2nd	8	6	0.8	1,020



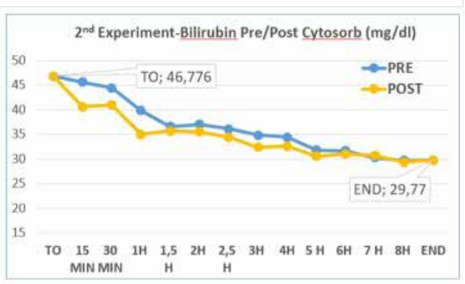


Figure 2: Two in vitro experiments demonstrating the capability of CytoSorb to adsorb bilirubin

Experiment	Time (h)	Vol. Solution (lt)	Bilirubin Conc. mmol/lt	Albumin Conc. mmol/lt	Bilibrubin Mass Balance	% Removal
3rd	24	6	0.8	0.4	2,499	90%

Figure 3: Experiments demonstrating no release of bilirubin by the resin, minimal loss of albumin and the capability of CytoSorb to maintain adsorption capacity for up to 24 hours

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CONCLUSIONS

- In Vitro
  - Ability to adsorb unconjugated bilirubin, breaking the albumin-bilirubin complex (strongly bound)
  - Active bilirubin removal all along 24 hours and no release of adsorbed bilirubin
  - Minimal loss of albumin in condition similar to clinical conditions
- In Vivo (preliminary)
  - Congruence with in vitro data
  - In vivo removal seems to work even better than in vitro
  - Use CytoSorb early and continue until homeostasis restores

Treatment experience with CytoSorb in severely burnt patients

C Calin, Bucharest, Romania

Dr. Calin reported on her experience with CytoSorb in three severely burnt patients after a fireworks accident at a Bucharest nightclub.

Importantly, this was not a specialized burn center. Patients were rather treated in the acute phase with the target of later transferral to specialized burn units.

Case presentation

- All three patients (22-35 years old) experienced burns on 30-47% of the skin surface (cervical, face, head, both arms, anterior and posterior thoracic segments severity IIa, IIb, III)
- Hot air, monoxide and toxic gas inhalation
- Respiratory failure with need for mechanical ventilation

Treatment

- Daily wound debridement
- Bacteriologic workup: at admission and then in 72 hours interval
- Antibiotic therapy with broad spectrum antibiotics according to the results of respiratory secretions, blood culture, urine culture and wound cultures
- Mechanical ventilation
- Severe respiratory failure with need of NO therapy in two of the three patients
- CO_2 removal device
- Bronchoaspiration
- Implantation of a veno-venous extracorporeal device (iLA) in one patient
- Start of CVVH with CytoSorb applied between two and up to 16 days (24 hours per treatment)

Measurements

- Hemodynamic parameters, biochemical assays and vasopressor need were recorded especially after wound debridement

Results

- In one patient after removal of CytoSorb therapy increasing needs of vasopressors, fever, increase of serum presepsine levels
- Vasopressors dosages could be significantly decreased during treatment
- Improvement of hemodynamics with a stabilized MAP
- After the initiation of the therapy with CytoSorb and NO the respiratory dysfunction improved
- Improvement of oxygenation PaO_2/FiO_2 and decrease of inspiratory oxygen need with subsequent stop of CO_2 removal and NO therapy
- Remission of leukocytopenia and drop in serum presepsin level in one patient

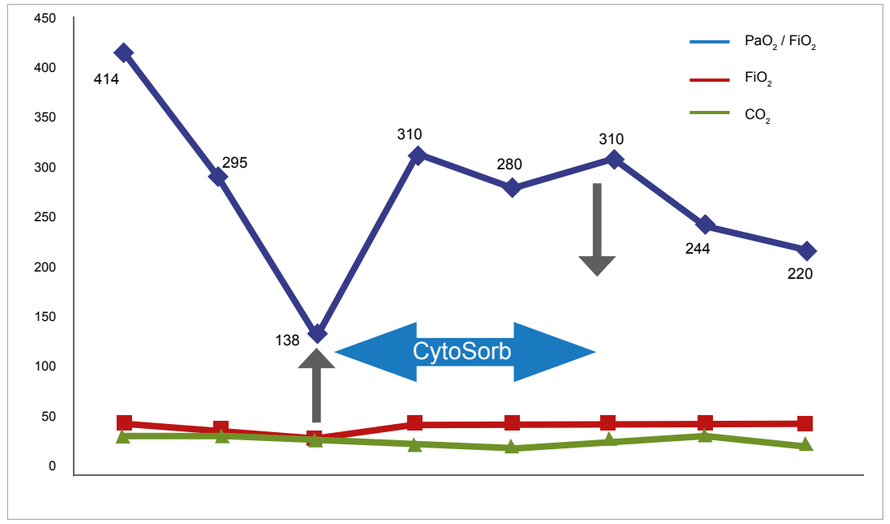


Figure 1: Course of PaO_2/FiO_2 ratio, CO_2, FiO_2 before, during and after CytoSorb treatment in a severely burnt patient

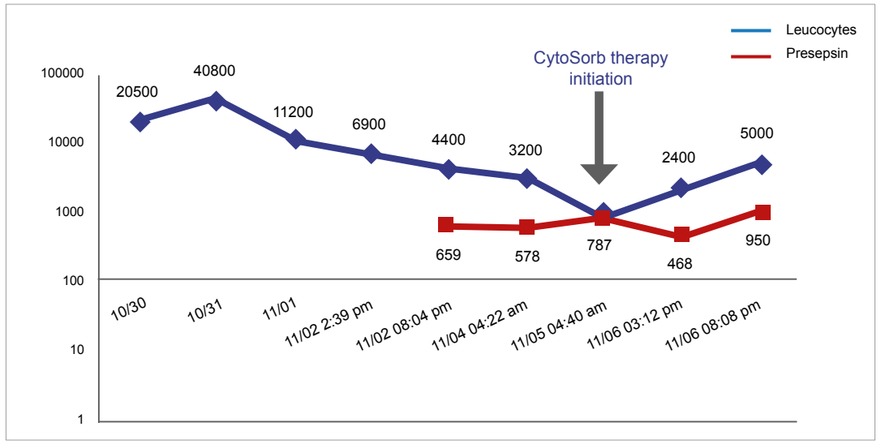


Figure 2: Course of leucocytes and presepsin before, during and after CytoSorb treatment in a severely burnt patient

view full presentation

CONCLUSIONS

- CytoSorb therapy was safe and easy to apply
- The use of CytoSorb therapy in combination with NO led to an improvement of oxygenation and hypercapnia under CO_2 removal device
- The use of CytoSorb was associated with an improvement in hemodynamics and inflammatory status
- The control of excessive inflammatory response with CytoSorb helped in improving gas exchange, allowing to use protective ventilation
- This therapy might be useful in circumstances like wound debridement when large quantities of inflammatory mediators are released
- The optimal point of time for use in burns remains to be determined

Role of CytoSorb in the therapy of severe acute pancreatitis

A Faltlhauser, Weiden, Germany

Dr. Falthausers group works on the use of CytoSorb in the early treatment of acute severe pancreatitis. The idea is to alleviate the side effects of the hefty cytokine storm in the early phase of this disease. The results of a clinical workup of a small cohort of patients will help to plan the upcoming PACIFIC (Pancreatitis CytoSorb Inflammatory Cytokine Removal)trial, which will target the use of CytoSorb in this clientele in a prospective fashion.

Up to now, Dr. Faltlhauser and his team have treated 7 patients with acute severe pancreatitis with CytoSorb. Three exemplary patients with two contrary courses were presented at the meeting.

- **Patient 1, male (early treatment)**
  - alcohol related toxic acute severe pancreatitis
  - Came into hospital very early
  - 14 hours after onset of the typical pain

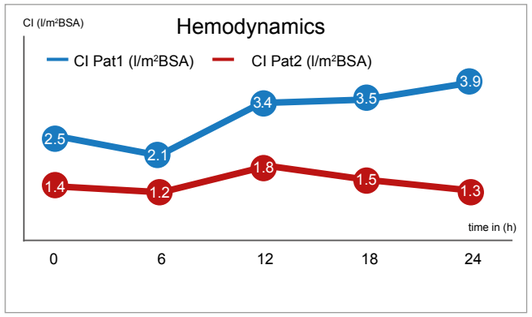
- **Patient 2, male (late treatment)**
  - alcohol related toxic acute severe pancreatitis
  - Came into hospital very late
  - 44 hours after onset of the typical pain with a much more pronounced pathophysiology and a delay in treatment

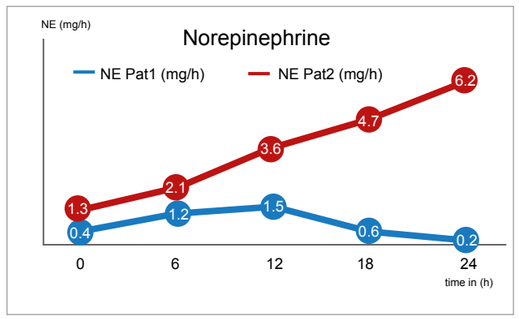
Immediate CVVH with CytoSorb was initiated in both cases. During the course of the treatment patient 1 recovered quickly, as represented by an improvement in hemodynamics, decreased needs for catecholamines and dropping IL-6 levels.

Patient 2 however after initial low level stabilization deteriorated in all of the three measures. These effects could be seen already in the first 12 to 18 hours of treatment.

Dr. Faltlhauser presented a third case of pancreatitis with subsequent development of acute peritonitis and a severe septic course.

- **Patient 3**
  - Female with acute severe pancreatitis initially treated with very aggressive therapy however not sick enough to be treated with CytoSorb
  - 3 weeks later she developed acute peritonitis and abdominal compartment after transgastric revision of a huge pancreatic cyst. After surgery in a detrimental situation (massive hemodynamic instability with highest levels of vasopressor support and peripheral vasoplegia in massive cytokine storm)
  - CytoSorb treatment in this patient aided stabilization of hemodynamics, evidenced by swift reduction of catecholamine requirement and also showcased by reduced IL-6 levels within only 6 to 12 hours





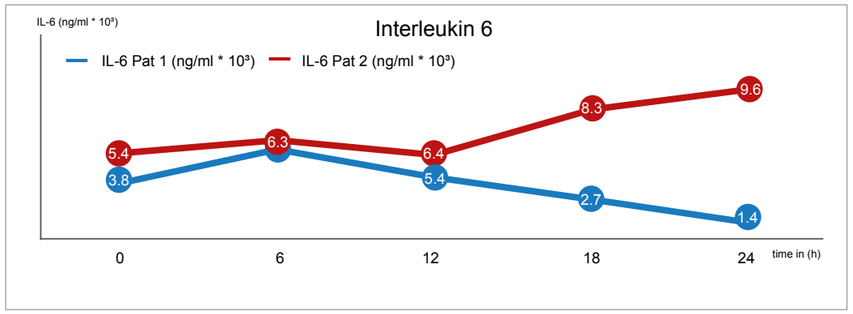
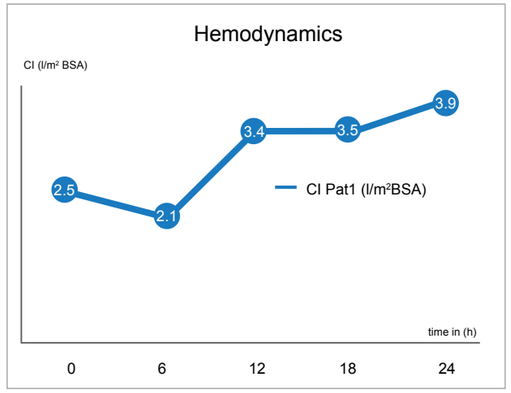
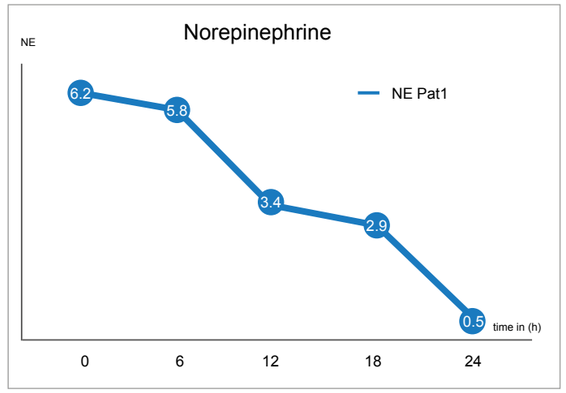


Fig 1: Two exemplary patients (pt. 1 and 2) same pathology - two contrary courses





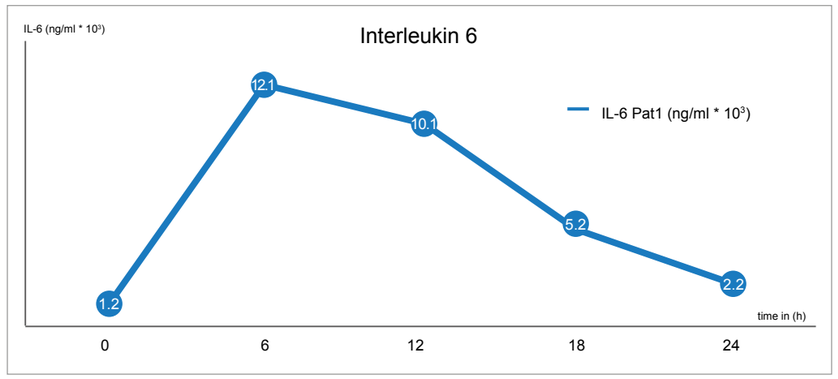


Fig 2: Typical severe septic course under CytoSorb treatment (patient 3)

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CONCLUSIONS

- Proof of safety: CytoSorb treatment can be performed safely
- Proof of concept: IL-6 as key inflammatory marker can be significantly reduced
- CytoSorb treatment aids to reduce vasopressor use and improves global hemodynamics
- However, there are still questions to answer that include
  - Does CytoSorb treatment provide
    - Reduction of morbidity
    - Reduction of mortality
  - Dosing of CytoSorb treatment
  - Drug dosing under CytoSorb treatment
  - Cost benefit evaluation

Treatment support of rhabdomyolysis patients by CytoSorb

D Fries, Innsbruck, Austria

In his talk Prof. Fries presented his experience using CytoSorb in patients with severe myoglobinemia due to rhabdomyolysis.

Prof. Fries again specified that CytoSorb does not eliminate the following substances (partly own research):

- Immunoglobulins
  - IgG:150 KD
  - IgM: 971KD
  - IgE:198 KD
  - IgA: Monomer: 160 KD, Dimer: 385 KD
  - IgD: 172 KD
- Coagulation and complement is not activated
  - No elimination of:
    - o fibrinogen: 340 KD
    - o coagulation factors
    - o AT III, Prot. C: 65 KD
  - No relevant elimination of albumin
  - Only small decrease of platelets
  - No activation of complement factors C3a and C5a

Case presentations

- **Case 1**
  - 68 year-old male with myocardial infarction
  - ECMO implantation during ongoing mechanical cardiopulmonary resuscitation
  - In persistent cardiogenic shock ECMO stayed in situ
  - An external LVAD (left ventricular assist device) was implanted in order to wean the patient from ECMO
  - After removal of the ECMO and LVAD the patient suffered from a combination of sepsis (chlamydial pneumonia) and low output syndrome
  - Myoglobin (32.189 µg/l) and bilirubin increased dramatically
  - In the course of CytoSorb treatment myoglobin levels as well as bilirubin levels could be reduced significantly
- **Case 2**
  - 59 year-old male suffering from multiple organ failure, acute necrotizing pancreatitis, lactacidosis, severe septic shock, massive bleeding/massive transfusion, acute renal failure, rhabdomyolysis, ARDS, DIC with pulmonary bleeding, liver failure, pneumonia, colitis
  - Again, bilirubin as well as myoglobin could be reduced significantly using CytoSorb

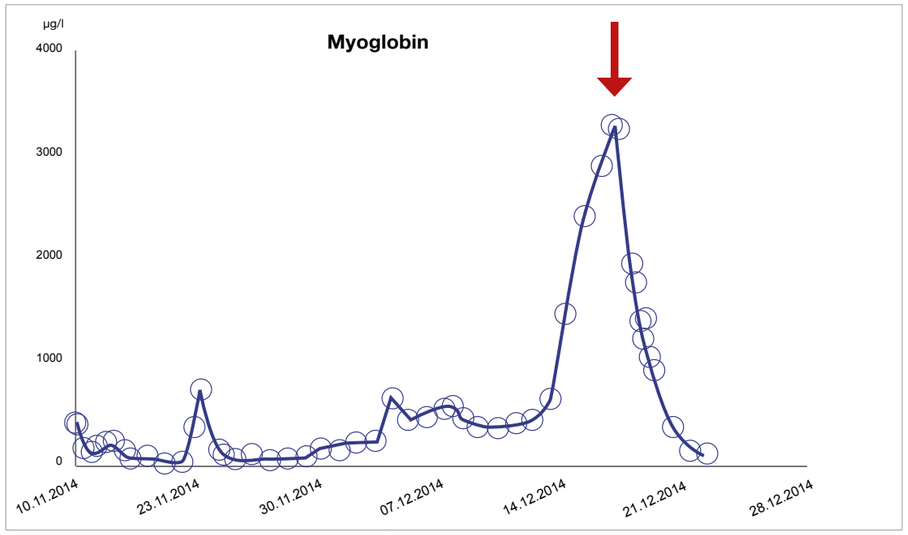

Fig 1: Course of myoglobin before and after initiation of CytoSorb (red arrow) in a patient suffering from a combination of sepsis (chlamydial pneumonia) and low output

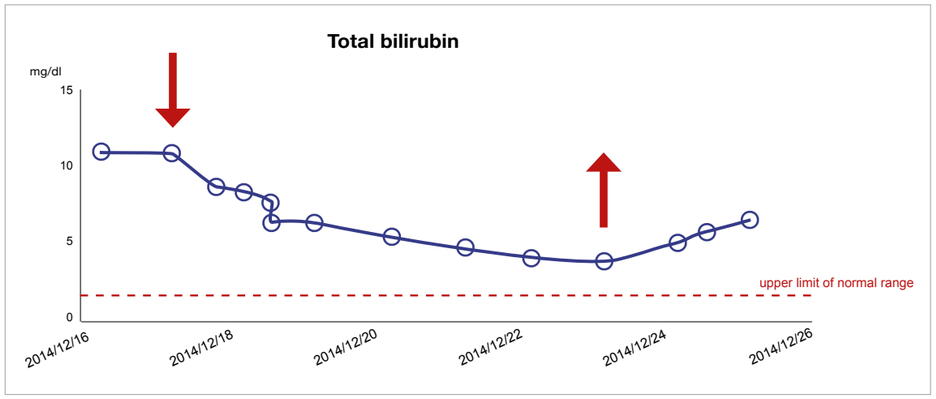

Fig 2: Course of bilirubin before and after initiation of CytoSorb (start and stop red arrows) in a patient suffering from a combination of sepsis (chlamydial pneumonia) and low output

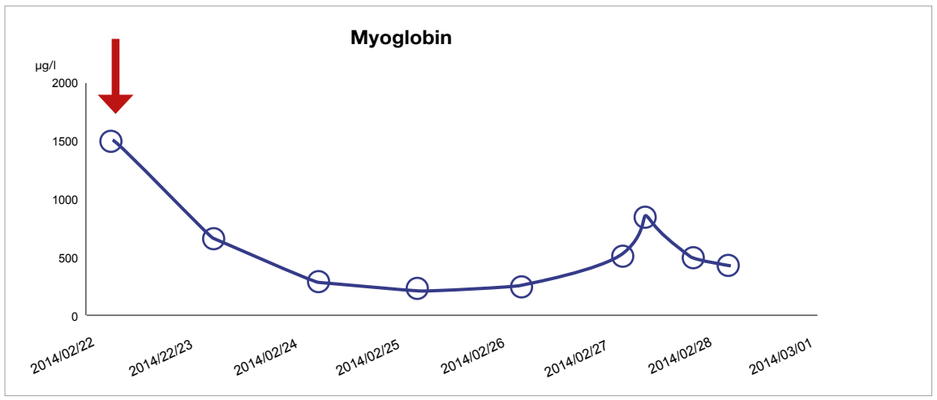

Fig 3: Course of myoglobin after initiation of CytoSorb (red arrow) in a patient suffering from septic shock, multiple organ failure and rhabdomyolysis

view full presentation

CONCLUSIONS

- Prof. Fries stated that if there is a clear target such as reducing the inflammatory response, the need for catecholamines, bilirubin or myoglobin, CytoSorb is well suitable to have a positive effect on these measures
- In his patients CytoSorb was able to significantly reduce plasma levels of bilirubin and myoglobin
- There is no elimination of important immunglobulines nor an activation of coagulation and the complement system

CytoSorb®

SIRS and Sepsis

REGAIN CONTROL

CytoSorbents Europe GmbH
Bölschestraße 116
12587 Berlin, Germany

Office +49 30 654 99 145
Fax +49 30 654 99 146
support@cytosorbents.com

www.cytosorb.com