Proceedings
5th International CytoSorb Users’ Meeting

Brussels, Belgium, March 19th 2018
COMMUNITY AREA

Please find selected presentations from the 5th International CytoSorb Users’ Meeting also online

Just scan the QR-Code and register

http://cytosorb-therapy.com/cytosorb-community-area/
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5th International CytoSorb Users’ Meeting fosters expedient discussions about how to best optimize treatment in a wide range of different applications

Just prior to the International Symposium on Intensive Care and Emergency Medicine (ISICEM), CytoSorbents held its 5th International CytoSorb Users’ Meeting, relocating from the Hotel Marivaux in previous years to the Square congress centre to accommodate nearly 150 participants from the growing global CytoSorb community, including physicians, partners, and distributors. The goal of the meeting was to invite CytoSorb users to share their treatment experiences and research with the group, fostering healthy discussion about how to best optimize treatment in a wide range of different applications. In all, twenty-three speakers and session chairs from ten countries contributed to the meeting, including many pioneers of the therapy. To date, evidence has migrated from single case reports to more recently 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 and liver failure. We thank all participants that joined 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 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 evidence.

Key findings of the symposium include

Numbers

- 600* active users worldwide
- More than 35,000* CytoSorb human treatments in various indications (septic shock, cardiac surgery both intraoperative & postoperative, myoglobinemia, liver dysfunction/failure, severe acute pancreatitis, viral sepsis, intoxications)
- Growing Registry database – more than 480* patients have already been included in the registry and 328* in the current interim analysis
- Number of peer-reviewed publications rises to nearly 50*

*Status March 2018
Extended CE approval for removal of bilirubin and myoglobin and liver failure

- The indications of myoglobinemia and hyperbilirubinemia are now covered by the intended use in the CE markets

Safety

- To date, more than 35,000* CytoSorb human treatments have been safely performed in more than 20,000* 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

Clinical effects and mechanistic insights

- One common theme throughout the majority of the clinical presentations was the valuable role that CytoSorb plays in helping to restore hemodynamic stability and metabolic balance
- For the first time, a significant reduction in norepinephrine requirement by the use of CytoSorb hemoadsorption could be shown in a randomized, controlled setup during a 48 hour observation period in septic patients as compared to a control group
- In addition, exciting new mechanistic data highlight the ability of CytoSorb to improve microcirculation and tissue oxygenation, a key physiologic deficit in septic shock, as well as to modulate the immune system on both a cellular and molecular level
- In vitro data show the efficient removal of the anticoagulants Rivaroxaban and Ticagrelor to lower the risk of intra- and postoperative bleeding

Consensus on the strategy to confirm effectiveness of CytoSorb therapy

- Broad support for CytoSorbents’ approach to conduct smaller, but targeted studies in well-defined patient populations, further building the registry database and enable direct communication of all stakeholders through User Meetings
- Consent on the increasing significance of personalized medicine and thus reliance not only on large RCTs is of growing importance for generating evidence
- The statement on the efficiency of CytoSorb should not only address mortality (JL Vincent & F Brunkhorst)

Early and if needed more intense use

- Several recent results have confirmed earlier 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 hours in individual cases might contribute to further improvements in the therapeutic success

On the following pages, you have the opportunity to glance through important information from a large selection of the presentations. Enjoy.
The role of personalized medicine in the ICU

JL Vincent, Brussels, Belgium

Professor Vincent shared his insights on the role of personalized medicine in the ICU as well as future perspectives, and summarized the existing evidence concerning extracorporeal blood purification including the CytoSorb technology.

Current status on the evidence for extracorporeal blood purification therapies

- Despite the logical rationale for purifying blood from broad spectrum inflammatory mediators, to date there is scare data that provides evidence on improved outcomes (e.g. for high-flux hemofiltration)
- In this context, the Surviving Sepsis Guidelines stopped recommendations for high-flux hemofiltration since too many beneficial substances including antibiotics were also removed by the procedure
- Studies on immobilized polymyxin-B (PMX) are incongruent demonstrating either benefit (Cruz DN et al., JAMA. 2009 Jun 17;301(23):2445-52) or even harmful (Payen DM et al., Intensive Care Med. 2015 Jun;41(6):975-84). A recent meta-analysis (Fujii T et al. Intensive Care Med. 2018 Feb;44(2):167-178) came to the conclusion that there is currently insufficient evidence to support the routine use of PMX-HP to treat patients with sepsis or septic shock.

Revisiting the strategy

- Professor Vincent raised the question as to whether survival/mortality is a reasonable endpoint for studies in the field of critical care
- Based on failed trials from the past he emphasized caution in not taking too large a step at a time.
- Furthermore, he pointed out the problem that randomized controlled trials may potentially not be the right tool to assess the efficacy and viability of extracorporeal blood purification therapies and that perhaps Users Meetings (with interactive discussions, sharing of experiences etc.) and Registries are more likely the right approach to refine application for those technologies
- Professor Vincent proactively supports CytoSorbents’ strategy of conducting smaller, but targeted studies in well-defined patient populations

The dual problem with clinical trials in critical care medicine

1. Choice of the right patient population – there is an urgent need to better characterize and to select the patients who might benefit (in the future perhaps through artificial intelligence)
2. Outcome (mortality rate) is probably the wrong endpoint, too many potentially beneficial drugs and procedures have been withdrawn from the market due to failure to meet this endpoint, with companies now not willing to develop new drugs for critically ill patients

CONCLUSIONS

- The community should not be too ambitious about producing “hard evidence“ on new therapy options for critically ill patients jeopardizing the commercialization of potentially promising treatments by using the wrong endpoints. In the words of Professor Vincent we should rather be good clinicians at the bedside precisely evaluating the effect of our individualized therapy given to these patients
- On the ICU, infectious source control and hemodynamic stabilization are mandatory, however, in the broad sense, there is also a place for the modulation of the host response – therefore extracorporeal blood purification techniques should be listed among other strategies, and the community needs to make progress by trying to do the right thing for the right patient
Case of the week – Invitation to publish

Have you recently treated a patient with CytoSorb?
Interested in sharing your clinical experience with a wide audience?
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 has published a different patient case every week since 2015.

We look forward to receiving your case report,

Your CytoSorbents Team

CASES
All cases are welcome, including
• Sepsis
• Cardiac surgery
• Liver failure
• Rhabdomyolysis
• Special treatment cases

SUBMISSION
Online or contact your regional sales representative

http://cytosorb-therapy.com/the-studies/submit-case-of-the-week/
Current state of the art of CytoSorb in systemic hyperinflammation

S Mitzner, Rostock, Germany

Professor Mitzner gave a comprehensive overview on the current evidence available on CytoSorb therapy for treating systemic hyperinflammation.

Cytokine patterns and survival in community acquired pneumonia

- Association of different IL-6 and IL-10 levels with mortality in pneumonia and sepsis (Kellum JA et al. Arch Intern Med 2007; 167:1655-63)
- Based on these observations, various studies have been initiated to investigate the effects of removal of these mediators using extracorporeal blood purification

The CytoSorb adsorber cartridge and its adsorption characteristics

- 300 ml cartridge filled with divinylbenzol/polyvinylpyrrolidon “beads”
- Adsorption of hydrophobic substances with a size selectivity <55kD
- Broad removal spectrum, but still selective

First published case report - CytoSorb hemoadsorption for septic AKI

- 80 year-old male with pneumogenic sepsis and an APACHE II of 33 and a SAPS II of 48
- Treatment with CVVHD and CytoSorb (for 24 hours)
- Decrease in serum IL-6 and norepinephrine dosage
- Treatment was well-tolerated

Review of references emphasizing the efficient removal of IL-6, hemodynamic and metabolic stabilization and reduction of capillary leakage/endothelial protection

- A yet unpublished case series in 9 patients carried out by Professor Mitzner’s team in patients with acute kidney injury showed a clear reduction in IL-6 levels from 6,727 to 438 pg/ml (median reduction of 87%) and a substantial reduction in norepinephrine dosage accompanied by a stabilization in mean arterial pressure
- Data from the study on the effects of CytoSorb in refractory septic shock (Friesecke S et al. J Artif Org 2017; 20(3): 252-9) showed no shock reversal with early death in n=7 patients (35%), whereas shock reversal (as defined by norepinephrine ≤ 0.005 µg/kg/min, lactate < 2.2 mmol/l) occurred in n=13 patients (65%) and of these n=9 patients (45%) were survivors
- Results from the 3rd Registry interim analysis including 198 patients showed an observed mortality of 63-67% vs a predicted hospital mortality of 77-81%

Case series in 30 patients with sepsis (Schipper et al., manuscript submitted)

- Impact of timing of CytoSorb treatment
  - Data from a case series in 30 patients with sepsis showed that early treatment (i.e. within 24 hours of ICU admission) is correlated with improved short term survival (> 3 days survival with early intervention was 8/13 (61.5%), whereas late intervention survival equaled 5/17 (29.4%), p=0.078)
- Impact of CytoSorb treatment on IL-6 levels
  - Efficient IL-6 removal during CytoSorb treatment is associated with improved short-term survival
  - Impact of length of CytoSorb treatment initiated early and undisrupted (for as long as possible, best case >24 hrs), resulted in lower IL6-serum levels and better survival

Preventive capacity of CytoSorb treatment

- Data on the intraoperative use of CytoSorb treatment in 16 matched paired patients undergoing orthotopic heart transplantation was associated with reduced vasopressor demand and less frequent renal replacement therapy with a favorable tendency in length of mechanical ventilation and ICU stay (Nemeth E et al. Clin Transpl 2018; 32(4): e13211)
CONCLUSIONS

- Hemoadsorption with CytoSorb is well tolerated by critically ill patients
- Treatments appeared clinically safe, hemocompatibility is excellent
- IL-6 can be removed efficiently, resulting in decreased serum levels
- Treatments can have a positive impact on hemodynamics (decreased vasopressor need, signs of improved organ perfusion)
- Early initiation and continuous treatment are correlated with better cytokine removal and improved short-term survival
- Open points: optimal timing, intensity, and frequency of treatments

Removal of anticoagulants from the blood stream


The paper also underlines the fact that there was no difference in the rate of complications, such as sepsis, bleeding or early graft dysfunction between the groups, which can be taken as proof of safety for CytoSorb also in this indication.

Tables / Figures from presentation not shown due to ongoing publication process.
The International CytoSorb Registry – Latest update

F Brunkhorst, Jena, Germany

Professor Brunkhorst reported on the results of the 4th interim analysis of the registry and a new case control study performed at his center.

Cytokine elimination by hemoadsorption
- Surviving Sepsis Campaign does not recommend using blood purification strategies in patients with severe sepsis due to insufficient data (“We make no recommendation regarding the use of blood purification techniques”) (Rhodes A et al. Intensive Care Med 2017; 43(3): 304-77)
- Meta-analysis by Zhou et al. found that blood purification techniques including hemoperfusion, plasma exchange, and hemofiltration were associated with lower mortality in patients with sepsis, however these results were mainly influenced by studies using polymyxin B hemoperfusion from Japan (Zhou et al. Crit Care Med 2013; 41(9): 2209-20)

Sepsis phase-3 trials: Time for improvement
- Overview of recent key critical care sepsis trials shows that in the last years no improvement in sepsis therapy has been achieved from evaluating 8,540 patients in 8 RCT’s showing no difference in short-term mortality rates between treatment arms (Mebazaa et al. Journal of Intensive Care 2016; 4: 24)

Priorities for future sepsis clinical trials
- Standardize care to reduce variability and random noise (CAVE external validity)
- Realistic expectations for treatment effect and power of trials (improvement already through introduction of Sepsis-3 definitions)
- Adaptive designs, when key variables are uncertain (e.g. event rates, effects)
- Involvement of very experienced study centers to conduct large trials
- Targeted primary endpoints with all-cause mortality reserved for safety
- Consensus for standard trial definitions/criteria for interventions if used as endpoints
- Collaborate with regulators to modify approach to clinical trial design in this field
- Robust registries to test external validity of the results of trials in broader patient populations

Why should we conduct registries?
- Randomized controlled trials deliver only a part of the information that patients and physicians need for decision making
- Other study types must be added and may be more important for the individual decision than quantifying efficacy by RCTs

Characteristics of registries
- No given intervention (non-interventional study)
- No randomization
- Precisely defined target population
- Representative or total inclusion of the target population
- Active, standardized data assessment

Latest update on the International CytoSorb Registry
Study population and indications
- Sepsis / septic shock
- Cardiac surgery with CPB (cardio-pulmonary 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

In-/Exclusion Criteria
- Inclusion Criteria
  - Use of CytoSorb
  - Age ≥ 18 years
  - Signed informed consent
- Exclusion Criteria
  - None

Current status
- Status March 2018: 180 registered sites from 25 countries, 58 in process, 42 sites ready for recruitment, 24 sites recruiting
- N=481 of registered and documented patients from May 2015 to February 28th, 2018

Results from the 4th Interim Analysis
- Patient characteristics
  - Low median age of 61 years in patients with septic shock
- Disease severity
  - APACHE II score of 31.8 on average and SAPS II score of 72.5 points significantly higher
than those known from former sepsis studies (SISPCT, VISEP, MAXSEP) worldwide

○ Correlation with mortality, which is significantly higher than in the aforementioned studies (hospital mortality 66.2%)

• None of the attending physicians stated that a septic patient has deteriorated after using CytoSorb, the majority however had the perception that the patients’ status improved during treatment

• This was similar in other indications

• There were no adverse device-related events reported

Data base status May 26, 2017: Patients with „completed“ visits N = 328

Fig 1: Population included into the 4th Interim analysis

Fig 2: Mortality in patients with septic shock as a function of disease severity grouped by APACHE II Score Level
CONCLUSION

- This is the first time a company dealing with blood purification techniques has pushed combined generation of evidence through investigator-initiated, sponsored randomized controlled trials and a treatment registry in a systematic manner, which is a valid way to generate more evidence.
- There will be sufficient data available in 2018 to provide further insights into the efficacy of the CytoSorb treatment, predominantly also on the dependence on the point of time of use.
- Therapy looks however very promising in the light of the current study situation.
- To clarify open questions, randomized controlled clinical trials are urgently needed.
Reasons why you should join the CytoSorb Registry...

► You want to learn more about extracorporeal adsorption methods
► You want to optimize your therapy
► You want to share your experiences with and learn from colleagues all over the world
► It requires little effort: no intervention or randomization
► It’s easy, fast and secure using OpenClinica®
► The highest quality standards with independent scientific supervision

Register here - it’s quick and easy
www.cytosorb-registry.org

ClinicalTrials.Gov ID: NCT02312024

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CytoSorb in early septic shock – The ACESS trial

Zsolt Molnar, Szeged, Hungary

Professor Molnar presented data from the ACESS trial (Adsorption of Cytokines Early in Septic Shock) which will be published in the near future.

ACCESS study characteristics
• Prospective, randomized, proof of concept pilot study
• 20 patients recruited in total
• CytoSorb application in hemoperfusion only mode for 24 hours as a single standalone treatment

Inclusion criteria
• Suspected sepsis of medical etiology <24 hours
• Mechanical ventilation (IPPV)
• PCT >3 ng/ml
• Norepinephrine ≥10 µg/min
• PiCCO confirmed normovolemia and Cardiac Output
• Signs of hypoperfusion: ScvO$_2$, lactate, oligo-anuria, metabolic acidosis
• Exclusion: need for CRRT

Primary endpoint
• Organ dysfunction 48 hours after treatment

Preliminary results of ACESS (Hachwar F et al., Paper submitted for publication)
• In total, 20 patients were randomized into a CytoSorb and a control arm (n=10 patients per arm)
• No difference in multiple organ dysfunction scores (MODS, SOFA) after 48 hours
• Significant reduction in norepinephrine dosages during the 48 hour observation period with a 70% decrease as compared to the norepinephrine requirement on inclusion. The most dramatic drop occurred during the first 12 hours, with no significant decline in norepinephrine dosages in the control group
• No difference in serum lactate levels between both groups
• Highly efficient removal of PCT in the CytoSorb group (over 90% within 12 hours), no significant decrease in PCT levels in the control group with the normal expected course of PCT
• Significant reduction in Big-ET-1 during the 48 hours observation period in the CytoSorb group, the most dramatic drop occurred during the first 12 hours

![Flowchart of patient screening and involvement](image-url)
CONCLUSIONS

- Hemodynamic stabilization and reduction of PCT plasma levels in the treatment group
- The first 12 hours of treatment seem to be the most efficient; an adsorber change <24h may be indicated in individual cases
- Performance of the adsorber changes over time which is why a way to monitor performance has to be established
- To define an even more homogenous group of patients the following prerequisites should be met as learned from this study: maintaining the short inclusion period of 24 hours, examine only medical patients with need for mechanical ventilation, PCT ~15-20 ng/ml, norepinephrine ~40-50µg/min, PICCO confirmed normovolemia and cardiac output and no renal failure
- The ACESS trial will help to better define future sepsis trials
**CLINICAL STUDIES AND EXPERIENCES IN SEPSIS**

**CytoSorb in sepsis – Clinical experiences from Switzerland**

M Maggiorini, Zurich, Switzerland

Professor Maggiorini reported on the clinical experience with the CytoSorb adsorber in his department and showed the first results from a comparison of CytoSorb treated patients with a historical control group.

Selection of the sickest patients with septic shock suitable for extracorporeal CytoSorb treatment

- Patients were selected following the new Sepsis 3 criteria (Singer M. et al. JAMA 2016; 315:801) within 24 hours of the diagnosis
- Vasopressor index (VPI) ≥ 3 (taking into account all the vasopressors used normalized for blood pressure, e.g. a patient of 70 kg requiring >15 µg/min norepinephrine)
- IL-6 ≥ 1000 ng/l
- Stratification of patients according to endotoxin activity (EAA) – included were patients with an EAA <0.6
- SOFA score was measured within 24 hours after admission to ICU

Setup for combined CRRT and CytoSorb treatment

- Application independent of whether the patient fulfilled criteria for acute kidney injury
- Treatment duration 72 hours
- The CytoSorb absorber and the CRRT set were changed every 24 hours

CytoSorb patient population characteristics

- From CytoSorb treatment candidates fulfilling the predetermined criteria (VPI ≥ 3, EAA <0.6) in total 47 patients were finally treated with CytoSorb, details are shown in Table 1

Effect of CytoSorb treatment on markers of inflammation

- Clear reduction of IL-6 and procalcitonin

Effect of CytoSorb treatment on patient hemodynamics

- Reduction in vasopressor support was possible after 24 hours followed by a dramatic decrease thereafter
- Stable hemodynamics under vasopressor support as seen by a steady cardiac index throughout the treatment phase
- Marked decrease in lactate

Effect of CytoSorb treatment on organ dysfunction

- No significant change in organ function during the 72 hours treatment, however lung function as well as extravascular lung water show a tendency towards improvement

Comparison to a control group (no data or graphs available)

- Comparison to a (less sick) historical control group of patients (n=26) with septic shock matched for age, SAPS2, SOFA (GenMatching)
- Differences between groups were observed for markers of inflammation (higher IL-6 in the CytoSorb group), lactate clearance, VPI (almost double in CytoSorb cohort), mortality, sepsis focus and ICU length of stay leaving the effect of CytoSorb treatment unclear
- Clearance of IL-6 was equal in both groups, reduction of PCT was more pronounced in the CytoSorb group, no differences in endotoxin levels between both groups
- Reduction of vasopressor support in the CytoSorb group was possible after 24 hours followed by a dramatic decrease thereafter, however there was a more progressive reduction of vasopressor demand in the control group, which is most likely due to the initially sicker patients in the CytoSorb group
- Both groups cleared lactate similarly
- Tendency towards a faster improvement in Horovitz quotient (paO₂, FiO₂) in the CytoSorb group, no differences in SOFA and ELWI between both groups

<table>
<thead>
<tr>
<th>CytoSorb group, n=47</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age [a]</td>
<td>55.22 ± 2.25</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>15/47</td>
</tr>
<tr>
<td>BMI [kg m⁻²]</td>
<td>26.32 ± 0.94</td>
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<tr>
<td>SAPS2 at admission</td>
<td>65.81 ± 2.66</td>
</tr>
<tr>
<td>SOFA at admission</td>
<td>14.19 ± 0.48</td>
</tr>
<tr>
<td>Interleukin-6 at admission (adjusted for dilution range) [ng l⁻¹]</td>
<td>1,216.94 ± 55.25</td>
</tr>
<tr>
<td>Vasopressor index at admission</td>
<td>11.99 ± 1.49</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>66%</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>68%</td>
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<tr>
<td>Sepsis focus:</td>
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<tr>
<td>Pulmonary</td>
<td>28%</td>
</tr>
<tr>
<td>Abdominal</td>
<td>30%</td>
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<tr>
<td>Urogenital</td>
<td>2%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0%</td>
</tr>
<tr>
<td>Skin / muscles / bones</td>
<td>0%</td>
</tr>
<tr>
<td>Unidentified</td>
<td>40%</td>
</tr>
<tr>
<td>ICU length of stay [d]</td>
<td>12.19 ± 1.88</td>
</tr>
<tr>
<td>Hospital length of stay [d]</td>
<td>21.66 ± 3.37</td>
</tr>
</tbody>
</table>

Table 1. CytoSorb patient population characteristics
CONCLUSIONS

- CytoSorb treatment was used in a subgroup of septic shock patients with a high need for vasoactive medication (VPI >3) and elevated IL-6 values (>1,000 ng/l) within 24 hours of the diagnosis.
- Over the treatment period of 72 hours, CytoSorb treatment was associated with a decrease in markers of inflammation and the vasopressor requirements, without reported impact on organ dysfunction.
- Treatment was safe and easy to apply.
- Further investigations using more comparable historical controls are needed to elucidate the full role of CytoSorb in the treatment of patients with septic shock.
Dr. Napp reported on the application of CytoSorb in combination with extracorporeal membrane oxygenation in different clinical situations, sharing his experience from several patients and provided an approach for cytokine hemoadsorption using CytoSorb after out-of-hospital cardiac arrest (with or without ECMO).

Notwithstanding the many - often life-saving - advantages of ECMO support, ECMO support per se induces inflammation:

- Cellular activation, fibrinolysis, complement activation, secondary von-Willebrand syndrome
- Surfaces of tubings and rotor/oxygenator
- Hemolysis
- Laminar non-pulsatile flow
- Unphysiologic retrograde blood supply by VA-ECMO
- End-organ hyperperfusion/oxygenation

Additionally, uncontrolled inflammation driven by the underlying condition is a major cause of ECMO support failure.

Set-up options of CytoSorb
- Hemoperfusion (standalone mode)
- Cardiopulmonary bypass
- Continuous renal replacement therapy
- Extracorporeal membrane oxygenation

Review of recent papers using CytoSorb in conjunction with ECMO

- A case report by Träger et al. demonstrated a significant reduction of IL-6 and IL-8 levels in a patient with ARDS and ECMO, which was associated with a decrease in vasopressor requirements, prototypically showing the effects of CytoSorb therapy in those patients (Träger K et al. Case Rep Crit Care. 2016;2016:9852073.)
- In another patient with heart failure, ARDS and influenza ECMO support showed hardly any effect on vasopressor demand and lactate levels, however with CytoSorb therapy, vasopressor doses and lactate levels started to decrease rapidly, again demonstrating the effect of CytoSorb in these patients (Lees NJ et al. J Artif Organs. 2016 Dec;19(4):399-402.)

Use of CytoSorb in Cardiac Arrest & Cardiogenic Shock

- Different etiologies can lead to cardiac arrest and cardiogenic shock exhibiting the following common phenotypes
  - Reduced systolic function
  - Increased diastolic filling pressures
  - Reduced coronary perfusion
  - Hyperinflammation (e.g. increased IL-6 levels)


- 24-year-old man
- Suicide attempt with venlafaxine (9 g)
- Severe cardiogenic shock in regional hospital
- Cardiopulmonary resuscitation for refractory shock
- ECMO under resuscitation
- After transport to Hannover Medical School an active left ventricular unloading with Impella CP was installed. For refractory right ventricular failure ECMO was upgraded to triple cannulation (VA-PA)
- Subsequent hemoadsorption with CytoSorb was associated with an immediate drop in catecholamines, with the patient being free from catecholamines 2 days after application. Lung function rapidly recovered within the next days.
- The patient was successfully weaned from all devices and could be discharged to rehabilitation in an ambulatory condition.

Another 5 case examples to demonstrate where to apply CytoSorb and where not

- Female 78-year-old patient with respiratory failure, resuscitation for asystole and transfer to Hannover Medical School. Clinical picture consistent with Takotsubo syndrome. Peripheral artery disease. On admission she was on high catecholamines, IL-6 levels were 14,267 ng/l. After the first cycle with CytoSorb IL-6 dropped to 2,259 ng/l and a second CytoSorb resulted in an IL-6 of 1,343 ng/l.
- Male 68-year-old patient, head trauma from fall, short cardiopulmonary resuscitation (CPR , 1 min.) for AV Block, intubation for unconsciousness, no catecholamines, no IL-6 measurement, no indication for CytoSorb as there was no catecholamine requirement. After hypothermia for 24 hours and awakening a pacemaker was implanted.
- Male 27-year-old patient, out-of-hospital cardiac arrest (OHCA) for asystole, no return of spontaneous circulation (ROSC), ECMO-CPR in the emergency room, IL-6 on admission 3055 ng/l. Immediate cytokine adsorption (installed into the ECMO) due to the high IL-6 level on admission and the very high chance of severe post-resuscitation syndrome.
- Male 58-year-old patient, OHCA for ventricular fibrillation, ROSC 20 min, Impella CP implantation, complete revascularization (PCI LMCA, LAD, LCX), coexisting myocarditis. He had very low catecholamines and an IL-6 of only 19 ng/l on admission. As there was no therapeutic goal for cytokine removal (low catecholamines and IL-6),
CytoSorb would not be indicated in these patients. He received levosimendan to facilitate weaning of the Impella.

- Male 67-year-old patient, OHCA for ventricular fibrillation, percutaneous coronary intervention, next day development of shock, ECMO implantation, transfer to Hannover Medical School. On admission he required high catecholamine doses, and had rhabdomyolysis as well as an IL-6 of 31,717 ng/l, thus two indications for CytoSorb.

### CytoSorb ECMO integration

![CytoSorb ECMO integration diagram](image)

Tables / Figures from presentation not shown due to ongoing publication process.

### CONCLUSIONS

- Inflammation is strongly associated with clinical deterioration and mortality
- In contrast to sepsis, in cardiology patients it is usually known when the problem has started
- According to Dr. Napp, CytoSorb represents the first major improvement in recent years for controlling the inflammatory response of critically ill patients
- There is a STRONG signal for beneficial effects of cytokine adsorption if the right patient is selected, with regard to:
  - Reduction in inflammation
  - Reduction in catecholamine doses
  - Shortening of ICU stay
CytoSorb and pancreatitis

A Faltlhauser, Weiden, Germany

Dr. Faltlhauser spoke about the pathophysiology of severe acute pancreatitis, reported on his experience with patients treated with CytoSorb and gave recommendations on timing and dosage of CytoSorb therapy.

Pathophysiology of severe acute pancreatitis
- Severe acute pancreatitis in the early phase (first 24-48 hours) after the pain event is characterized by a strong aseptic generalized inflammatory reaction in which mainly cytokines such as IL-6 are involved
- Pancreatitis associated complications in the early phase are not a specific problem of the pancreas but an organ dysfunction, patients never die from pancreatitis in the acute phase – but from secondary organ complications
- Severe acute pancreatitis has a predefined starting point of the inflammatory cascade – the initial massive pain event - comprised of a massive inflammatory response triggered by the autolysis of the organ
- Relatively homogeneous patient collective (no difference to whether the root cause is of biliary or of toxic origin)

Therapy - what do the guidelines say?
- Basic Support
- Diagnostics
- Interventions (esp. in biliary ethiology)
- Nutrition
- Therapy of local complications
- Guidelines, however, don’t make any statements on the modulation of acute inflammatory response

Presentation of 2 patients treated at different times after onset of the pain event (both male patients with acute severe pancreatitis)
- Patient 1 (early treatment)
  - Male with acute severe pancreatitis
  - Presented in the hospital very early - 14 hours after the onset of the typical pain
  - Start of CytoSorb therapy after 4.5 hours (i.e. 18.5 hours after the onset of pain)
- Patient 2 (late treatment)
  - Male with acute severe pancreatitis
  - Presented in the hospital very late - 44 hours after the onset of typical pain with already advanced pathophysiology
  - Start of CytoSorb therapy after 8 hours (i.e. 62 hours after the onset of pain)
- Patient 1 recovered during the course of the treatment, as evidenced by an improvement in hemodynamics, reduced need for catecholamines and a decrease in IL-6 levels, while patient 2 deteriorated in all three parameters and died in cardiovascular shock
- These effects could already be observed in the first 12 to 18 hours of treatment

Experiences from hospital Weiden
- Evaluation of clinical data from 14 patients with acute severe pancreatitis separated into early (<48 hours, n=9) and late (> 48 hours, n=5) start of treatment

<table>
<thead>
<tr>
<th></th>
<th>Early (&lt;48h)</th>
<th>Late (&gt;48h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 patients</td>
<td>5 patients</td>
</tr>
<tr>
<td>APACHE2:</td>
<td>21 (+/-3.4)</td>
<td>28 (+/-3.9)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Biliary 6/9</td>
<td>C2 4/5</td>
</tr>
<tr>
<td>Lipase</td>
<td>986 (+/- 342)</td>
<td>1,223 (+/- 451)</td>
</tr>
<tr>
<td>Ca+ion (mmol/l§)</td>
<td>1.13 (+/- 0.13)</td>
<td>1.03 (+/- 0.15)</td>
</tr>
<tr>
<td>Hct</td>
<td>43 % (+/- 5.9)</td>
<td>46 % (+/- 4.3)</td>
</tr>
<tr>
<td>GOT</td>
<td>159 (+/- 57)</td>
<td>278 (+/- 97)</td>
</tr>
<tr>
<td>INR</td>
<td>0.9 (+/- 0.23)</td>
<td>1.4 (+/- 0.43)</td>
</tr>
<tr>
<td>RIFLE</td>
<td>I/F</td>
<td>F/L</td>
</tr>
<tr>
<td>Breathing</td>
<td>Spontaneous (7)</td>
<td>Spontaneous (3)</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3 (+/- 0.12)</td>
<td>0.5 (+/- 0.21)</td>
</tr>
<tr>
<td>CVVH</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CytoSorb</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- In the group of late onset-treated patients (Figure 1 in red), patients who died (n=3) showed that it was not possible at any time to control their cytokine levels
- In these patients the initiation of CytoSorb therapy was too late, compared to the early onset-treated patients where the control of cytokine levels was possible
- Correlation of blood flow and elimination kinetics
  - Patients in whom a blood flow higher than 140 ml/min (Figure 2 in red) was established show faster and more pronounced elimination kinetics for IL-6
  - The adsorber takes some time to develop its effect (3-6 hours), this effect can obviously be mitigated by an increase in blood flow
Timing is of essence - what we know as of March 19th 2018

- Proof of Safety
  - Cytokine adsorption can be performed safely
- Proof of Concept
  - IL-6 as key inflammatory marker can be significantly reduced
- Cytokine adsorption aids in reducing catecholamine use and improves global hemodynamics

The „Weiden Pancreatitis Protocol“

- Basics come first - standard therapy corresponding to guidelines

• If there is no improvement, e.g.
  - Still increasing catecholamine dependency or in excess of 100 ml/kg fluids in 6hrs and still oliguric
  - Persistent metabolic acidosis pH < 7.25 despite adequate fluid resuscitation over 6 hrs

• CVVH + cytokine adsorption is initiated with the following settings
  - CVVH
  - Blood Flow >140 ml/min
  - Cytokine adsorber in pre-filter position
  - Check effectiveness at 6/12 hours
  - Change adsorber every 24 hours

• If there is no clinical effect, the following is considered
  - Treatment started too late?
  - Underdosing of treatment?
  - Cause of inflammation is not solved?

CONCLUSIONS

• In patients with acute severe pancreatitis, early start of treatment with CytoSorb is a prerequisite to ensure treatment success
• Blood flow through the adsorber is directly related to the elimination kinetics
• However, many questions remain unanswered
  - Does cytokine adsorption provide reduction of morbidity and mortality?
  - Dosing and timing of cytokine adsorption?
  - Drug dosing under cytokine adsorption?
  - Cost-benefit evaluation?
Dr. Aucella gave a presentation on the application of CytoSorb in patients with rhabdomyolysis and kidney failure.

**Definition of rhabdomyolysis**
- Destruction or disintegration of muscle cells resulting in the leakage of the intracellular muscle constituents into circulation and extracellular fluids
- Released constituents comprise of creatine kinase (CK), myoglobin, potassium, phosphorus transaminases, LDH
- Myoglobin is a dark red cytoplasmic hemoprotein that binds oxygen on a heme group, has a high affinity for oxygen, molecular weight is 17,800 Da, physiological plasma levels are 0-0.003 mg/dl
- Myoglobin represents the pathogenic factor in rhabdomyolysis-induced acute kidney injury (AKI)
- Causes of rhabdomyolysis include trauma, exertion, muscle hypoxia, genetic defects, infections, body temperature changes, metabolic and electrolyte disorders, drugs and toxins
- Complications of rhabdomyolysis are AKI, compartment syndrome, hyperlactatemia, hypovolemia along with several others

**Rhabdomyolysis and AKI**
- AKI associated with myoglobinuria is the most serious complication of rhabdomyolysis
- Among 10-50% of patients with rhabdomyolysis develop AKI
- There are three main mechanisms involved
  1. Renal vasoconstriction through hypovolemia and activation of cytokine cascade
  2. Tubular obstruction through the production of pigmented casts
  3. Direct toxicity of myoglobin

**Guidelines on rhabdomyolysis treatment**
- Focus is to preserve the renal function by reducing the circulating myoglobin
- Resolve muscle injury
- Preservation and treatment of renal function:
  - Early aggressive fluid replacement
  - Alkalization of urine
  - Forced diuresis
  - Early CRRT to remove the circulating nephrotoxic factors
- However, dialysis techniques have shown poor efficacy in the removal of circulating myoglobin and other muscle enzymes from the blood

**Use of CytoSorb in patients with hypermyoglobinemia following acute ischemia of the right lower limb (Cardiac Surgery Intensive Care Unit, San Giovanni Rotondo)**
- 68-year-old female
- Mitral valve replacement through a mini-thoracotomy
- Acute ischemia of the right lower limb
- Postoperative day 5: myoglobinemia >20,000 ng/ml
- Surgical resolution of the ischemic problem
- Start CVVHDF (blood flow rate 150ml/min; dialysate flow 1,500ml/h) plus CytoSorb for 4 days
- CytoSorb treatment resulted in
  - Stabilization of myoglobin and CPK levels
  - Renal function improvement
  - Normal diuresis achieved

**Use of CytoSorb in patients with AKI associated with rhabdomyolysis (Nephrology & Dialysis Unit and Intensive Care Unit Trieste)**
- 35-year-old male
- Polytrauma after cocaine intoxication: multiple fractures, rhabdomyolysis and acute kidney injury
- Before treatment: Myoglobin: >63,000 ng/ml; CPK: >54,000 U/L, Creatinine: 2.87 mg/dl
- Initiation of CVVHD+CytoSorb for 48 hours
- After 48 hours: Myoglobin: 11,570 ng/ml; CPK: 6,586 U/L
- Treatment was further associated with
  - Stabilization of myoglobin and CPK levels
  - Renal function improvement
  - Normal diuresis achieved after 6 days

**Extracorporeal therapies in the treatment of rhabdomyolysis-induced AKI**
- Plasma exchange, intermittent hemodialysis and conventional hemodialysis have shown only limited success in myoglobin removal
- Continuous veno-venous hemofiltration or hemodiafiltration with the use of super high-flux filters and high volumes of hemofiltration have also shown no evidence and the effect on outcomes is unknown (Ronco C. Critical Care. 2005;9(2):141-142.; Huerta-Aladin AL. Critical Care 2005, 9:158-169)
- A new solution is adsorption using CytoSorb which represents a new solution with its adsorption spectrum and capacity.
New treatment of rhabdomyolysis with AKI in patients with crush syndrome after an earthquake in Italy (Nephrology and Dialysis Unit, Rieti)

Case series of 3 male patients with crush syndrome of different severity after the central Italy earthquake (Average time under the rubble: 9 hours)

- High hematocrit and hemoglobin levels, hyperkalemia, hypercreatininemia
- Myoglobin >12,000 ng/ml
- Increase of LDH, GPT, GOT, anuria

- Standard treatment for rhabdomyolysis with CRRT using a high cut-off filter in the first 4 days
- Day 0-4: CRRT with high cut-off filters had no significant effect on myoglobin reduction
- With the start of CytoSorb from day 4 (3 days of treatment) the following clinical effects could be achieved:
  - Rapid reduction of both myoglobin and CPK
  - Renal function recovery
  - Normal diuresis recovery
Continuation: CytoSorb in rhabdomyolysis and kidney failure
F Aucella, San Giovanni Rotondo, Italy

Experience in a patient with Stanford type A aortic dissection and rhabdomyolysis (Intensive Care Unit, Udine)

- 34 year-old male patient, body builder
- Stanford type A aortic dissection, massive AR and cardiac tamponade
- CPB time 612 minutes, X-clamp time 340 minutes
- Aortic arch replacement and supra-aortic vessels re-implantation
- Severe biventricular failure during CPB weaning followed by initiation of peripheral VA-ECMO
- On ICU admission values were as follows:
  - Lactate 20 mmol/l
  - HR 110/min, MAP 62 mmHg, norepinephrine 0.6 µg/kg/min, epinephrine 0.085 µg/kg/min, levosimendan 0.05 µg/kg/min
  - CVVHDF was started on POD 1 due to anuria
  - Hyperkalemia (7.3 mmol/l) and peak of myoglobin 860,000 ng/ml and CPK 511,000 UI/l, total bilirubin was 2.87 mg/dl
  - Patient exhibited severe hemodynamic instability, liver dysfunction, rhabdomyolysis and multiple organ failure
- Start of CytoSorb after 5 days for a total of 5 treatments resulted in:
  - Rapid reduction of both myoglobin and CPK
  - Hemodynamic stabilization with clear reduction in catecholamine requirements (norepinephrine/epinephrine)

Figure 4. Course of myoglobin and catecholamines throughout the CytoSorb treatments in a patient with Stanford type A aortic dissection and rhabdomyolysis
CONCLUSIONS

- Acute renal failure is a common complication of rhabdomyolysis due to myoglobin nephrotoxicity and may lead to irreversible renal damage
- It is necessary to identify a proper and effective purification strategy for the removal of the nephrotoxic molecules circulating in the blood
- Adsorption may be the best technique to overcome the limits of dialysis
- Hemoadsorption with CytoSorb is an effective and rapid method for the removal of myoglobin and other muscle enzymes

Overview on clinical experiences with CytoSorb in rhabdomyolysis

<table>
<thead>
<tr>
<th>Institution</th>
<th>Clinical Condition</th>
<th>Number of Treatments / Total Duration</th>
<th>Myoglobin initial value</th>
<th>Myoglobin final value</th>
<th>Other Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Vienna</td>
<td>Legionella-Pneumonia Associated rhabdomyolysis</td>
<td>2 treatments / 24 h</td>
<td>18,390 ng/ml</td>
<td>8,352 ng/dl</td>
<td>- CytoSorb in HP - Renal function improvement</td>
</tr>
<tr>
<td>University of Lubeck</td>
<td>Septic Shock associated rhabdomyolysis</td>
<td>4 treatments / 80 h</td>
<td>30,000 ug/L</td>
<td>&lt; 1,000 ug/L</td>
<td>- IL6 reduction and inflammatory state improvement</td>
</tr>
<tr>
<td>Policlinico San Marco, Zingonia</td>
<td>Rhabdomyolysis with ARF after laparoscopic sleeve gastrectomy</td>
<td>1 treatment / 24 h</td>
<td>52,800 ng/dl</td>
<td>8,862 ng/dl</td>
<td>- CPK reduction (52%) - Renal function improvement</td>
</tr>
<tr>
<td>Villa Sofia, Palermo</td>
<td>Trauma associated rhabdomyolysis - Case series</td>
<td>1 treatment / 24 h</td>
<td>average value &gt; 10,000 ng/ml</td>
<td>average reduction: 58%</td>
<td>- CytoSorb in HP - ARF prevention, no need for CRRT</td>
</tr>
<tr>
<td>Baggiovara Hospital, Modena</td>
<td>Massive rhabdomyolysis due to cocaine overdose</td>
<td>3 treatments / 63 h</td>
<td>198,175 ng/ml</td>
<td>36,025 ng/ml</td>
<td>- Progressive recovery of diuresis</td>
</tr>
<tr>
<td>Cattinara Hospital, Trieste</td>
<td>Massive rhabdomyolysis due to cocaine overdose</td>
<td>2 treatments / 48 h</td>
<td>&gt; 63,000 ng/ml</td>
<td>11,570 ng/ml</td>
<td>- CK reduction - Renal function recovery</td>
</tr>
<tr>
<td>Chieti Hospital, Chieti</td>
<td>Crush induced rhabdomyolysis</td>
<td>2 treatments / 48 h</td>
<td>&gt; 20,000 ng/ml</td>
<td>1,480 ng/ml</td>
<td>Stabilization of all parameters</td>
</tr>
<tr>
<td>Rieti Hospital, Rieti</td>
<td>Crush induced rhabdomyolysis</td>
<td>On average 3 treatments / 48 h</td>
<td>&gt; 12,000 ng/ml</td>
<td>Physiological values</td>
<td>Recovery of diuresis and renal indices</td>
</tr>
</tbody>
</table>

CLINICAL EXPERIENCES FROM VARIOUSFields OF APPLICATION
My special CytoSorb case: XTC-Intoxication

FS Taccone, Brussels, Belgium

Professor Taccone presented his experiences in a special case session.

Case presentation

- 27 year-old woman, 45 kg with an unknown medical history
- Admission to the emergency department of another hospital in Brussels because of “intoxication”, after she had been in a nightclub and was found on the floor with rigor, tachycardia, hypertension (190/100 mmHg), hyperthermia (41.6°C), agitated and obtunded
- Direct intubation on site
- Suspected drug was ECSTASY, however with unknown dose, unknown association with other drugs and concomitant alcohol intake
- On admission to the emergency department she was sedated and paralyzed, had dilated pupils, heart rate was 130 bpm, blood pressure 75/35 mmHg, body temperature 41.8°C
- She showed no signs of cyanosis or hypoperfusion
- Initial FAST ECHO was negative, Echocardiography showed a left ventricular ejection fraction of 50%, chest X-ray showed bilateral infiltrates (probably through inhalation or vomiting on site), and ECG showed sinus tachycardia
- Initial blood sample was as follows: pH 7.28, PaCO$_2$ 32 mmHg, PaO$_2$ 182 mmHg (FiO$_2$ 100%), lactate 3.0 mmol/l, base excess 10.9 mmol/l, metHb 1.1%, WBC 8,000/mm$^3$, Hb 13.1 g/dl, platelets 317,000/mm$^3$, aPTT 19 secs; INR 0.98, fibrinogen: 215 mg/dl, Na+ 139 mmol/l; K+ 4.9 mmol/l; albumin 4.8 g/l, urea 29 mg/dl; creatinine 1.6 mg/dl, CK 220 IU/l, glucose 55 mg/dl, CRP 4.9 mg/l, ethanol: <0.1 g/l
- Development of a severe shock state within the next 2 hours necessitating start of norepinephrine (NE) infusion, lactate was 8.5 mmol/l, she exhibited diffuse bleeding in the throat, from puncture sites, the bladder probe but also “rectal” bleeding
- Initial therapy comprised of administration of fluids (6,000 ml crystalloids), norepinephrine 0.4 µg/kg/min, IV glucose, 600 ml fresh frozen plasma, prothrombin complex concentrates, 2 g tranexamic acid, 2 g fibrinogen, 8 mg/h midazolam, 5 mg/h morphine
- The patient had hepatic failure, distributive shock, hypoglycaemia, acute kidney injury due to rhabdomyolysis and severe ARDS
- Due to the option for liver transplantation the patient was transferred to the Department of Intensive Care at the Hôpital Erasme, Brussels
- Methamphetamine was the only (toxic) drug detected by toxicology
- Upon admission, she now exhibited severe ARDS, hemodynamic instability (norepinephrine 1.3 µg/kg/min), metabolic acidosis, myoglobinemia and capillary leakage
- As a consequence, antibiotic therapy with amoxicillin/clavulanic acid (2 g), continuous renal replacement therapy (CRRT) and a few hours later VV-ECMO were started
- Additionally, administration of methylene blue (2 mg/kg, a nitric oxide scavenger) was given to reduce vasoplegia and to reduce the dependency on norepinephrine
- During the night, SpO$_2$ fell to 75% and blood analysis revealed a MetHb of 21% (tissue hypoxia with oxygen unable to be delivered to end organs)
- It was discovered that erroneously patent blue (used in lymphangiography and sentinel node biopsy as dye to color lymph vessels, with the side effect of having an inhibitory effect on human mitochondrial respiration and being highly bound to albumin) had been administered instead of methylene blue resulting in this severe clinical picture of methemoglobinemia (MetHb 21%) and tissue hypoxia necessitating immediate therapeutic intervention

Treatment and results

- As a therapeutic attempt to clear the plasma of patent blue, CytoSorb therapy was initiated for 24 hours
- Due to a plateau phase and a presumed saturation of the adsorber, a second device was connected after 24 hours
- Treatments resulted in a steady and clear reduction of plasma metHb accompanied by a decrease in norepinephrine and normalized lactate levels (see figure)
- Treatment further contributed to a removal of toxic patent blue, a reduction of myoglobinemia and a reduction of tissue hypoxia

Patient Follow-Up

- The follow-up period after cessation of CytoSorb treatment consisted of weaning from ECMO on day 5, tracheostomy on day 19, weaning from MV on day 26, discharge from ICU on day 30, weaning from tracheostomy on day 41, discharge into rehabilitation on day 56 and back home on day 75
CONCLUSIONS

- This is the first described case report on severe intoxication with MDMA (methamphetamine) associated with multiple organ failure and an iatrogenic intoxication to Patent Blue which was successfully treated with CytoSorb.
- CytoSorb use was associated with reduced Methb, lactate levels and improved hemodynamics.
- There is a potential role for CytoSorb in drug intoxication, which however needs to be verified on a larger scale.
CytoSorb Therapy - REGAIN CONTROL