Symposium 63: The Immunosuppressed ICU Patients

Modulation of Immunoinflammatory Response with Continuous Hemodiafiltration Using A Cytokine-Adsorbing Hemofilter

Hiroyuki Hirasawa, MD, PhD
Professor Emeritus
Department of Emergency and Critical Care Medicine
Chiba University Graduate School of Medicine, Japan
August 31 (Monday), 2015
Infection

Sterile (host) products
- HMGB1
- Uric acid
- mDNA

Alarmins

Infectious products
- LPS
- CpG DNA
- Double-stranded DNA
- Lipids

Pattern Recognition Receptors
- Innate immunity products
  - TLRs
  - NODs
  - NLRs
  - RIGs

PAMPS

Cytokines
- TNF
- Interleukin 1
- Interleukin 6
- HMGB1

Hypercytokinemia

Sepsis

(Lancet 2013;381:774-5)
COMPARISON OF IL-6 BLOOD LEVELS AMONG SIRS, SEPSIS, SEVERE SEPSIS AND SEPTIC MOF

 IL-6

pg/mL

mean±SD ANOVA

p<0.0001

Non-infectious SIRS (n=8)

sepsis (n=7)

severe sepsis (n=11)

septic shock (n=14)

Correlation between IL-6 Blood Level and Blood Lactate Level in Septic Patients

Log Y = 2.4 + 0.02X
r = 0.57, p < 0.01

mean ± SD, unpaired t-test

sepsis (n=37)
severe sepsis (n=39)
septic shock (n=39)
SEPSIS-RELATED PATHOPHYSIOLOGY AND HYPERCYTOKINEMIA

- Dysoxia
- Hyperglycemia
- Immunoparalysis
- DIC NETTING
- Hyperpyrexia

Endothelial Hyperpermeability

Proinflammatory hypercytokinemia
Anti-inflammatory hypercytokinemia
Pro- and Anti-Inflammatory Response in Sepsis

New Concept of the Correlation between Pro- and Anti-Inflammatory Response

Comparison of MOF Incidence and Mortality between HLA-DR<30% Group and HLA-DR≥30% Group

- **MOF Incidence**
  - HLA-DR<30% group (n=7), p<0.05
  - HLA-DR≥30% group (n=23)

- **Mortality**
  - HLA-DR<30% group (n=7), p<0.02
  - Chi-square test
  - HLA-DR≥30% group (n=23)
Immunoinflammatory Response and Immunosuppression in Sepsis

Pathophysiology of Immunosuppression in Sepsis and Possible Countermeasures against Immunosuppression

Hotchkiss RS
Opal S

Figure 1. Reversal of Immunosuppression in Sepsis.
CORRELATION BETWEEN MONOCYTIC HLA-DR EXPRESSION RATE AND IL-10 BLOOD LEVEL

※ minimum value of monocytic HLA-DR expression during ICU stay

y = 73.2 - 24.9x
r = -0.52, p < 0.01

y = 77.6 - 28.0x
r = -0.66, p < 0.0005

y = 65.6 - 17.7x
r = -0.45, p < 0.05

IL-10 blood level on 2 days before HLA-DR measurement

IL-10 blood level on one day before HLA-DR measurement

IL-10 blood level
Countermeasures Against Overwhelming Immunoinflammatory Response

1) Prevention of Excess Release of Cytokines
   2) Immunotherapy
   3) Pharmacotherapy
   4) Biological Therapy
   5) Blood Purification
   6) Gene Therapy
   7) Immunomodulation
   8) Autonomic Nerve Modulation
   9) Others
ALARMIN PATHWAY AND THERAPEUTIC APPROACH

(Chan JK et al, J Clin Invest 2012;122:2711-9)
Our (negative) results with the highly active LPS inhibitor eritoran in critically ill septic patients call into question the role of an endotoxin-blocking agent in halting the inflammatory progression and organ dysfunction once sepsis is already underway.

EUPHAS STUDY (PMX-DHP on Abdominal Sepsis)

1) Too low survival in control group
2) Questionable statistical analysis

(Log-rank p=0.03)

Survival

Polymyxin B hemoperfusion therapy

Conventional therapy

CHDF Chiba Series: 82%
SSCG Phase III: 70%
E5564 Study Control: 67%

(Cruz DN, et al: JAMA 2009;301:2445-52)
In this retrospective study, postoperative polymyxin B hemoperfusion did not show any survival benefit for the overall study population or any of the studied subgroups of patients with abdominal septic shock. A large multicentered prospective randomized trial is warranted to identify the true role of polymyxin B hemoperfusion in sepsis caused by Gram-negative bacteria.
Conclusion: This multicenter randomized controlled study demonstrated a non–significant increase in mortality and no improvement in organ failure with PMX HP treatment compared to conventional treatment of peritonitis induced septic shock.
Acute Blood Purification Modalities for Removal of Cytokines and Other Humoral Mediators from Blood Stream

1) High Filtration Volume Continuous Hemofiltration (CHF) or Continuous Hemodiafiltration (CHDF)

2) Continuous Hemodiafiltration (CHDF) with a Cytokine-Adsorbing Hemofilter

3) Direct Hemoperfusion (DHP) with Endotoxin Adsorbing Polymyxin B Immobilized Column (PMX)

4) Plasma Exchange

5) Coupled Plasma Filtration Adsorption
ALARMIN PATHWAY AND THERAPEUTIC APPROACH

Removal of pro-inflammatory cytokines with renal replacement therapy: Sense or nonsense?

Management of renal replacement therapy in ICU patients: an international survey

Continuous, Non-selective, Effective Removal of Cytokine from Blood Stream with Continuous Hemodiafiltration using a Cytokine-Adsorbing Hemofilter (AN69ST:sepXiris)
A Recent Study on Efficacy of CHDF with a Cytokine-Adsorbing Hemofilter on Septic Patients

Multicenter study with AN69ST in severe sepsis/septic shock

**Study design:**
Prospective multicenter single-arm study setting, 6 Japanese intensive care units.

**Inclusion criteria:**
1. Sepsis (Infection-induced SIRS)
2. Blood lactate concentration ≥36mg/dL (4.0 mmol/L)
3. CHDF is applied even when a septic patient has normal renal function

**Endpoint:**
28 day mortality
Blood lactate concentration (72 hrs follow-up period)
Blood IL-6 concentration (72 hrs follow-up period)
# Patients Background

**Basic characteristics of severe sepsis/septic shock patients**

<table>
<thead>
<tr>
<th></th>
<th>N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>67.1 (12.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (55.9%)</td>
</tr>
<tr>
<td>APACHE II, mean (SD)</td>
<td>32.4 (10.4)</td>
</tr>
<tr>
<td>Lactate (mg/dL), mean (SD)</td>
<td>69.9 (42.1)</td>
</tr>
<tr>
<td>IL-6 (pg/mL), mean (SD)</td>
<td>44,797 (77,705)</td>
</tr>
<tr>
<td>IL-8 (pg/mL), mean (SD)</td>
<td>6,605 (12,389)</td>
</tr>
<tr>
<td>IL-10 (pg/mL), mean (SD)</td>
<td>664 (1,295)</td>
</tr>
</tbody>
</table>

**Source of infections**

<table>
<thead>
<tr>
<th>Source of infections</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal</td>
<td>15</td>
<td>(44.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>(29.4)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>6</td>
<td>(17.6)</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>(8.8)</td>
</tr>
</tbody>
</table>
Changes in Cytokine Blood Levels with CHDF with a Cytokine-Adsorbing Hemofilter (AN69ST) CHDF(#1)

**TNF-α**
- High (n=13)
- Low (n=15)
- Measurement sensitivity: 0.6 pg/mL
- P<0.01

**IL-1β**
- High (n=11)
- Low (n=17)
- Measurement sensitivity: 10 pg/mL
- N.S.

**IL-6**
- High (n=26)
- Low (n=2)
- Measurement sensitivity: 4.0 pg/mL
- P<0.01
Changes in Cytokine Blood Levels with CHDF with a Cytokine-Adsorbing Hemofilter (AN69ST) CHDF (#2)

**IL-8**
- High (n=21)
- Low (n=7)
- Measurement sensitivity: 2.0 pg/mL
- P<0.01
- P<0.05

**IL-10**
- High (n=20)
- Low (n=8)
- Measurement sensitivity: 2.0 pg/mL
- P<0.01
- N.S.

**HMGB1**
- High (n=17)
- Low (n=11)
- Measurement sensitivity: 2.5 ng/mL
- P<0.05
- N.S.
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>31.6 ± 14.2 mL/min</td>
<td>15</td>
</tr>
<tr>
<td>IL-1β</td>
<td>18.0 ± 32.7 mL/min</td>
<td>19</td>
</tr>
<tr>
<td>IL-6</td>
<td>11.0 ± 11.3 mL/min</td>
<td>32</td>
</tr>
<tr>
<td>IL-8</td>
<td>57.1 ± 46.0 mL/min</td>
<td>23</td>
</tr>
<tr>
<td>IL-10</td>
<td>19.6 ± 18.5 mL/min</td>
<td>32</td>
</tr>
<tr>
<td>HMGB1</td>
<td>6.44 ± 63.6 mL/min</td>
<td>18</td>
</tr>
</tbody>
</table>
Changes in Blood Lactate and IL-6 Levels in Septic Shock Patients Treated with Cytokine-Adsorbing Hemofilter (AN69ST) CHDF

![Graph of Blood Lactate Levels](image)

- **Blood Lactate**
  - AN69ST-CHDF
  - **n=28**
  - mean ± SD

![Graph of Blood IL-6 Levels](image)

- **Blood IL-6**
  - AN69ST-CHDF
  - **n=28**
  - mean ± SD
CHANGES IN IL-10 BLOOD LEVEL AND MONOCYTIC HLA-DR EXPRESSION RATIO WITH CAH-CHDF

Paired t-test (mean ± SD)

- all cases (n=18)
- cases with HLA-DR<30% (n=4)

**IL-10**

- before
- 4 days
- 7 days

- p<0.05
- p<0.005

**HLA-DR**

- before
- 4 days
- 7 days

- p<0.05
PREDICTED SURVIVAL AND OBSERVED 28 DAY SURVIVAL OF SEPTIC SHOCK PATIENTS TREATED WITH AN69ST–CHDF

# COMPARISON OF THE SURVIVAL OF THE PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK TREATED ACCORDING TO SSCG

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year of Publication</th>
<th>Number of Cases</th>
<th>Age (years)</th>
<th>APACHE II score (predicted survival)</th>
<th>28 day survival</th>
<th>Ratio to Predicted Survival</th>
<th>CAH-CHDF PMMA-CHDF AN69ST-CHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro</td>
<td>US</td>
<td>2006</td>
<td>116</td>
<td>68.0±16.0</td>
<td>22.6±8.8 (57.6%)</td>
<td>79.7%</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>Shorr</td>
<td>US</td>
<td>2007</td>
<td>60</td>
<td>61.4±20.0</td>
<td>23.3±9.6 (54.0%)</td>
<td>70.0%</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>Ferrer</td>
<td>Spain</td>
<td>2008</td>
<td>1,465</td>
<td>62.1±16.3</td>
<td>21.3±7.8 (61.1%)</td>
<td>68.9%</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>Ortega</td>
<td>Spain</td>
<td>2010</td>
<td>384</td>
<td>64.5±15.1</td>
<td>23.2±7.8 (54.0%)</td>
<td>62.5%</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>Levy</td>
<td>(SSCG database)</td>
<td>2010</td>
<td>15,022</td>
<td>64.5±15.1</td>
<td>23.2±7.8 (54.0%)</td>
<td>65.2%</td>
<td>1.82</td>
<td></td>
</tr>
<tr>
<td>Opal</td>
<td>International (ACCESS)</td>
<td>2013</td>
<td>1304</td>
<td>-</td>
<td>27.2±4.5 (39.5%)</td>
<td>71.9%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nakada</td>
<td>Japan</td>
<td>2008</td>
<td>43</td>
<td>63.5±13.3</td>
<td>29.4±8.4 (32.8%)</td>
<td>79.1%</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td>Shiga</td>
<td>Japan</td>
<td>2012</td>
<td>34</td>
<td>67.1±12.1</td>
<td>32.7±9.8 (20.3%)</td>
<td>73.5%</td>
<td>3.62</td>
<td></td>
</tr>
</tbody>
</table>

Survival after implementation of SSCG

- **CAH-CHDF**: mean ± SD
- **PMMA-CHDF**: mean ± SD
- **AN69ST-CHDF**: mean ± SD
Continuous Hemodiafiltration with a Cytokine-Adsorbing Hemofilter in Patients with Septic Shock: A Preliminary Report

Hidetoshi Shiga\textsuperscript{a}  Hiroyuki Hirasawa\textsuperscript{b}  Osamu Nishida\textsuperscript{c}  Shigeto Oda\textsuperscript{b}  Masataka Nakamura\textsuperscript{b}  Kunihiro Mashiko\textsuperscript{d}  Kenich Matsuda\textsuperscript{e}  Nobuya Kitamura\textsuperscript{f}  Yoshihiko Kikuchi\textsuperscript{a}  Nobuo Fuke\textsuperscript{a}
Thus, continuous removal of pro- and anti-inflammatory cytokines with a cytokine-adsorbing hemofilter is very effective as countermeasure against overwhelming immunoinflammatory responses in clinical settings and results in better survival.