Proceedings
4th International CytoSorb Users` Meeting

March 23rd 2017, Brussels, Belgium
17 speakers
122 participants
22 countries
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4th International CytoSorb Users` Meeting shows continuing experience of positive results

One day before the International Symposium of Intensive Care and Emergency Medicine (ISICEM) the 4th International CytoSorb Users` Meeting took place. 122 members of the CytoSorbents community from a total of 22 countries gathered at the Marivaux Hotel, Brussels to share their experiences with CytoSorb. Until recently, data came from single case reports, however, now data is being gathered in case series and randomized clinical trials in a broad field of applications, ranging from sepsis to heart surgery, to other indications such as myoglobinemia, ECMO, liver failure, burns and organ transplantation. We would like to thank all participants who joined us on this platform that enabled users, partners and distributors to exchange their experiences with CytoSorb and transfer the knowledge assembled to date. The lessons learned will help inform how best to design large-scaled pivotal trials that will help to definitively answer outstanding topics of interest 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 20,000* CytoSorb human treatments have been safely performed in more than 12,000* patients worldwide with an outstanding safety profile
- All presenters once more acknowledged the safety and excellent tolerance of the device in the various, reported fields of application

Growing Registry database

- Nearly 300* patients have already been included in the registry and nearly 200* in the current interim analysis
- Every second case included in the registry was rated by the user as improving the patient’s condition through the use of CytoSorb by ‘much’ or ‘very much’
- A comparison of observed with predicted mortality based on the APACHE II score showed a relative reduction of 18 % in septic shock patients

*Status March 2017
• With the anticipated rapid and ongoing growth of included patients in the near future, results become more robust, building on the evidence base

**Early and if needed more intense use**

• Several new results have confirmed previous findings that early intervention is superior to late intervention in terms of clinical outcomes
• Additionally, an earlier exchange of the adsorber after less than 24 hrs. in individual cases might contribute to further improvement in the therapeutic success

**Endocarditis, ECMO, LVAD implantation, transplant surgery, liver failure and rhabdomyolysis: New or confirmed promising fields of application for CytoSorb therapy**

• An intraoperative case series of 39 patients with infective endocarditis reported successful treatments with sustained clinical stabilization in regard to hemodynamic and metabolic parameters
• CytoSorb in ECMO after cardiac arrest as well as in LVAD implantation showed very promising and encouraging first results with randomized controlled studies for the latter being planned
• The use of CytoSorb in intraoperative heart transplant surgery (in comparison to conventional therapy) was associated with various outcome benefits such as renal replacement therapy, shorter duration of mechanical ventilation and reduced length of stay in ICU
• Use of CytoSorb in liver transplant patients was related to excellent graft function and in hyper acute graft rejection after kidney transplantation. Extremely successful cases were also shown
• CytoSorb in postcardiotomy VA ECMO might serve as a rescue therapy
• First results in traumatic rhabdomyolysis suggest that CytoSorb can possibly prevent the development of AKI in this setting
• In acute liver failure CytoSorb was shown to be a safe detoxification alternative to albumin dialysis

On the following pages, you will have the opportunity to go through all the important information from most of the presentations at a glance. Enjoy your reading.
Professor Brunkhorst reported on the results of the third interim analysis of the registry and for the first time on very new plans for a study in patients with endocarditis.

**Aims of the CytoSorb Registry**
- To record the use of CytoSorb under real life conditions in as many cases as possible
- All CytoSorb applications in different clinical settings and in all patients who are treated with this technology are planned to be included
- The gathered information will be used to augment the knowledge on the clinical efficacy of the CytoSorb technology, to optimize the quality of its therapeutic application, and to identify and promptly handle possible complications

**Study population and indications**
- Sepsis / septic shock
- Cardiac surgery with CPB (cardiopulmonary bypass)
  - preemptive CytoSorb use in OR
  - postoperative CytoSorb use in ICU
- Other indications
  - Liver failure
  - Acute pancreatitis
  - Trauma
  - Burns
  - ARDS with ECMO
  - Other indication with ECLS

**Current status**
- Status March 2017: 133 registered sites, 33 sites ready for recruitment, 23 sites recruiting
- N=288 of registered and documented patients from May 2015 to March 2017
- 3rd interim analysis – submitted for publication: 198 patients (135 patients with septic shock, 8 patients with intraoperative application in cardiac surgery, 17 patients post cardiopulmonary bypass, 38 patients with other indications)
- Publication in process

**Results from the 3rd Interim analysis**
- Sepsis group extremely sick
  - (mean APACHE II >30, mean SAPS II 74.3, initial SOFA >17, PCT 40 ng/ml, CRP 166 mg/l, IL-6 5,000 pg/ml, APACHE II predicted mortality of 77.6%)
  - Clear reduction of IL-6 from 5,000 to 289 pg/ml after treatment and of PCT from 40 to 25 ng/ml
  - Predicted hospital mortality: 77-81% vs. observed mortality: 63-67%
  - 48% of septic shock patients have improved “much” or “very much” according to treating physicians
  - 62% of the patients with other indications improved “much” or “very much” according to treating physicians

In the following, a pilot study (REMOVE Pilot) as well as a planned multicentric study (REMOVE) examining the effects of CytoSorb in endocarditis were discussed.

**REMOVE PILOT STUDY**
(Inflammatory and vasoactive mediator profiles and pathogen characterization during heart valve replacement surgery)
- Pilot observational study as preparation for a planned randomized-controlled study (REMOVE) using CytoSorb intervention in endocarditis
- Monocentric case-control diagnostic study including patients diagnosed with infective endocarditis or valvular heart disease, undergoing cardiac surgery with cardiopulmonary bypass
- Endocarditis group (N=20) vs. control group (N=20) comprising non-infected patients who underwent cardiac surgery i.e. patients with valvular heart disease (VHD)
- Main objective: Release profiles of selected inflammatory and vasoactive mediators

**REMOVE STUDY**
(Revealing mechanisms and investigating efficacy of hemoadsorption for prevention of vasodilatory shock in cardiac surgery patients with infective endocarditis – a multicentric randomized controlled trial – )
- Publicly funded RCT (German Ministry BMBF)
- Projected multicentric study with 6 centres and a total of 550 patients (including dropouts) running for 24 months starting 2017
- Primary endpoint In-hospital mortality over 30 days post-surgery
CONCLUSIONS

• There will be sufficient data available in 2017 to provide further insights into the efficacy of the CytoSorb treatment, predominantly also on the dependence of the time of use
• Therapy is very promising in the light of the current study situation
• To clarify the open questions, randomized clinical trials are needed
CytoSorb in early septic shock – The ACESS trial

Zsolt Molnar, Szeged, Hungary

Professor Molnar gave an overview on the evolution from a localized insult to life-threatening organ dysfunction caused by a dysregulated host response, discussed the issue of individualizing treatment with the help of biomarkers (e.g. PCT) and presented data gained so far for the ACESS trial (Adsorption of Cytokines Early in Septic Shock)

**ACESS study characteristics**
- 20 patients to be recruited in total
- CytoSorb application in hemoperfusion only mode (no concomitant renal replacement therapy)

**Inclusion criteria**
- Suspected sepsis of medical etiology
- Mechanical ventilation
- PCT >3 ng/ml
- Norepinephrine ≥ 10 µg/min
- PiCCO confirmed normovolemia and CO
- Signs of hypoperfusion: ScvO₂, lactate, dCO₂, oligo-anuria metabolic acidosis
- No acute renal failure

**Preliminary results of ACESS**
- In total 17 patients included in the treatment group so far
- Trend towards a reduction in norepinephrine
- Improvement in oxygenation (PaO₂/FiO₂) mainly within the first 24 hours
- Decline of PCT, IL-8 and IL-10 within the first 24 hours
- Trend towards an improvement of SOFA score
- Considerable decline of extravascular lung water (EVLW)
- Interim analysis showed strong correlation of PCT and measured cytokines

### Table: Correlation between PCT and measured cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-10</th>
<th>IL-1ra</th>
<th>IL-6</th>
<th>IL-8</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/ml)</td>
<td></td>
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<tr>
<td>CRP (mg/l)</td>
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</tbody>
</table>

**Fig 1: Correlation between PCT and measured cytokines**
CONCLUSIONS

- Hemodynamic stabilization and cytokine reduction in the treatment group
- Performance of the adsorber changes over time which is why a way to monitor performance has to be established
- An adsorber change <24 hours may be indicated in individual cases
- Patient heterogeneity and huge scatter in cytokine levels remain a problem which is why multicentric studies are needed
- Preliminary results of this study indicate better SOFA scores in the CytoSorb group

Fig 2: Course of norepinephrine and organ dysfunction parameters throughout the CytoSorb treatment in the ACESS trial
Clinical experiences with CytoSorb in sepsis – A 30 patient case series

S Mitzner, Rostock, Germany

Professor Mitzner reviewed their first published case and reported on the results of a series of 9 patients with acute kidney injury and of a case series in 30 patients with sepsis.

First published case - CytoSorb hemoadsorption for septic AKI
• 80y old male with pneumogenic sepsis and an APACHE II of 33 and a SAPS II of 48
• Treatment with CVVHD and CytoSorb
• Decrease in serum IL-6 and norepinephrine dosage
• Treatment was well tolerated

Case series in 9 patients with acute kidney injury
• Clear reduction in IL-6 levels from 6,727 to 438 pg/ml (median reduction of 87%)
• Substantial reduction in norepinephrine dosage accompanied by a stabilization in mean arterial pressure

Case series in 30 patients with sepsis (manuscript submitted)
• Early (i.e. within 24 hours of ICU admission) and intense treatment (i.e. uninterrupted treatment for > 24 hours) is correlated with improved short term survival

Fig 1: Levels of IL-6 from 9 patients before and after treatment with CytoSorb

<table>
<thead>
<tr>
<th>Median IL-6 (pg/ml)</th>
<th>All patients (n=9)</th>
<th>Survival &gt; 24h after therapy (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“pre”</td>
<td>6,727</td>
<td>6,727</td>
</tr>
<tr>
<td>“after”</td>
<td>438</td>
<td>438</td>
</tr>
</tbody>
</table>

Trend IL-6

- lower 7
- equal 0
- higher 0
- exitus <24h 2
- median decrease -87% (-26 to -96%)
CONCLUSIONS

- Hemoadsorption with CytoSorb is safe and well tolerated by critically ill patients
- IL-6 can be removed efficiently, resulting in decreased serum levels
- Excellent hemocompatibility was also once more confirmed
- Treatments can have a positive impact on hemodynamics (decreased vasopressor need, signs of improved organ perfusion)
- Open points: optimal timing, intensity, and frequency of treatments
- Early initiation and continuous treatment are correlated with better cytokine removal and improved short-term survival
Dr. Nierhaus gave a comprehensive talk on the safety and the effects of CytoSorb on the immune system and provided recent clinical data.

**Effects of CytoSorb as a promising extracorporeal therapy in sepsis**
- CytoSorb can reduce (mostly hydrophobic) substances of middle molecular weight (<60 kDa) from whole blood
- Goal is to cut the peaks of excessively released cytokines in order to regain control over the systemic inflammatory process and to enable recovery

**Presentation of data for the study on the effects of CytoSorb in refractory septic shock (Friesecke S et al. J Artif Organs 2017 epub)**
- **Study Hypothesis**
  o Can cytokine adsorption therapy affect hemodynamics in established refractory septic shock?
- **Patients (n=22)**
  o Septic shock (IL-6 >1,000 pg/ml)
  o Guideline-oriented treatment for 4-6 h completed
  o Persisting hemodynamic shock with tendency to further deterioration:
    - Further increase of lactate concentration OR
    - Further increase of noradrenaline requirements (> 0.3 µg/kg/min)
- **Study protocol: Intervention, Endpoint**
  o Hemoadsorption with CytoSorb
  o Anticoagulation with heparin or citrate
  o Increase of antibiotic dose to 1.5x
  o Endpoints:
    - Change of noradrenaline requirements after 6 and 12 h
    - Lactate clearance / SOFA score / shock resolution
- **Characteristics and baseline data of the study cohort**
  o Mean age of 59.6 ± 19.2 years
  o Male: female = 18:4
  o Focus: pneumonia (11), abdominal (7), urogenital (1), other (2), non-infectious SIRS (2)
  o Blood culture positive n=12
  o Mean SOFA score 15 ± 3
  o Mean IL-6 of 87,039 ± 126,869 pg/ml
  o Mean PCT of 89 ± 182 ng/ml
- **Results in the CytoSorb treated patients**
  o Clear and consistent reductions of IL-6 plasma concentrations
  o Reduction in arterial lactate concentrations and improved lactate clearance
  o No shock reversal with early death in n=7 patients (32%)
  o Shock reversal (Norad ≤ 0.005 µg/kg/min, Lactate < 2.2 mmol/l) in n=15 patients (68%) and of those n=9 patients (41%) were survivors
  o Open Questions remaining
    o Reproducibility, lack of control group
    o Frequency of adsorber exchange and treatment duration
    o Possible drug adsorption

To shed more light on safety, Dr. Nierhaus further discussed direct as well as indirect considerations when introducing a new device such as CytoSorb.

**Safety Considerations**

**General aspects to assess the safety of a device**
- **Direct:**
  - Effectiveness, biocompatibility, simplicity/feasibility
- **Indirect:**
  - Drug adsorption, endocrine effects, thrombocytopenia, leucosequestration, immunodepression
- **Risk/benefit ratio**

**Efficacy and safety**
- Efficacy and safety have been shown in the Schädler study (Schädler D et al. PLOS ONE 2017, accepted for publication)
- No adverse and device related events reported

**Effects on the immune function**
- Potential approaches to test:
  o HLA-DR expression on monocytes
  o Ex-vivo LPS-stimulation
- Single cases point towards an improvement of the immune response via CytoSorb therapy and an increased ability of initially anergic immune cells to mount a pro-inflammatory immune response over the course of the treatment (ex-vivo LPS stimulation)
  o 24 year-old female patient with microbiologically proven meningococcemia (Fig. 1)
  o 54 year-old male patient with postoperative SIRS and shock after abdomino-thoracic esophagectomy (Fig. 2)
CONCLUSIONS

- New sepsis trials should consider the substantial heterogeneity in patients and type of infections
- Evidence for safety of CytoSorb has broadened over the last years and will increase further
- Current status of data shows that the treatment is safe
Clinical experiences in endocarditis – An intraoperative case series

K Traeger, Ulm, Germany

Professor Traeger reported on the results of a case series in 39 patients with infective endocarditis with a preemptive application of CytoSorb during cardiopulmonary bypass.

Infective Endocarditis – clinical symptoms

- Septic shock
- Multiple organ dysfunction
- Multiorgan septic embolization

Review of recent studies using CytoSorb in cardiac surgery

- Bernardi M et al. (2016) Effect of hemoadsorption during cardiopulmonary bypass surgery – A blinded randomized, controlled pilot study using a novel adsorbant
- Born F et al. (2014). SIRS in cardiac surgery: new therapy options by use of a cytokine adsorber during an extracorporeal circuit (Systemic Inflammatory Response Syndrome in der Herzchirurgie: Neue Therapiemöglichkeiten durch den Einsatz eines Zytokin-Adsorbers während EKZ?)

Results from: “Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass – A case series”

Traeger K et al., Int J Artif Organs 2017, in press

- Retrospective case series evaluating the clinical course of 39 consecutive cardiac surgery patients with infective endocarditis, treated with CytoSorb intraoperatively
- CytoSorb use ranged from 64 to 477 minutes (median 132 minutes)
- CytoSorb patients showed a noticeable intraoperative increase in IL-6 and IL-8 with peak levels directly after completion of the surgical procedure. Levels then decreased markedly on post op day 1 with return to preoperative levels on postop day 3
- Metabolic variables (lactate and base excess) showed a comparable pattern with the most pronounced change postoperatively and return to baseline levels on postop day 3
- Hemodynamic parameters stabilized as demonstrated by a consistent and maintained increase in MAP postoperatively and a concomitant reduction in catecholamines
- APACHE II (median) trended towards improvement from 31 to 20 one day post-surgery
- 18 patients were weaned from mechanical ventilation within 24 hours after surgery while 21 patients required prolonged ventilation from 1 – 12 days.
- Five patients required ECMO (up to 5 days)
- High grade acute kidney injury requiring CRRT (up to 4 days) observed in 16 patients
- Length of ICU stay in the CytoSorb group ranged between 1 – 32 days (median 5), while in a comparative historical control group length of ICU stay was between 2 and 96 days (median 7.5)

Open questions with CytoSorb treatment during CPB

- Do bacteria adhere on bead surface - Own investigations detected no microbes in microbiological cultures
- Can viable bacteria be cultured from CytoSorb beads - Own investigations showed no positive bacterial cultures detected via electron microscopy
- Is there a decreased capillary leakage?
- Is there less organ dysfunction?
- Is there an improved outcome?
CONCLUSIONS

• Effects of CytoSorb therapy with preemptive use in patients with acute infective endocarditis during surgery with cardiopulmonary bypass showed:
  
  o Marked reduction in IL-6 and IL-8 plasma levels, with a well controlled cytokine response and a maintained immune response
  
  o Stabilization in hemodynamic parameters during and after surgery, as demonstrated by a rapid reduction in need for catecholamine support and increase in MAP
  
  o Rapid normalization of lactate and base excess back to preoperative baseline levels within 3 days
Dr. Németh presented his experience with the use of CytoSorb in heart transplantation.

**Objective**
- Patients undergoing orthotopic heart transplantation are among those with higher risk for vasoplegic syndrome representing an important complication after cardiac surgery (reported incidence > 20%)
- In case of norepinephrine refractory vasoplegia the mortality can be as high as 25%
- The etiology includes
  - Exaggerated inflammatory response (immune activation + cardiopulmonary bypass)
  - Endothelial injury
  - Dysfunction of arginin-vasopressin system

**Observational study**
- Clinical data were collected prospectively and analysed retrospectively
- No change in perioperative care of the patients, except for the incorporation of CytoSorb into the transplant protocol
- Measurements assessing the impact of preemptive intraoperative use of CytoSorb on:
  - Severity of vasoplegia → vasopressor requirement
  - Postoperative inflammatory response → Procalcitonin, CRP
  - Postoperative complications
  - Length of ICU stay
- **Patient selection based on expert opinion**
  - ‘High Risk’ orthotopic heart transplantation patient
  - Presence of chronic kidney disease or chronic liver disease related to heart failure

**Propensity score matching**
- Resulted in 16 pairs in which the pre- and intraoperative covariates were well balanced

**Results**
- No difference in intraoperative noradrenaline requirement, but significantly lower on first and second postoperative days in the CytoSorb group
- Required terlipressin doses less in the CytoSorb group in the early postoperative period (not statistically significant, n.s.)
- Patients from the CytoSorb group admitted to ICU with lower lactate levels than control patients. CytoSorb group achieved normal lactate levels by the end of the first postoperative day while controls did not (n.s.)
- No differences in postoperative bleedings, rate of reoperation, number of given blood products, rate of sepsis and rate of early graft rejection measured at the end of the first week
- Postoperative complications included significantly less primary graft failure, need for postoperative MCS support, renal replacement therapy and rate of acute kidney injury (n.s.) in the CytoSorb group
- Median ventilation time was 24 hours in the CytoSorb group and 5 times longer in the control group (n.s.)
- Length of ICU stay was halved in CytoSorb patients (10 days) vs. Control group (20 days) (n.s.)
- No death in the first postoperative month in the CytoSorb group compared with two cases in the control group
CONCLUSIONS

- CytoSorb treatment was associated with
  - Reduced vasopressor requirements in the first 48 hours postoperatively
  - Shorter duration of mechanical ventilation
  - Less renal replacement therapy
  - Shorter length-of-stay in intensive care unit

- No association of CytoSorb treatment with major adverse events, such as postoperative bleeding, sepsis, or early graft rejection
CytoSorb for LVAD implantation – Part 1: Clinical experiences

N Marczin, Harefield, UK & E de Waal, Utrecht, Netherlands

Dr. de Waal gave a presentation on the application of CytoSorb in patients undergoing cardiac surgery for implantation of a left-ventricular assist device.

Background
- Heart failure is accompanied by a major inflammatory state
- Continuous flow left ventricular assist devices (cfLVADs) represent the most innovative progress in surgical treatment of heart failure, yet the procedure is invasive, requires CPB in most cases and is associated with right ventricular failure, SIRS and vasoplegia
- CytoSorb might prevent these inflammatory complications

Objectives
- To test in high risk clinical scenarios whether
  - CytoSorb is clinically feasible in cfLVAD patients
  - CytoSorb application has any obvious clinical outcome benefits
  - CytoSorb affects
    - Routine clinical markers of inflammation
    - Renal and hepatic function

Patients
- Small case series of heart failure patients scheduled for cfLVAD implantation in UMC-Utrecht (5 patients with CytoSorb, 6 patients without) and RBHT (Royal Brompton & Harefield Trust) Harefield (8 patients with CytoSorb, 8 patients without)

Results
- No significant difference in CRP, creatinine, white blood count and total bilirubin between both groups
- No differences in development of vasoplegia, ICU length of stay, ICU-, hospital and 30-day mortality

Summary
- Successful introduction of CytoSorb into routine clinical practice of high risk cfLVAD implantations in 2 centres
  - After local Clinical Practice Committee approval
  - During cardiopulmonary bypass
- Use of CytoSorb seems feasible in cfLVAD patients
- Compared data to a historic group at Utrecht and a simultaneous contemporary cohort at Harefield showed promising clinical outcomes
  - Despite older and likely higher risk patients were included clinical outcomes are good and comparable to the control group
  - The rate of complications was not higher in the CytoSorb group
  - Serious clinical problems especially during late ICU stay were most likely unrelated to CytoSorb
  - CytoSorb was only used during CPB, so patients may not have benefitted from postoperatively continued applications
Part 2: Scientific plans for CytoSorb in mechanical support and transplantation

N Marczin, Harefield, UK & E de Waal, Utrecht, Netherlands

Dr. Marczin gave insights into the planned CYCLONE LVAD trial (CytoSorb Modulation of Surgical Inflammation During LVAD Insertion) and the CYCLONE HEART trial (CytoSorb Modulation of Surgical Inflammation During Heart Transplantation). He also proposed a major international collaboration to fully develop a coordinated basic science domain (CU-BioSORB (Consortium for Unbiased Biological evaluation of CytoSorb Therapy)) to compliment the clinical trials and registry towards broader mechanistic studies.

Design - CYCLONE LVAD trial
- Prospective randomized, controlled trial in 2 centres (Harefield/Utrecht) including N=60 LVAD patients
- Endpoints
  - Primary: IL-6
  - Secondary: feasibility, organ dysfunction, vasoplegia/SIRS, microcirculation
  - Biology: cytokine network, SIRS candidates, systems biology

Design - CYCLONE HEART trial
- Prospective-large randomized, controlled, multi-centric trial around Europe including approximately n=400 orthotopic heart transplant patients with adaptive trial design
- Under auspices of E ActA/EACTS, ESOT/ISHLT
- Primary: Clinical UK Primary Graft Dysfunction
- Secondary:
  - ISHLT Primary Graft Dysfunction
  - Organ dysfunction
  - Vasoplegia/SIRS
  - Microcirculation

Proposal of CU-BioSORB - Consortium for Unbiased Biological evaluation of CytoSorb Therapy
- Proposal to bring together all ongoing clinical trials in cardiac surgery for international collaboration to advance a basic science mechanistic arm.
- Aim is to fully utilize the excellent trials portfolio of the company and the registry and to provide a third basic science component i.e. CU-BioSorb
- Unified methodology to build new Bio-Clinical Matrices by combining the clinical trials through individual patient metaanalysis, and broader biological analysis including metabolic, genetic and proteomic profiling.
- The scope would span from predictive studies (using existing LVAD samples from Utrecht) through biomonitoring (Cyclone trials) to therapeutic improvement of cardiopulmonary bypass (Bio metaanalysis of completed and ongoing cardiac surgical trials).

CONCLUSIONS
- CytoSorb treatment is promising for cfLVAD implantation
- The application appeared to be easy and safe, without any device-related adverse events
- Its clinical efficiency in this subset of patients needs to be assessed in a randomized controlled trial
- Various other scientific plans for the future are in preparation
Clinical experiences in the treatment of severe burns
K Houschyar, Halle, Germany

Dr. Houschyar presented several clinical cases from their burn unit and their experience in septic burn patients treated with CytoSorb.

**Case Study 1**
- 72-year-old patient, 2a-2b-grade scalding of 8% of the total body surface area (%TBSA) during cooking
- Affected areas: parts of the thorax, back, right foot and lower left leg
- Patient suffered from Parkinson’s and coronary heart disease
- After surgery, pulmonary worsening of the patient with start of invasive ventilation
- With increased circulatory instability and decompensated renal function, continuous venous hemodiafiltration (CVVHDF) in combination with CytoSorb was performed
- CytoSorb was applied from day 6 to 17 and from day 21 to 29
- In the further course markers of inflammation and cytokines were congruent with clinical improvement of the patient

**Case Study 2**
- 47-year-old patient, transferred to ICU due to pneumococcal sepsis with disseminated intravascular coagulation
- Known medical history: splenectomy after a bilateral splenic rupture with no pneumococcal vaccination postoperatively
- In 2014, condition of the patient deteriorated dramatically after a dental treatment
- Affected areas were both feet, lower legs and right hand
- Catecholamine dependent circulatory failure and renal insufficiency
- Stamping biopsy for differential diagnosis of toxic epidermal necrolysis (TEN) confirmed a Waterhouse-Friederichen syndrome
- Start of hemodiafiltration in combination with CytoSorb
- Ambutation of both lower limbs due to septic microembolism of both feet and lower limbs
- Three days later ongoing debridement of the right lower limb
- Later, revision of both stumps and defect cover with split-thickness skin graft
- Amputation of the right thumb with several debridements thereafter
- After hemodiafiltration with a CytoSorb adsorber, levels of IL-6 and IL-10 decreased

**Case Study 3**
- 21-year-old patient, 2b-3 burn degree (60% of the body surface) and inhalation trauma grade II after an explosion in the home environment
- Affected were both arms, face, thorax as well as both thighs
- ABSt score (abbreviated burn severity index) of 10 points
- Pre-existing diseases: epilepsy and multifactorial drug abuse
- Due to burns grade III, escharotomy was performed on both arms and thorax on the day of admission
- Multiple operations including Meek-transplantations 1: 6 on lower abdomen, both upper arms, the upper thorax and both forearms
- Residual necrotic tissue removal (back, face) using epifascial debridements
- Commencement of hemofiltration plus CytoSorb due to persistently elevated inflammatory (leukocytes, C-reactive protein [CRP], procalcitonin), renal function parameters, positive blood cultures and wound smears confirming Acinetobacter baumannii 4MRGN [multiresistant gram-negative pathogen]
- Application of CytoSorb from the 9th to the 17th day and from the 32nd to the 52nd day (28 cycles in total)
- Use of CytoSorb showed a significant decrease in inflammatory mediators with improved hemodynamics, reduction in noradrenaline and prolongation of the patient’s survival time

**Discussion**
- These are the first described cases of standard treatments with the CytoSorb adsorber as an adjuvant therapy for burn patients with a septic episode
- CytoSorb therapy resulted in a significant reduction in inflammatory mediators (IL-6, IL-10)
- The adsorber improved hemodynamics as evidenced by a reduction in noradrenaline and had a significant impact on the patients survival time
- CytoSorb seems effective in reducing postoperative systemic inflammatory response syndrome in burn patients
CONCLUSIONS

- Treatments have been considered safe and well-tolerated
- By the early application of CytoSorb, the septic episode in burn patients can be potentially improved and the survival time can be prolonged
- CytoSorb therapy in septic shock patients with multi-organ failure might be an option as rescue therapy
- However, further studies with prospective randomized controlled design would be necessary to establish the benefit of this therapy in septic shock
Dr. Martinez shared her experiences with the application of CytoSorb in patients with rhabdomyolysis.

Rhabdomyolysis
- Destruction of striated muscle producing a non-specific clinical syndrome due to the extravasation of toxic intracellular contents from the myocytes into the circulatory system
- Global incidence unknown, global mortality 2-46%
- Population risks groups:
  o Crush syndrome (direct trauma, injury or compression)
  o Chronic users of statins
  o Postoperative patients
  o Morbid obese patients
- Etiology
  o Traumatic: Crush syndrome
  o Non traumatic: Drugs, infection, surgery (immobilization), extreme temperatures, inherited or acquired myopathies, toxins, extreme physical exercise
- Clinical symptoms
  o Acute kidney injury is the most common systemic complication of rhabdomyolysis
  o 20-50% of patients with some degree of rhabdomyolysis develop AKI and this is associated with poor outcome
  o Rhabdomyolysis contributes to 5-25% of all cases of AKI
- Mortality
  o Mortality of ARF secondary to rhabdomyolisis 59% vs. 22% in case of normal renal function

Case report
- 34 year old male (body builder)
- Emergency ascending aorta and aortic arch replacement with aortic vessels reimplantation due to Stanford type A aortic dissection
- CPB time 612 min, X clamp 340 minutes
- Severe biventricular failure during CPB weaning, necessitating V-A ECMO
- Log EuroSCORE 8 %, APACHE II score 24, SOFA score 10
- On ICU admission: Lactate 20 mmol/l, HR 110/min, MAP 62 mmHg, ECMO blood flow 6 L/min, norepinephrine 0.6 µg/kg/min, epinephrine 0.085 µg/kg/min, levosimendan 0.05 µg/kg/min
- Myoglobin 24178 ng/mL, CPK 17,843 UI/L, total bilirubin 2.87 mg/dl
- Anuria: CVVHDF started on postoperative day 1
- Hydrocortisone started on postoperative day 1
- Multiple organ failure, liver dysfunction and rhabdomyolysis (swelling and stiffness of legs) on postoperative day 4
- Hyperkalemia (7.3 mM/L) and peak of myoglobin 860,000 ng/ml and CPK 511,000 UI/L
- Installation of CytoSorb into the CVVHDF circuit to protect the kidney, to reduce vasopressors and to prevent further myocardial dysfunction
- 5 CytoSorb treatments in total
- Results were a clear reduction in CPK and myoglobin levels as well as a significant reduction in vasopressor levels
- Weaning from VA ECMO on postoperative day 14
CONCLUSIONS

• CytoSorb associated with CVVH might represent a novel approach in the treatment of acute rhabdomyolysis because a potential protective effect can be envisaged in the rapid and efficient removal of circulating myoglobin

• CytoSorb Therapy is easy to perform, safe and well tolerated in combination with ECMO as well as with CRRT

• Randomized-controlled trials would be of interest in comparing innovative and traditional approaches

Fig. 1. Course of CPK and myoglobin in a patient with severe rhabdomyolysis
Dr. Fazakas reported on his experiences using CytoSorb in patients, predominantly with acute liver failure and undergoing kidney and liver transplantations.

**CytoSorb experience**
- 29 treatments, 18 patients, 16 alive
- Of those 18 patients there were 5 patients with acute liver failure (13 treatments, 5 patients alive) treated either before (bridging), during (mainly ischemia-reperfusion, cytokine storm) or after orthotopic liver transplantation
- These 5 patients showed
  - Improved hemodynamic stability
  - Reduced vasopressor needs
  - Less pronounced cell lysis
  - Excellent graft function
  - Shortened ICU and hospital length of stay
  - Lower than expected mortality (50%): all 5 patients survived

**Case report 1 – CytoSorb during orthotopic liver transplantation**
- 16 year-old female patient with acute Wilson disease + pulmonary sepsis undergoing orthotopic liver transplantation
  - She received CRRT + CytoSorb intra- as well as postoperatively and was further given additionally pentaglobin + antibiotic therapy
  - PCT and CRP levels clearly diminished from postoperative day 1
  - She was extubated after 72 hours, ICU stay was 6 days, hospital stay was 15 days

**Case report 2 – CytoSorb during anaphylactic shock**
- 53 year old male patient receiving 1 mg adrenaline; 1 mg atropine and 100 mg hydrocortisone after an anaphylactic shock
  - APACHE II: 13; SAPS II: 43; SOFA: 9
  - CVVH in combination with CytoSorb (for 4 hours) was applied
  - In the next hours vasopressor dosages (epinephrine, norepinephrine) and lactate could be significantly reduced
  - Patient stayed in ICU for 5 days and was then discharged

**Fig. 1. Experiences in acute liver failure**
Two cases of hyperacute graft rejection
- 19 year-old male patient with polycystic renal disease and 37 year-old male patient with glomerulonephritis both treated with a combination of CVVH and CytoSorb
- Again, vasopressor dosages (epinephrine, norepinephrine) and lactate could be significantly reduced

In both patients, successful 2nd kidney transplantation 11-15 months later

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CONCLUSIONS
- In acute liver failure the CytoSorb treatment is a safe detoxification alternative to plasma albumin dialysis
- In addition to detoxification, CytoSorb can reduce the systemic immune response associated with the acute liver failure or graft necrosis, so the early use can prevent multiple organ failure
- Although studies are lacking, it seems that based on the immunomodulation of the innate immune response in early graftectomys, the CytoSorb treatment positively influences cellular and humoral immune response and increases the success of the secondary transplantation
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CytoSorbents invites you to submit your patient case for publication on the **CytoSorb website as Case of the week.**

This highly popular feature on [cytosorb.com](http://literature.cytosorb.com) publishes a different patient case every week.

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