Cytokin-Adsorption in der Sepsis

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Klinik für Anästhesiologie
Universitätsklinikum Düsseldorf

Cytokin-Adsorption in der Sepsis

- Epidemiologie und Pathophysiologie
- Rationale für Cytokin-Elimination
- Konventionelle Techniken
- Unspezifische adsorptive Verfahren

Erstbeschreibung des sept. Schocks

Septic Shock:
Clinical, Physiological, and Pathological Survey of 244 Patients

William A. Necky, M.D., F.A.C.S., Don W. Berry, M.D.,
Fred W. Risher, B.A., James D. Harry, M.D., F.A.C.S.

From the Department of Surgery, The University of Mississippi Medical Center,
Jackson, Mississippi

Ann. Surg. - May 1971
Vol. 173 - Nr. 3
Erstbeschreibung des sept. Schocks

Sepsis continues to be a leading cause of hospital, and especially surgical, mortality. Reports from many clinics have attested the gravity of gram negative shock, but two of the more impressive were those of Waisbren and Borden, both of whom in 1951 described a shock syndrome associated with gram negative enteric bacteria. Weil and Spink reported on 278 cases of bacteremia observed at the University of Minnesota Hospitals. Forty-three patients in their study developed shock, of whom 25 died. Bacteremia was found to be the most

Letalität 65 %

Erstbeschreibung des sept. Schocks

myocardial infarction. Although sepsis often occurs in debilitated and malnourished patients with poor general hygiene, Hannigan et al. found a surprisingly high incidence in private patients. Weil reported

Sepsis-incidence

Sepsis following elective surgery

Temporal Trends in the Epidemiology of Severe Postoperative Sepsis after Elective Surgery

A Large, Nationwide Sample

Brian T. Batey, M.D., Ulrich Schmidt, M.D., Ph.D., Mitchell F. Bernstein, M.D., M.P.H., Edward A. Ellker, M.D., Ph.D.,
Sepsis following elective surgery

Incidence of septic shock 1997-2010

ICU: Incidence of infection & sepsis

International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

- sepsis occurs in ~50% of all critically ill pts
- most frequent infection:
  - (1)pneumonia (2)abdominal
- AKI + Sepsis: mortality exceeds 50%

ICU: Site of infection
ICU: Incidence of gram-negative bugs

<table>
<thead>
<tr>
<th>Gram-negative</th>
<th>3077 (62.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>792 (16.0)</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>345 (7.0)</td>
</tr>
<tr>
<td><em>Klebsiella species</em></td>
<td>627 (12.7)</td>
</tr>
<tr>
<td><em>Pseudomonas species</em></td>
<td>984 (19.9)</td>
</tr>
<tr>
<td><em>Acinetobacter species</em></td>
<td>435 (8.8)</td>
</tr>
<tr>
<td>Other</td>
<td>840 (17.0)</td>
</tr>
</tbody>
</table>

AKI-EPI study 2015

Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study

- 97 ICUs world wide
- point prevalence study for 1 week
- incidence and outcome AKI

AKI: Increasing incidence

Denmark 2015

Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes
AKI-EPI study 2015

This is the first multinational cross-sectional study where the epidemiology of AKI in ICU patients was explored using the complete KDIGO criteria. We found that AKI occurred in more than half of ICU patients. Approximately one-fifth of ICU patients had a maximum AKI stage 1, one-tenth AKI stage 2, and one-third 3 AKI stage 3. RRT was used in 13.5% of ICU patients.

Etiology of AKI [%]

<table>
<thead>
<tr>
<th>Etiology of AKI</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>41%</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>34%</td>
</tr>
<tr>
<td>Drug related</td>
<td>14%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>13%</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>3%</td>
</tr>
</tbody>
</table>

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**Sepsis & AKI**

**Pathophysiology**

*The New England Journal of Medicine*

**REVIEW ARTICLE**

**CRITICAL CARE MEDICINE**

Sjoerd R. Fidler, M.D., and Jean Louis Vincent, M.D., Ph.D. Editors

*Severe Sepsis and Septic Shock*

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

In addition: AKI causes inflammation

AKI: Loss of renal cytokine clearance
Plasma cytokine levels increase with AKI severity

Full circles = AKIN 3

Effects independent from vasoconstrictor dependency

Pathogenic pathways involved in sepsis

Zarjou et al. (2011) JASN 22:99

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**Defining a “normal” dose for CRRT**

![Diagram showing dose dependent areas for CRRT]

25 ml/kg/h = 2 l/h in 80 kg

**“High-dose” RRT**

<table>
<thead>
<tr>
<th>CRRT</th>
<th>Dose [ml/kg/h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>25</td>
</tr>
<tr>
<td>Intensivied</td>
<td>25 - 45</td>
</tr>
<tr>
<td>High-volume</td>
<td>&gt; 45 - 50</td>
</tr>
<tr>
<td>Intermittent</td>
<td>HD(F)</td>
</tr>
<tr>
<td>Online HDF</td>
<td>i.e. 200 ml/kg/h</td>
</tr>
</tbody>
</table>
Own data: „Intractable“ septic shock
Salvage therapy with high-volume-dialysis (SLEDD QD 300 ml/min), n = 20
No difference in Mortality (64 %)

High volume CRRT in sepsis

Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: a single-center randomized clinical trial

Feng Zhang1, Yi Yang1, Rong Li1, Yantao Zhang2, Weiqing Xie3 and Shuhua Chen3

1. Nephrology Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, People’s Republic of China and Renal Intensive Care Unit, The First Affiliated Hospital, College of Medicine, Zhejiang University-Hangzhou, Hangzhou, People’s Republic of China

Higher dialysis dose in sepsis?

- n = 280 with severe sepsis or septic shock
- septic shock (50 %) – mechanic. ventilated 82 %
- prospective-randomized
- 2004 - 2009
- 50 ml/kg/h versus 85 ml/kg/h
- pre-/postdilution 2:1
- Dose delivered for at least 3 d (Median 8 d)

No effect on mortality
High-volume CRRT in sepsis: IVOIRE Study

- IVOIRE Study (high VOlume in Intensive caRE)
- CVVH: 70 ml/kg/h versus 35 ml/kg/h
- Stopped after 140 Patienten

Meta-Analysis: HVHF in Sepsis

- RCT design
- Patients admitted to ICU
- Adults age ≥18 years
- Diagnosis of sepsis/septic shock
- Report specifically on outcomes of comparator/control group
- Treatment with HVHF defined according to an effluent rate of ≥50 ml/kg/hour, continuously, or intermittent very high-volume treatment with an effluent rate of 100 to 200 ml/kg/hour for a 4- to 8-hour period followed by conventional renal-dose continuous renal-replacement therapy (CRRT).
- Reporting of the primary outcome (mortality) for any time point.
Meta-Analysis: **HVHF in Sepsis**

No effect on mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HVHF</th>
<th>Control</th>
<th>Odds Ratio M.A. Random 95%</th>
<th>Odds Ratio M.A. Random 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shamsuzzaman et al.</td>
<td>6</td>
<td>9</td>
<td>0.69 (0.45, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Sanchis et al.</td>
<td>10</td>
<td>7</td>
<td>0.91 (0.35, 2.45)</td>
<td></td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>91</td>
<td>141</td>
<td>0.89 (0.86, 1.50)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>111</td>
<td>122</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hochvolumige Therapien
  - hochvolumige Kaskadenfiltration
  - 120 ml/kg/h
  - n = 60
Hochvolumige Therapien

- Kaplan-Meier survival estimates
- p-value = 0.2849
- Wall structure
  - prospective – randomised
  - n = 30 in severe sepsis plus AKF
  - Hemofiltration with 31 ml / kgKG / h
  - High-cutoff (60 kDa) vs Standard-Filter

New membranes with large pores/high cut-off

Sieving coefficients of cytokines
Prospective RCT investigating high-cut-off membranes in humans sepsis (60 kDa)

High Cut-Off Continuous Veno-venous Hemodialysis (CVVHD) in Patients Treated for Acute Renal Failure After Systemic Inflammatory Response Syndrome (SIRS)/Septic Shock (HICSS)

Primary objective:
Reduction of catecholamine requirements by High Cut off-CVVHD on day 5
(35 ml/kg/h plus filter change every 24 h)

Secondary objectives:
disease severity scores (SOFA) and clinical improvements

Vorzeitiger Studienabbruch

High Cut-Off Continuous Veno-venous Hemodialysis (CVVHD) in Patients Treated for Acute Renal Failure After Inflammatory Response Syndrome (SIRS)/Septic Shock (HICSS)

- Studienziel:  n = 120
- Abbruch nach  n = 81
- Endpunkte nicht erreichbar
Cytokine-Adsorption in der Sepsis

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- Konventionelle Techniken
- Unspezifische adsorptive Verfahren

Unspezifische Zytokine - Adsorption

- CE certified
- Polymer beads
- biocompatible
- adsorbs molecules up to 55 kDa

Größenselektivität der Adsorption

- CE certified
- Polymer beads
- biocompatible
- adsorbs molecules up to 55 kDa
Beads adsorb Cytokines

Adsorption of Cytokins in vitro

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Molecular weight</th>
<th>% removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>8 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>17 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-1α</td>
<td>17 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-10</td>
<td>18 kDa</td>
<td>85%</td>
</tr>
<tr>
<td>IL-6</td>
<td>26 kDa</td>
<td>87%</td>
</tr>
<tr>
<td>HMGB1</td>
<td>30 kDa</td>
<td>80%</td>
</tr>
<tr>
<td>TNF-α trimer</td>
<td>51 kDa</td>
<td>55%</td>
</tr>
</tbody>
</table>

Cytokine adsorption in rats

Less hemodynamic alteration
**Lower mortality**

![Graph showing lower mortality over time](image)

**Erste Anwendungen am Menschen**

Feasibility study of cytokine removal by hemoadsorption in brain-dead humans

John A. Kellum, MD, FCCM; Ranesh Venkataraman, MD; David Power, MD, FCCM; Michele Elder, RN; Giorgioe Hergenroeder, RN; Multino Carter, BS

**Background:** Inflammatory cytokines occur in the circulation and in the tissues after brain death and have been associated with dysfunction of donor organs before and after transplantation.

**Objective:** To determine the feasibility of removing cytokines using a hemoadsorption device.

**Design:** Two-center, randomized, open-label, feasibility study in which brain-dead subjects were randomized to two treatment groups.

**Setting:** Two U.S. academic hospitals.

**Participants:** Eight brain-dead subjects deemed unsuitable for organ donation by respective organ procurement organizations.

**Main Outcome Measures:** After obtaining consent from families, subjects were treated with hemoadsorption for 4 hrs using Cytosil (Effekto on cytokines, tumor necrosis factor, interleukin

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**Erste Anwendungen am Menschen**

Cytokinspiegel vor und nach dem Adsorber

<table>
<thead>
<tr>
<th></th>
<th>TNF</th>
<th>IL-6</th>
<th>IL-10</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre</strong></td>
<td>11.4</td>
<td>374.4</td>
<td>22.6</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td>11.0</td>
<td>314.4</td>
<td>19.0</td>
<td>4.2</td>
</tr>
<tr>
<td>% change</td>
<td>−3.0</td>
<td>−19.2</td>
<td>−15.6</td>
<td>−4.9</td>
</tr>
</tbody>
</table>

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**CE-Zulassungs-Studie**

- Nachweis von Patientensicherheit und Effektivität (IL6-Senkung) als primäre Endpunkte
- Klinische Parameter als sekundäre Endpunkte
- Patienten mit schwerer Sepsis/septischem Schock mit ALI/ARDS
- Pilotstudie (n=22) und kontrollierte randomisierte Studie (manuelle R n=31; elektron. R n=47)
First clinical study in Europe

- 43 ventilated pts with ALI & septic shock
- randomized open-label
- hemoperfusion 6 h / day for 7 days
- 18 treatments – 25 controls
- safety
- reduction of cytokines

Significant reduction of cytokin - levels

Patienten (elektron. Randomisierung)

<table>
<thead>
<tr>
<th>Characteristics of Electronic Randomization Cohort</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number completing study (43 total)</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Withdrawn or died before treatment started</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>% Male</td>
<td>76%</td>
<td>72%</td>
</tr>
<tr>
<td>Mean Age</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Median Age</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Primary Diagnosis (1st/2nd Diagnosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Pneumonia (%)</td>
<td>44% (44/96)</td>
<td>61% (51/22)</td>
</tr>
<tr>
<td>Aspiration (%)</td>
<td>12% (12/0)</td>
<td>11% (11/0)</td>
</tr>
<tr>
<td>Transfusion (%)</td>
<td>8% (8/0)</td>
<td>0% (0/11)</td>
</tr>
<tr>
<td>Trauma (%)</td>
<td>8% (8/0)</td>
<td>6% (6/0)</td>
</tr>
<tr>
<td>Pancreatitis (%)</td>
<td>8% (8/0)</td>
<td>6% (6/0)</td>
</tr>
<tr>
<td>Other infection</td>
<td>0%</td>
<td>6% (6/0)</td>
</tr>
<tr>
<td>Comorbid Condition (at Enrollment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic Shock (%)</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>Renal Failure on Dialysis (%)</td>
<td>24%</td>
<td>39%</td>
</tr>
<tr>
<td>Acute Respiratory Distress Syndrome (%)</td>
<td>50%</td>
<td>67%</td>
</tr>
</tbody>
</table>
19

Trend zu reduzierter Sterblichkeit bei extrem hohen Cytokin-Spiegeln ??

Einsatz während EKZ

Systemic Inflammatory Response Syndrome in der Herzchirurgie: Neue Therapie-möglichkeiten durch den Einsatz eines Cytokin-Adsorbers während EKZ?

2 x 20 Patienten mit/ohne CS-Adsorber

Einsatz während EKZ

IL 6-Verlauf

IL 6 A ng/l - IL 6 C ng/l
Einsatz während EKZ

Case Reports

- male, 71 y
- collapse: dens-fracture
- osteosynthesis
- normal ward
- aspiration
- septic shock caused by pneumonia

Staphylokokkus aureus (MSSA)
Case Report
Staphylokokkus aureus (MSSA)

• Therapy according to sepsis-guidelines
  – Correct antibiotics treatment
  – Mechanical ventilation in line with ARDS-Network
  – NO-Inhalation / hydrocortison
  – Pulmonary artery catheter
  – KDIGO-III AKI with anuria - CVVHD

• Refractory septic shock
  – ARDS (FiO2 0,8 – PEEP 15= PaO2/FiO2: 178
    • Noradrenaline 91 µg/min
    • Vasopressin 2 I.E. / h

24 hours later:
– Noradrenalin 0
– Vasopressin 0
– FiO2 = 0,35 with PEEP = 10
– Return of diuresis

Blood cultures: Staph. aureus
22 hours later:
- Noradrenalin 0
- Vasopressin 0
- FiO2 = 0.35 with PEEP = 10
- Return of diuresis

Blood cultures: Staph. aureus

CAUTION

Just a case
Optimal timing ?
High toxin load ?
...... ?

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