Blood Purification for Sepsis - Which Molecules Should We Remove Endotoxin or Cytokines?

Hiroyuki Hirasawa, MD, PhD

Professor Emeritus, Department of Emergency and Critical Care Medicine
Chiba University Graduate School of Medicine, Chiba, Japan

Professor, Graduate School of Medicine
International University of Health and Welfare, Chiba, Japan

(March 8, Thursday, 2018)
Keywords in a New Pathophysiology of Sepsis

**PRRs (pattern-recognition receptors):**
A primitive part of the immune system. They are proteins expressed by cells of the innate immune system to identify pathogen-associated molecular patterns (PAMPs), and/or damage-associated molecular patterns (DAMPs) or alarmins.

**PAMPS (pathogen-associated molecular patterns):**
Molecules associated with groups of pathogens, that are recognized by cells of the innate immune system.

**DAMPs (damage-associated molecular patterns), Alarmins:**
An array of structurally diverse multifunctional host proteins that are rapidly released during infection or tissue damage, and that have mobilizing and activating effects on receptor-expressing cells engaged in host defense and tissue repair.
Immuno-inflammatory Response Triggered by PAMPs and DAMPs / Alarmins through Toll-like Receptors

Exogenous Ligands (PAMPs)
- Triacyl lipopeptide
- Diacyl lipopeptide
- dsRNA
- LPS
- Imidazoquinolines
- ssRNA
- CpG DNA
- Hemopozin
- Flagellin
- Profilin-like protein
- Uropathogenic Bacteria (E.coli)

Endogenous Ligands (DAMPs Alarmin)
- Peptidoglycan Lipoprotein
- Necrotic cells
- HSPs
- Biglycan
- Fibrinogen
- HSPs
- NE
- Biglycan
- HMGB1
- β-Defensin2
- Heparan sulfate
- Hyaluronic acid
- Chromatin
- Ig-G complex

Endogenous Ligands (Alarmin)
- Self mRNA

Adapters
- TIRAP
- MyD88
- Trif
- TRAM
- TIRAP
- MyD88
- MyD88
- MyD88
- MyD88

Inflammatory cytokines

(Adapted from Kawai T, Akira S: Cell Death Differ 2006;13:816-25)
## A List of PAMPS and DAMPs / Alarmins

<table>
<thead>
<tr>
<th><strong>PAMPS (Exogenous)</strong></th>
<th><strong>DAMPs / Alarmins (Endogenous)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Triacyl lipopeptide</td>
<td>Necrotic tissue</td>
</tr>
<tr>
<td>Peptidoglycan</td>
<td>HSPs (HSP-60, HSP-70, Gp-96)</td>
</tr>
<tr>
<td>Lipoprotein</td>
<td>Biglycan</td>
</tr>
<tr>
<td>Double-stranded RNA</td>
<td>Self-messenger RNA</td>
</tr>
<tr>
<td><strong>endotoxin</strong></td>
<td>Extra domain A-containing fibronectin</td>
</tr>
<tr>
<td>Flagellin</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Diacyl lipopeptide</td>
<td>Polysaccharide fragments of heparin sulfate</td>
</tr>
<tr>
<td>Single-stranded RNA</td>
<td>Oligosaccharides of hyaluronic acid</td>
</tr>
<tr>
<td>Unmethylated CpG DNA</td>
<td>Oxidized low-density lipoprotein</td>
</tr>
<tr>
<td>Uropathogenic <em>Echerichia coli</em></td>
<td>Surfactant protein A in the lung epithelium 1</td>
</tr>
<tr>
<td>Lipoteicoic acid</td>
<td>Neutrophil elastase</td>
</tr>
<tr>
<td></td>
<td>Chromatin-IgG complex</td>
</tr>
<tr>
<td></td>
<td>β-Defensin 2</td>
</tr>
<tr>
<td></td>
<td>HMGB1</td>
</tr>
<tr>
<td></td>
<td>S100s</td>
</tr>
<tr>
<td></td>
<td>HDGF</td>
</tr>
<tr>
<td></td>
<td>IL-1a</td>
</tr>
<tr>
<td></td>
<td>Uric acid</td>
</tr>
<tr>
<td></td>
<td>Cathelicidins</td>
</tr>
<tr>
<td></td>
<td>Defensins</td>
</tr>
<tr>
<td></td>
<td>EDN</td>
</tr>
<tr>
<td></td>
<td>Galectins</td>
</tr>
<tr>
<td></td>
<td>Thymosins</td>
</tr>
<tr>
<td></td>
<td>Nucleolin</td>
</tr>
<tr>
<td></td>
<td>Annexins</td>
</tr>
</tbody>
</table>
Comparison of Severity and Survival between Endotoxin Positive and Negative Septic Patients

(mean ± SD, Unpaired t-test)

<table>
<thead>
<tr>
<th></th>
<th>Endotoxin (+) (32 cases)</th>
<th>Endotoxin (-) (83 cases)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>25.1±9.4</td>
<td>22.8±9.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>SOFA score</td>
<td>10.8±4.7</td>
<td>10.6±4.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Survival</td>
<td>69.1%</td>
<td>59.8%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
Correlation between Blood Endotoxin Level and Severity

Endotoxin (pg/mL) vs. APACHE II score

Endotoxin (pg/mL) vs. SOFA score

N.S.

n=32
Antagonist of MD2-TLR4 to block cytokine release by LPS is not effective on the patients with severe sepsis. This is the another evidence that LPS is not a central player in the pathophysiology of sepsis.
Therapeutic Approach to PAMPs and DAMPs / Alarmins Pathway

- **PAMPs Blockade**
  - Infectious products
    - LPS
    - CpG DNA
    - Double-stranded DNA
    - Lipids
  - Sterile (host) products
    - HMGB1
    - Uric acid
    - mDNA

- **PRRs Blockade**
  - Innate immunity products
    - TLRs
    - NODs
    - NLRs
    - RIGs

- **Cytokine Blockade**
  - Cytokines
    - TNF
    - Interleukin 1
    - Interleukin 6
    - HMGB1

- **Infection**

- **Alarmins**

- **Damps or Alarmins Blockade**
EUPHAS Study (PMX-DHP on Abdominal Sepsis)

![Survival graph](image)

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

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

(Log-rank p=0.03)

(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 multicenterd prospective randomized trial is warranted to identify the true role of polymyxin B hemoperfusion in sepsis caused by Gram-negative bacteria.

Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial

(Payen DM for ABDOMIX group: Intensive Care Med:2015;41:975-984)

This multicenter randomized controlled study demonstrated a non-significant increase in mortality and no improvement in organ failure with direct hemoperfusion with polymyxin-immobilized endotoxin adsorbing column compared to conventional treatment of peritonitis-induced septic shock.
This was a retrospective, multicenter study. We performed propensity-score matching analyses of the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) Study database. Our results strongly suggest that PMX-HP reduced hospital mortality and length of ICU stay in patients with septic shock.
We conclude that PMX-based endotoxin adsorption within 24 hours from ICU admission was not associated with mortality among patients with septic shock due to Gram-negative bacillus.

(28 day survival: PMXHP 29.1% vs Conventional treatment 29.0%, p=0.98)
Conclusion: There is currently insufficient evidence to support the routine use of PMX-HP to treat patients with sepsis or septic shock.
Endotoxin is only one of PAMPs, not a key player in the pathophphysiology of septic shock. There are many septic shock patients without endotoxemia. Therefore, the efficacy of the modality solely aiming at the removal of endotoxin in septic shock treatment is questionable.
Overall, the EAA kit could not measure clinically relevant dose of endotoxin. Because IL-8 induced an increase in EAA level, it is suggested that the EAA level reflects the primed site of polymorphonuclear leukocytes.

(J Infect Chemother 2013;19:825-32)
Sepsis-Related Pathophysiology and Hypercytokininemia

- Dysoxia
- Immunoparalysis
- Hyperglycemia
- Hyperpyrexia
- Endothelial Hyperpermeability
- Mediator Network Activation
- D I C NETTING

- Hypercytokininemia
  - Proinflammatory hypercytokininemia
  - Anti-inflammatory hypercytokininemia
Cytokine Theory of Disease

- Shock
- Organ failure
- Tissue damage
- Arthritis
- Psoriasis
- Depression
- Fever
- Anorexia
- Pain
- Edema
- Ileus
- Colitis
- Leukocyte recruitment
- Antibacterial activity
- DC maturation

Physiological manifestation

(Tracey KJ. J Clin Invest 2007; 117: 289-96)
Correlation between IL-6 and Lactate Blood Level in Septic Patients

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

sepsis
(n=37)

severe sepsis
(n=39)

septic shock
(n=39)

mean ± SD, unpaired t-test
Correlation between Monocytic HLA-DR Expression Rate and IL-10 Blood Level

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

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

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

\[ y = 65.6 - 17.7x \]
\[ r = -0.45, \ p < 0.05 \]
Pathophysiology of Sepsis and Septic Shock

Infection

- PAMPs
- PRRs (TLRs, NLRs, RLRs, CLR)

Pro-Inflammatory Cytokines

- Hypercytokinemia

Anti-Inflammatory Cytokines

Dysregulation of

- Host Immune Mechanism
- Inflammatory Response
- NETTING
- Coagulation System

- Disruption of Tight Junction and Glycocalyx
- Endothelial Hyperpermeability
- Capillary Leak Syndrome
- Interstitial Edema
- Dysoxia
- Cell Dysfunction / Death (necrosis, apoptosis, necroptosis, stunning, autophagy)
- Organ Failure

Circulatory Failure

(Hirasawa H: Blood Purif 2012;34:164-70)
Continuous Hemodiafiltration with AN69ST (a Cytokine-Adsorbing Hemofilter) for the Patients with Septic Shock
Patients and Methods

Study design:
Prospective multicenter single-arm study involving intensive care units of 6 university hospitals in Japan

Inclusion criteria:
1. Sepsis (infection-induced SIRS)
2. Blood lactate concentration ≥36 mg/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>Characteristic</th>
<th>Mean (SD)</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>32.7 (9.8)</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</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 Blood Lactate and IL-6 Levels in Septic Shock Patients Treated with AN69ST-CHDF

Blood Lactate

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>AN69ST-CHDF (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>72</td>
<td>60</td>
</tr>
</tbody>
</table>

n=28, mean±SD

Blood IL-6

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>AN69ST-CHDF (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10^6</td>
</tr>
<tr>
<td>24</td>
<td>10^5</td>
</tr>
<tr>
<td>48</td>
<td>10^4</td>
</tr>
<tr>
<td>72</td>
<td>10^3</td>
</tr>
</tbody>
</table>

n=28, mean±SD
Changes in Blood Levels of Cytokines with AN69ST-CHDF(#1)

(measurement sensitivity: 0.6 pg/mL) (measurement sensitivity: 10 pg/mL) (measurement sensitivity: 4.0 pg/mL)
Changes in Blood Levels of Cytokines with AN69ST-CHDF (#2)

(mean ± SD)

**IL-8**
- High (n=21)
- Low (n=7)
- P<0.01

**IL-10**
- High (n=20)
- Low (n=8)
- P<0.01

**HMGB1**
- High (n=17)
- Low (n=11)
- P<0.05

(measurement sensitivity: 2.0 pg/mL) (measurement sensitivity: 2.0 pg/mL) (measurement sensitivity: 2.5 ng/mL)
# Cytokine Clearance with AN69ST-CHDF

(Values at 3 hours after the initiation of CHDF)

<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>
Predicted Survival and Observed 28 DAY Survival of Septic Shock Patients Treated with AN69ST–CHDF:

- Predicted survival (predicted with APACHE II score):
  - All patients (n = 34): 20.3%
  - APACHE II ≤ 25 (n = 9): 58.4%
  - 26 ≤ APACHE II ≤ 30 (n = 6): 36.2%
  - 31 ≤ APACHE II ≤ 35 (n = 6): 20.0%
  - 36 ≤ APACHE II (n = 13): 5.3%

- Observed 28-day survival (AN69ST-CHDF trial):
  - All patients (n = 34): 73.5%
  - APACHE II ≤ 25 (n = 9): 100.0%
  - 26 ≤ APACHE II ≤ 30 (n = 6): 66.7%
  - 31 ≤ APACHE II ≤ 35 (n = 6): 100.0%
  - 36 ≤ APACHE II (n = 13): 53.8%

APACHE II score: 32.7 ± 9.8 (mean ± S.D.)

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}
## Comparison of Survival of 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 (predicted survival)</th>
<th>Survival</th>
<th>Ratio to Predicted Survival</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>
</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>
</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>
</tr>
<tr>
<td>Castellanos 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>
</tr>
<tr>
<td>Levy</td>
<td>(SSC database)</td>
<td>2010</td>
<td>15,022</td>
<td>unavailable</td>
<td>unavailable</td>
<td>65.2%</td>
<td>—</td>
</tr>
<tr>
<td>Chiba PMMA-CHDF</td>
<td>Japan</td>
<td>2009</td>
<td>114</td>
<td>63.5±15.2</td>
<td>27.0±7.7 (39.5%)</td>
<td>82.4%</td>
<td>2.09</td>
</tr>
<tr>
<td>Japan AN69ST-CHDF</td>
<td>Japan</td>
<td>2014</td>
<td>34</td>
<td>67.1±12.1</td>
<td>32.5±10.2 (22.7%)</td>
<td>73.5%</td>
<td>3.24</td>
</tr>
</tbody>
</table>
We retrospectively investigated whether AN69ST membrane hemofilter would have salutary effect on survival compared to other membranes using a Japanese Health Insurance data base.

Of 2,469 patients, 156 were treated by AN69ST membrane. Adjusted odds ratio of AN69ST membrane use for in-hospital mortality was 0.65 (95% IC 0.45 ~ 0.93). The use of AN69ST membrane was also independently associated with shorter ICU-LOS.

Thus, this retrospective observational study suggested that CRRT with AN69ST membrane might be associated with better in-hospital outcomes.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>APACHE II</th>
<th>Predicted survival</th>
<th>Observed 28d survival</th>
<th>Observed/predicted survival ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honore et al</td>
<td>2000</td>
<td>20</td>
<td>31.5 ± 4.2</td>
<td>26.7%</td>
<td>55.0%</td>
<td>2.06</td>
</tr>
<tr>
<td>Piccinni P et al</td>
<td>2006</td>
<td>40</td>
<td>27.2 ± 2.8</td>
<td>39.5%</td>
<td>55.0%</td>
<td>1.39</td>
</tr>
<tr>
<td>Cornejo R et al</td>
<td>2006</td>
<td>20</td>
<td>26.1 ± 3.1</td>
<td>43.1%</td>
<td>60.0%</td>
<td>1.39</td>
</tr>
<tr>
<td>Boussekey N et al</td>
<td>2008</td>
<td>9</td>
<td>30.3 ± 4.1</td>
<td>29.7%</td>
<td>66.7%</td>
<td>2.25</td>
</tr>
<tr>
<td>PMX-DHP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincent JL et al</td>
<td>2005</td>
<td>17</td>
<td>16.7 ± 5.9</td>
<td>73.8%</td>
<td>70.6%</td>
<td>0.97</td>
</tr>
<tr>
<td>Kojika M et al</td>
<td>2006</td>
<td>24</td>
<td>16.8 ± 4.1</td>
<td>73.8%</td>
<td>87.5%</td>
<td>1.19</td>
</tr>
<tr>
<td>Nakamura T et al</td>
<td>2009</td>
<td>40</td>
<td>21.5 ± 4.5</td>
<td>57.6%</td>
<td>70.0%</td>
<td>1.22</td>
</tr>
<tr>
<td>Cruz DN et al</td>
<td>2009</td>
<td>34</td>
<td>21 (19-23)</td>
<td>61.1%</td>
<td>67.7%</td>
<td>1.11</td>
</tr>
<tr>
<td>CAH-CHDF (Chiba Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMMA-CHDF</td>
<td>2008</td>
<td>43</td>
<td>29.4 ± 8.4</td>
<td>32.8%</td>
<td>79.1%</td>
<td>2.41</td>
</tr>
<tr>
<td>AN69ST-CHDF</td>
<td>2014</td>
<td>34</td>
<td>32.7 ± 9.8</td>
<td>20.3%</td>
<td>73.5%</td>
<td>3.62</td>
</tr>
</tbody>
</table>

HVHF: high volume hemofiltration, PMX-DHP: direct hemoperfusion with an endotoxin-adsorbing column, CAH-CHDF: continuous hemodiafiltration using cytokine-adsorbing membrane hemofilter, PMMA: polymethyl-methacrylate
Conclusion

Thus, causative substances of sepsis which should be removed with blood purification modality seem not to be endotoxin but rather to be pro- and anti-inflammatory cytokines.

We have reported that continuous hemodiafiltration with cytokine-adsorbing hemofilters such as PMMA And AN69ST hemofilter can remove various cytokines from blood stream of patients and that CAH-CHDF is very effective in the treatment of sepsis.

In Japan, now CAH-CHDF is approved to be applied on septic patients even when those patients have normal kidney function.
Comparison of IL-6 Blood Levels among SIRS, SEPSIS, Severe Sepsis and Septic Shock

Comparison of Survival of Severe Sepsis / Septic Shock Patients Treated with PMMA-CHDF or AN69ST-CHDF

2010.01 ~ 2012.12

survival (%)
Pro- and Anti-Inflammatory Response in Sepsis

Sepsis definitions: time for change

Jean-Louis Vincent, Steven M Opal, John C Marshall, Kevin J Tracey

(Lancet 2013;381:774-5)
Endotoxin and Sepsis

Endotoxin as a therapeutic target in septic shock
(Corriveau CC et al: Infect Agents Dis 1993;2:35-43)

The importance of a lipopolysaccharide-initiated, cytokine-mediated host defense mechanism in mice against extraintestinally invasive Escherichia coli
(Cross A et al: J Clin Invest 1995;96:676-86)

Mucosal and enterocyte IL-6 production during sepsis and endotoxemia-role of transcription factors and regulation by the stress response
Efficacy of PMX-DHP AND CAH-CHDF for Humoral Mediator Network

Hypercytokinemia

Production of Cytokine

Production of Anandamide

Monocyte/Macrophage

G(-) Bacteria

G(+) Bacteria

Trauma

Pancreatitis

Burn

Others

PMX-DHP

CAH-CHDF

Endotoxin

Exotoxin

Endotoxin

PAMPS

ALARMINs

MOF

CAH-CHDF also can remove metabolic waste products and can maintain body water balance

(Hirasawa H: Contrib Nephrol 2010; 166:21-30)
Introduction

There has been much advance in the application of various blood purification modality in emergency and critical care medicine. And blood purifications are reported to be especially effective in the treatment of sepsis. Now blood purification is applied not only as artificial support for failing organs but also as remover of causative substances of sepsis.

Traditionally endotoxin is thought to play a key role in the pathophysiology of sepsis. Accordingly direct hemoperfusion with polymyxin-B immobilized endotoxin adsorbing column (PMX-DHP) has been widely applied on septic patients to remove causative endotoxin. However, recent elucidation on the pathophysiology of sepsis casts a shadow on the efficacy of PMX-DHP in sepsis.
Pathophysiology of Sepsis

**Infection**
- PAMPs
- PRRs (TLRs, NLRs, RLRs, CLR)

**Pro-Inflammatory Cytokines**

**Anti-Inflammatory Cytokine**

**Hypercytokinemia**

**Dysregulation of**
- Host Immune Mechanism
- Inflammatory Response
- NETTING
- Coagulation System

**Disruption of Tight Junction and Glycocalyx**
- Endothelial Hyperpermeability
- Capillary Leak Syndrome
- Interstitial Edema

**Circulatory Failure**
- Dysoxia

**Cell Dysfunction / Death**
- necrosis, apoptosis, necroptosis
- stunning, autophagy

**Organ Failure**

(Hirasawa H: Blood Purif 2012;34:164-70)
Countermeasures against Hypercytokinemia

1) Prevention of Excess Release
   2) Immunotherapy
   3) Pharmacotherapy
   4) Biological Therapy
   5) Blood Purification
   6) Gene Therapy
   7) Immunomodulation
   8) Autonomic Nerve Modulation
   9) Others
Acute Blood Purification Modalities for Removal of Cytokines and Other Humoral Mediators

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

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

3) On-line Hemodiafiltration

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

5) Plasma Exchange

6) Coupled Plasma Filtration Adsorption
Removal of pro-inflammatory cytokines with renal replacement therapy: Sense or nonsense?

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