NEW OPTIONS FOR PATIENTS WITH SIRS
DURING AND AFTER CARDIAC SURGERY
Disclosure

- CytoSorbents Europe
- Fresenius Medical Care
- OrionPharma
History of cardiopulmonary bypass CPB

- **1953**
  John Gibbon

  Surgical repair of atrial septum defect in 18 years old patient

- **1954**
  CW Lillehei (cardiac surgeon) and R DeWall

  CPB with bubble oxygenator
Problem of SIRS post CPB
Taylor KM: SIRS - the systemic inflammatory response syndrome after cardiac operations

Pathophysiology

- Inflammatory stimulation by surface contact
  The systemic inflammatory response syndrome and cardiopulmonary bypass
  Systemic inflammatory response syndrome after cardiac surgery under cardiopulmonary bypass

- Inflammatory cytokines
  Evidence of systemic cytokine release in patients undergoing cardiopulmonary bypass

Clinical symptoms

- Capillary leak
- Vasoplegia
- Hypotension
- Pulmonary dysfunction
- Renal dysfunction
- MODS
Strategies to fight SIRS post CPB

„Arrest the usual suspects ...“

- **Prophylaxis**
  - **Statins**
    Effects of simvastatin on systemic inflammatory responses after cardiopulmonary bypass
  - **MECC** (mini extracorporeal circulation)
    The inflammatory response to miniaturised extracorporeal circulation: a review of the literature
    Vohra HA et al.: Mediators Inflamm 2009: 707042

- **Suppression**
  - **Steroids**
    Pulse low dose steroids attenuate post-cardiopulmonary bypass SIRS
  - **Leucodepletion**
    The effects of leucodepletion in patients who develop SIRS following cardiopulmonary bypass
Strategies to fight SIRS post CPB

„Arrest the usual suspects ...“

- **Treatment (ICU)**
  - Catecholamines
  - Vasopressin
  - Methylene blue
  - Organ support therapy

- **Cytokine elimination**
  Cytokines in the systemic inflammatory response syndrome: a review
Cytokine storm induced multi organ failure

Cytokine storm

Pro-Inflammation

Anti-Inflammation

TOXIC

INSULT

Organ failure

recovery

Time (days / weeks)

dead
Cardio-Pulmonary-Bypass (CPB) as a paradigm of an inflammatory insult
Controlling cytokine storm in SIRS and SEPSIS
Blood purification and mortality in sepsis: a meta-analysis of randomized trials.
Zhou F et al., Crit Care Med 2013, 41: 2209

- Blood purification
  - Hemofiltration
  - Hemoperfusion
  - High volume hemofiltration
  - Pulsed high volume hemofiltration
  - Plasma separation
  - Adsorption (Polymyxin B)
  - CPFA (coupled plasma filtration adsorption)
  - Middle molecule filters
    (high cutoff Filter)
Blood purification and mortality in sepsis: a meta-analysis of randomized trials
Zhou F et al., Crit Care Med 2013, 41: 2209

**CONCLUSION:**
In conclusion, pooled results of multiple small studies of moderate study quality show that blood purification (including hemoperfusion or plasma exchange alone, hemofiltration combined with hemoperfusion) is associated with lower mortality in patients with sepsis.

These results were mainly influenced by studies using hemoperfusion with PMX-B...

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<th>Year</th>
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<th>Weight</th>
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... that blood purification is associated with lower mortality in patients with sepsis

... mainly influenced by studies using hemoperfusion with PMX-B...
Controlling cytokine storm during SIRS and SEPSIS by ADSORPTION (CytoSorb)

- **EFFICACY**
  - Reducing increased cytokine levels
  - Reduced cytokine production

- **REGISTERED CYTOKINE ADSORBER (EUROPE)**

- **SAFETY**
  - High biocompatibility (ISO 10993)

- **FAST SETUP AND EASY HANDLING**
  - Use with conventional CRRT devices
  - Whole blood hemoperfusion

- **REIMBURSEMENT**
Controlling cytokine storm in the cardiosurgical patient

Preemptive approach

- During CPB

Therapeutic approach

- Adjunctive therapy postoperative / ICU
Start of implementing CytoSorb therapy in 2013 ...

- 51 patients
- 102 treatments

Indications
- SIRS post CPB
- Septic shock
- VA/VV ECMO
- During CPB

Effects on
- Cytokine levels
- Clinical parameters
CytoSorb treatments
SURVIVORS (n=25) und NON-SURVIVORS (n=19)

<table>
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<td>Cytosorb treatment time</td>
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- septic shock 18%
- SIRS post CPB 40%
- VA ECMO 22%
- during CPB 20%
CytoSorb treatment during CPB

? DOES IT PREVENT OR AT LEAST MITIGATE POST CPB SIRS ?

- Potential indications
  - Endocarditis
  - Local infection
  - Complex, long lasting surgery
  - Long CPB and x-clamp time
  - Re-do
  - ...

...
Systemic Inflammatory Response Syndrome in Cardiac Surgery. Use of a cytokine adsorber as a new therapeutic approach?

<table>
<thead>
<tr>
<th>Gruppen</th>
<th>HLM Zeit</th>
<th>Cross Clamp</th>
<th>Reperfusion</th>
<th>Stillstand</th>
<th>Hirnperfusion</th>
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<td>138,55</td>
<td>59,20</td>
<td>40,80</td>
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</table>

Tab. 1: Charakterisierung der Patientenkollektive bezüglich Maschinenzeiten, Ischämie- und Reperfusionszeiten, Zeit des Herzstillstandes und der Hirnperfusion (Zeiten in Minuten)

- Max. Blutfluss: 400 ml/min
- Max. Druck: 500 mmHg
- Oberfläche: 40,000 m²
- Priming Volumen: 275 ml
Systemic Inflammatory Response Syndrome in Cardiac Surgery. Use of a cytokine adsorber as a new therapeutic approach?

CytoSorb treatment during CPB

- Parallel in CPB circuit (flow 350 ml/min)

**IL8 [ng/l]**
- Pre CytoSorb: 13.7
- Post CytoSorb: 11.6

**IL6 [pg/ml]**
- Pre CytoSorb: 151.5
- Post CytoSorb: 133.7

**PCT [μg/l]**
- Pre CytoSorb: 0.095
- Post CytoSorb: 0.075
## CytoSorb treatments during CPB (n=9)

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<th>In</th>
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<th>Indication1</th>
<th>Indication2</th>
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<td>w</td>
<td>during CPB</td>
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<td>Surv</td>
<td>AV prosthesis endocarditis</td>
<td>Anular ring abscess</td>
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<td>Anular ring abscess</td>
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<td>Surv</td>
<td>AV endocarditis</td>
<td>Multiple peripheral septic emboli</td>
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<td>Surv</td>
<td>AV insufficiency</td>
<td>LCOS</td>
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<td>Died</td>
<td>DCM, post CPR and LCOS</td>
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<td>Surv</td>
<td>AV endocarditis</td>
<td>septic shock</td>
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<td>during CPB</td>
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<td>Died</td>
<td>MV prosthesis dislocation</td>
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CytoSorb treatment during CPB
SURVIVORS (n=6) und NON-SURVIVORS (n=3)

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<td>Total treatment time</td>
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<td>NON-SURVIVORS</td>
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<td>Per Adsorber treatment</td>
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<tr>
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<td>NON-SURVIVORS</td>
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IL 6 after CytoSorb treatment during CPB

IL6 after CytoSorb use during CPB

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<tr>
<th>Time</th>
<th>IL6_base</th>
<th>IL6_6h</th>
<th>IL6_12h</th>
<th>IL6_18h</th>
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<th>IL6_48h</th>
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Time

IL6_base, IL6_6h, IL6_12h, IL6_18h, IL6_24h, IL6_36h, IL6_48h

Graph: Line graph showing IL6 levels over time with different time points labeled.
IL 8 after CytoSorb treatment during CPB

IL8 after CytoSorb use during CPB

IL8 [ng/l]

Time

IL8_base IL8_6h IL8_12h IL8_18h IL8_24h IL8_36h IL8_48h

all all mean line
CRP after CytoSorb treatment during CPB

CRP after CytoSorb use during CPB

<table>
<thead>
<tr>
<th>Time</th>
<th>CRP [mg/l]</th>
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<td>CRP_48h</td>
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all mean line
Catecholamines after CytoSorb treatment during CPB

Time

NOR_base NOR_6h NOR_12h NOR_18h NOR_24h NOR_36h NOR_48h

NOR [µg/kg/min]

0,0 0,2 0,4 0,6 0,8 1,0

all

all mean line

nonsurvivors mean line
Metabolic parameters after CytoSorb treatment during CPB

### Lactate after CytoSorb use during CPB

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<tr>
<th>Time</th>
<th>Lac_base</th>
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- **all**: blue bars
- **all mean line**: blue dotted line
- **nonsurvivors mean line**: red dotted line

### pH after CytoSorb use during CPB

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### Base excess after CytoSorb use during CPB

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- **all**: blue bars
- **all mean line**: blue dotted line
- **nonsurvivors mean line**: red dotted line
CytoSorb treatments:  SIRS post CPB (n=18)

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</table>
CytoSorb treatment in SIRS post CPB

**CPB time**
- Mean 175 min
- Min. 107 min
- Max. 392 min

**Cross clamp time**
- Mean 108 min
- Min. 56 min
- Max. 247 min
CytoSorb treatment in SIRS post CPB
SURVIVORS (n=11) und NON-SURVIVORS (n=7)

<table>
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<tr>
<th></th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>Total treatment time</td>
<td>59</td>
<td>5</td>
<td>179</td>
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<tr>
<td>Per Adsorber treatment time</td>
<td>30</td>
<td>1,5</td>
<td>50</td>
</tr>
<tr>
<td>Total treatment time</td>
<td>51</td>
<td>29</td>
<td>112</td>
</tr>
<tr>
<td>NON-SURVIVORS</td>
<td>72</td>
<td>5</td>
<td>179</td>
</tr>
<tr>
<td>Per adsorber t. time</td>
<td>33</td>
<td>1,5</td>
<td>50</td>
</tr>
<tr>
<td>SURVIVORS</td>
<td>28</td>
<td>2</td>
<td>45</td>
</tr>
</tbody>
</table>
CytoSorb treatment in SIRS post CPB

- Effects on cytokine levels?
- Effects on inflammatory parameters?
- Effects on clinical parameters?
IL6 after CytoSorb treatment in SIRS post CPB

IL6 in SIRS post CPB

CytoSorb

IL6 [pg/ml]

0 1000 2000 3000 4000 5000

Time

IL6_base IL6_6h IL6_12h IL6_18h IL6_24h IL6_36h IL6_48h

all mean line

all
IL6 after CytoSorb treatment in SIRS post CPB
CRP after CytoSorb treatment in SIRS post CPB

CRP in SIRS post CPB

<table>
<thead>
<tr>
<th>Time</th>
<th>CRP_base</th>
<th>CRP_6h</th>
<th>CRP_12h</th>
<th>CRP_18h</th>
<th>CRP_24h</th>
<th>CRP_36h</th>
<th>CRP_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP [mg/l]</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
<td></td>
</tr>
</tbody>
</table>

Survivors: mean line
Nonsurvivors: mean line

Survivors
Nonsurvivors
CytoSorb treatment in SIRS post CPB

- Effects on cytokine levels?
- Effects on inflammatory parameters?
- Effects on clinical parameters?
Hemodynamic parameters after CytoSorb treatment in SIRS post CPB

**MAP in SIRS post CPB**

<table>
<thead>
<tr>
<th>Time</th>
<th>MAP_base</th>
<th>MAP_6h</th>
<th>MAP_12h</th>
<th>MAP_18h</th>
<th>MAP_24h</th>
<th>MAP_36h</th>
<th>MAP_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heart Rate in SIRS post CPB**

<table>
<thead>
<tr>
<th>Time</th>
<th>HR_base</th>
<th>HR_6h</th>
<th>HR_12h</th>
<th>HR_18h</th>
<th>HR_24h</th>
<th>HR_36h</th>
<th>HR_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Noradrenaline after CytoSorb treatment in SIRS post CPB

NOR in SIRS post CPB

Time

NOR_base NOR_6h NOR_12h NOR_18h NOR_24h NOR_36h NOR_48h

NOR [µg/kg/min]

CytoSorb
Noradrenaline after CytoSorb treatment in SIRS post CPB

<table>
<thead>
<tr>
<th>Time</th>
<th>NOR_base</th>
<th>NOR_6h</th>
<th>NOR_12h</th>
<th>NOR_18h</th>
<th>NOR_24h</th>
<th>NOR_36h</th>
<th>NOR_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0,0</td>
<td>0,2</td>
<td>0,4</td>
<td>0,6</td>
<td>0,8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CytoSorb**

- Survivors mean line
- Nonsurvivors mean line

![Graph showing Noradrenaline levels over time for survivors and nonsurvivors with CytoSorb treatment](image-url)
Adrenaline after CytoSorb treatment in SIRS post CPB

EPI in SIRS post CPB

Time

EPI [µg/kg/min]

survivors
nonsurvivors
survivors mean line
nonsurvivors mean line

CytoSorb

EPI_base  EPI_6h  EPI_12h  EPI_18h  EPI_24h  EPI_36h  EPI_48h

survivors
nonsurvivors
survivors mean line
nonsurvivors mean line
Lactate after CytoSorb treatment in SIRS post CPB

Lactate in SIRS post CPB

CytoSorb

Lactate [mmol/l]

survivors mean line
nonsurvivors mean line

Time

Lac_base Lac_6h Lac_12h Lac_18h Lac_24h Lac_36h Lac_48h

survivors
nonsurvivors

Lactate [mmol/l]

0 5 10 15 20 25 30

0 5 10 15 20 25 30

Survivors and nonsurvivors mean lines are indicated in the graph.
pH and BE after CytoSorb treatment in SIRS post CPB

### pH in SIRS post CPB

<table>
<thead>
<tr>
<th>Time</th>
<th>pH_base</th>
<th>pH_6h</th>
<th>pH_12h</th>
<th>pH_18h</th>
<th>pH_24h</th>
<th>pH_36h</th>
<th>pH_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.0</td>
<td>7.1</td>
<td>7.2</td>
<td>7.3</td>
<td>7.4</td>
<td>7.5</td>
<td>7.6</td>
</tr>
</tbody>
</table>

**CytoSorb**

### Base excess in SIRS post CPB

<table>
<thead>
<tr>
<th>Time</th>
<th>BE_base</th>
<th>BE_6h</th>
<th>BE_12h</th>
<th>BE_18h</th>
<th>BE_24h</th>
<th>BE_36h</th>
<th>BE_48h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-15</td>
<td>-10</td>
<td>-5</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

**CytoSorb**

**Survivors**

**Nonsurvivors**

**Survivors mean line**

**Nonsurvivors mean line**
SAPS II after CytoSorb treatment in SIRS post CPB

**SAPS II in SIRS post CPB**

**SAPS II**

- **SAPSII_base**
  - Time: 20
  - SAPS II: 40
  - SAPS II: 60
  - SAPS II: 80

- **SAPSII_36h**
  - Time: 20
  - SAPS II: 40
  - SAPS II: 60
  - SAPS II: 80

**Time**

- **SAPSII_base**
- **SAPSII_36h**

**Survivors**

- **Survivors mean line**

**Nonsurvivors**

- **Nonsurvivors mean line**

**Figure legend**

- **Blue** all
- **Blue dotted line** all mean line
- **Green** survivors
- **Green dotted line** survivors mean line
- **Red** nonsurvivors
- **Red dotted line** nonsurvivors mean line
Other effects of CytoSorb treatment

Elimination of

- Free hemoglobin, 35 KD
- Myoglobin, 17 kD
- Bilirubin, 8 KD
- ?
Bilirubin elimination during CytoSorb treatment
Case 34: m, 67
Elimination of free hemoglobin during CytoSorb treatment
Case 14: m, 76

<table>
<thead>
<tr>
<th>Treatment time</th>
<th>Free hemoglobin [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHB_BASE</td>
<td>1800</td>
</tr>
<tr>
<td>12H</td>
<td>1336</td>
</tr>
<tr>
<td>24H</td>
<td>262</td>
</tr>
<tr>
<td>36H</td>
<td>200</td>
</tr>
<tr>
<td>48H</td>
<td>202</td>
</tr>
</tbody>
</table>
Future perspective: CytoSorb treatment in the OR and in the ICU...
CYTOSORB THERAPY
ACHIEVABLE EFFECTS WITH THERAPEUTIC AND PREVENTIVE USE

- Reduction of cytokine levels
- Mitigation of cytokine storm
- Maintained immune response
- Faster stabilization of clinical parameters
  - hemodynamic
  - metabolic

POTENTIAL EFFECTS
- Decreased capillary leak
- Better organ recovery
- Outcome
CONCLUSION

CytoSorb treatment in cardiac surgery

**Preemptive approach**
- Acute endocarditis
- Local infections
- Complex and long lasting surgery
- Long CPB and X-clamp time
- Re-do

**Therapeutic approach**
- SIRS post CPB
- Septic schock
- Septic surgery (during CPB)
- Severe reperfusion
- Hyperbilirubinemia
- Severe hemolysis

...