NEW MEMBRANES At The HORIZON: New Data on Recent Properties, In Vivo Experiments & Potential Efficacy

1. Rationale of New Modified Membranes

2. How to Increase Removal: Porosity or Adsorption?

3. Recent Data on Hyperpermeable Membranes

4. Most Recent Data on Modified AN 69 Membranes

5. Recently Completed Trials...

6. Conclusions-Perspectives

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Head of Clinics ICU, UZ-VUB University, Jette (Bxl, Bel)

16th Annual CRRT Congress
Hilton San Diego Bayfront, California, Feb 2011
Solute Classes by Molecular Weight

- **“small”**
  - Albumin (55,000 - 60,000)
  - Inflammatory Mediators (1,200-50,000)
  - Myoglobin (17,800)
  - Beta 2 Microglobulin (11,800)
  - Inulin (5,200)

- **“middle”**
  - Vitamin B12 (1,355)
  - Aluminium/Desferoxamine Complex (700)
  - Glucose (180)
  - Uric Acid (168)
  - Creatinine (113)
  - Phosphate (80)

- **“large”**
  - Urea (60)
  - Potassium (35)
  - Phosphorus (31)
  - Sodium (23)
Adapted Approaches for Enhanced Mediator Removal

- Increased rate of fluid exchange ("high-volume hemofiltration")
- Membrane modifications
  - Permeability (HCO; septeX)
  - Surface properties (oXiris)
Variation of membrane pore sizes

Electron micrographs of inner membrane surface

∅: pore diameter
∅ < 0.01 µm
∅ < 0.02 µm
∅ ~ 0.09 µm
∅ ~ 0.30 µm

protein separation membrane
plasma separation membrane

high flux
high cut-off*

Should We Target SIRS, Immunoparalysis or Both?

Time: Hyperinflammation - Immunoparalysis

IL-1
IL-6
TNF
IL-10

Anti-LPS
Anti-TNF
Anti-IL-1
Anti-IL-10
Blood Purif.

Immunologic Support

Recovery
Should We Target SIRS, Immunoparalysis or Both?

Cox Model in GenMS Study Kellum et al, Arch Intern Med 2007
Recent HPHF Studies in Sepsis:

IL-6 Clearance

Sieving coefficient:

<table>
<thead>
<tr>
<th></th>
<th>standard</th>
<th>high flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5h</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>4h</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>24h</td>
<td>0.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>


CVVH UF-rate 2.5L/h
Recent HPHF Studies in Sepsis:

**HICOSS (High Cut-Off Sepsis Study)**

Multicenter study with septeX / HCO in septic AKI

PI Dr. Morgera (Berlin), Prof. Joannidis (Innsbruck), Prof. Risler (Tübingen),
Prof. Max (Marburg), Prof. Schindler (Berlin)

**Primary objective:** Reduction of catecholamine requirements by High Cut off-CVVHD

**Secondary objectives:** clinical improvements and Safety (albumin levels), SOFA

**Study design:**

- Prospective, randomized, double-blinded multicenter study
- Two parallel study-arms: High Cut Off (HCO/Septex 1.1m2) compared to high flux (Polyflux 1.1m2)
- 120 pts, powered to show a 50% reduction in catecholamine use
  (at interims analysis: 81 patients enrolled, 7 drop outs)
- Stratification for disease severity (APACHE score 19 to 30) and age
- 5 days treatment period (CVVHD) and follow up of catecholamine use
- 28 days follow-up period

In preparation for publication

Honore PM et al. 10th Congress of WFSICCM.Florence 2009
Recent HPHF Studies in Sepsis:

**HICOSS Study Results – Day 28**

HCO versus standard high flux

- Days on Norephrinine (10.0 ± 9 vs 11.3 ± 9)
- Days on Ventilation (13.9 ± 11 vs 16.1 ± 11)
- Need for RRT (9.1 ± 8 vs 9.5 ± 8)

In preparation for publication

Honore PM et al. 10th Congress of WFSICCM.Florence 2009
HICOSS study results – day 28

HCO vs standard high flux

- Mortality (31 vs 33%)
- Both groups lower than predicted by APACHE score
- Days in ICU (19±12 vs 19±11)

In preparation for publication

Honore PM et al. 10th Congress of WFSICCM. Florence 2009
Recent HPHF Studies in Sepsis:

Safety: Stable plasma albumin levels with septeX/ HCO compared to standard high flux -CVVHD

N= 81 pts CVVHD

Honore PM et al. 10th Congress of WFSICCM.Florence 2009
Recent HPHF Studies in Sepsis: Synergy with HVHF?

CVVH + HPHF = 1l/h = 16.6 ml/kg/h

HVHF + HPHF = 6 l/h = 80 ml/kg/h

Uchino el al, Int Care Med 2002; 28: 651-655
Surface Treatment: Principle

Polyethyleneimine

AN69 membrane

AN69 ST membrane*

About 10 mg/m²

< 100Å
AN69 ST* and Heparin Adsorption

Polyethyleneimine → heparin
Effect of Surface Modification on Membrane Properties of AN69ST

Permeability
mL/(h.m.mmHg)

Adsorption TNF (ng/mL)

Adsorption kinetics of IL-6 in plasma
oXiris: Grafting Mechanism (Heparin)

Unfractionated heparin without chemical modification

Available active sites for AT link

Free amine groups

CH₂─CH─

CH₂

CH₃

C─SO₃Na

CH₂

NH

NH₂

NH

NH

NH

NH

Free amine groups

Available active sites for AT link

Unfractionated heparin without chemical modification
oXiris: Adsorption of Low-Molecular Weight Proteins

AN69 membrane:
- symmetrical / dense microstructure
- homogeneous distribution of sulphonate groups
- high sieving coefficient for low molecular weight proteins (< 40 000Da)

Adsorption mechanism based on ionic binding in bulk 600 nm
2M Adsorption Isotherms

Clark et al, Kidney Int 1994
• Adsorption of low molecular weight proteins to hemodialysis membranes: experimental results and simulations - P. Valette, M. Thomas, P. Déjardin Biomaterials, 20, 1999, 1621
• Influence of the charge of low molecular weight proteins on their efficiency of filtration and/or adsorption on dialysis membranes with different intrinsic properties - N. Moachon, M. Thomas, G. Quash Biomaterials, 23, 2002, 651
oXiris: Action Mode
Endotoxin adsorption

Endotoxin:
- large MW molecule (100 000 to 5M)
- major component of gram – bacteria
- chemical composition: polysaccharide, carbohydrate and lipid A (LPS)

Lipid A (active part of endotoxin)

Ionic bonding with free amine groups of PEI

** S. Morimoto et al, Polymer journal, vol.27, 8, 1995, 831
S. Mitzner et al, Artificial organs, 17 (9), 1993, 775
Cytokine adsorption: adsorption takes place in the membrane bulk mainly on the sulfonic groups (negligible influence of the surface treatment).

Endotoxin adsorption: adsorption only due to the surface treatment (interaction between amine groups of PEI and phosphate groups of lipid A).
oXiris® - no contact phase activation

Contact phase activation is evaluated in-vitro through the measurement of kallikrein generation level (contact phase activation marker) after contact of the membrane with diluted human plasma.

Bradykinine generation is a concern in septic patients as it amplifies the hypotension; thanks to the modified surface charges of the membrane, the contact phase is not activated with this membrane in CRRT³
Heparin grafting improves the device’s haemocompatibility thus allowing use of no heparin for patient at risk of bleeding.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Median set lifespan (interquartiles)</th>
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<tbody>
<tr>
<td>All treatments (n=83)</td>
<td>19.83 [9.92 – 38.42]</td>
</tr>
<tr>
<td>Without anticoagulant in circuit (n=49)</td>
<td>15.37** [7.92 – 38.42]</td>
</tr>
<tr>
<td>With anticoagulant in circuit (n=34)</td>
<td>26.00** [17.32 – 42.42]</td>
</tr>
<tr>
<td>Patients without bleeding risks* (n=32)</td>
<td>19.83 # [15.58 – 37.00]</td>
</tr>
<tr>
<td>Patients with bleeding risks* (n=34)</td>
<td>30.75# [14.75 – 60.50]</td>
</tr>
</tbody>
</table>

Ref 4: In-vivo data

Ability to be used without heparin, showing a median lifespan of the set compatible with an adequate treatment.

*The use of this pre-heparinised membrane could be a simple and safe alternative to circuit heparinisation for high bleeding risk patients and even an alternative to citrate anticoagulation in case this one is contra-indicated. **NS (p=0.61 test log rank), #NS (p=0.19 test log rank)
oXiris: membrane adsorption capacity

Rimmele et al., Nephrol Dial Transplant 2008

Strong irreversible bonds in-between sulfonic groups of membrane hydro-gel and basic amino acid groups of proteins: No desorption during therapy.
**oXiris: membrane adsorption capacity**

**Experimental in-vitro conditions**
- Saline (NaCl 9g/L) and bovine blood (60g/L of protein, Hc 32%)
- Saline or blood volume: 500 mL
- Saline or blood flow rate: 150 mL/min (closed circuit)
- Ultrafiltration rate: 2 L/h (recirculating)
- Endotoxin from E. Coli (O55:B5)
- Initial concentration: 10 EU/mL in saline, 40 EU/mL in blood
- Test duration: 1 or 4h

**Results**

<table>
<thead>
<tr>
<th>Media</th>
<th>Initial endotoxin concentration EU/mL</th>
<th>Adsorption capacity EU/device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>10</td>
<td>3000</td>
</tr>
<tr>
<td>Bovine blood</td>
<td>40</td>
<td>13000</td>
</tr>
</tbody>
</table>

Cytokines and endotoxins adsorption: These adsorption mechanisms are governed by Langmuir physical law. It means that the adsorption capacity is directly linked to the initial concentration. For this reason, the given data should be considered only as information.
Endotoxin Removal - oXiris

**Endotoxin plasma concentration**

<table>
<thead>
<tr>
<th>cytokine</th>
<th>AN69 mb (n = 10)</th>
<th>Treated mb (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.30</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.30</td>
</tr>
<tr>
<td>TNF-α</td>
<td>192 (67–826)</td>
<td>1247 (235–1846)</td>
<td>0.08</td>
</tr>
<tr>
<td>IL-6</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.30</td>
</tr>
<tr>
<td>T0</td>
<td>230 (126–350)</td>
<td>98 (49–205)</td>
<td>0.04</td>
</tr>
<tr>
<td>T1</td>
<td>1434 (1053–1662)</td>
<td>1254 (803–1490)</td>
<td>0.50</td>
</tr>
<tr>
<td>T6</td>
<td>280 (174–409)</td>
<td>227 (139–302)</td>
<td>0.60</td>
</tr>
<tr>
<td>IL-6</td>
<td>104 (77–412)</td>
<td>66 (60–244)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

T0 = beginning of HVHF, T1 = time after 1 h of HVHF, T6 = time after 6 h of HVHF.

Statistics: ANOVA for repeated measurements followed by a Duncan post test. P = 0.014 for the time factor, P = 0.064 for the type of membrane. Using a Duncan post test, we found a significant difference at T1 between groups (P = 0.035)².

Rimmele et al., Nephrol Dial Transplant 2008
Risk

Failure

Loss

ESRD

GFR Criteria*

Increased creatinine x1.5 or GFR decrease > 25%

Increased creatinine x2 or GFR decrease > 50%

Increased creatinine x3 or GFR decrease > 75% or creatinine ≥4mg/dl (Acute rise of ≥0.5 mg/dl)

Urine Output Criteria

UO < .5ml/kg/h x 6 hr

UO < .5ml/kg/h x 12 hr

UO < .3ml/kg/h x 24 hr or Anuria x 12 hrs

Persistent ARF** = complete loss of renal function > 4 weeks

End Stage Renal Disease

High Sensitivity

High Specificity

Joannes-Boyau O, Honore PM. www.clinicaltrials.gov/ct/Show/NCT00241228
End of 2009:
- 140 patients included, Study ended.
- Mortality at Day 28: 39%
- Mortality at Day 90: 48%
- Expected Mortality by 3 severity scores:
  - SOFA, SAPS II & LOD: 68%
Classical Techniques with Standard Cut-off may not target most of the mediators seen during Sepsis & SIRS…

Timing of Intervention Regarding SIRS or CARS shows that Intervention on both Sides might be Beneficial.

Recent Hyperpermeable (Septex) Studies are showing that the Technique is safe concerning Albumin losses…

Modified Membranes such as oXiris may improve cytokine adsorption, endotoxin adsorption and may promote regional anticoagulation..

Results of Studies like IVOIRE & Beyond are Awaited with Eagerness…and do carrying for the time being a Very Low Global Mortality Rate..

Synergy between HVHF & Hyperpermeable membrane should be investigated

35 ml/kg/h + septeX vs 35 ml/kg/h + classical membrane maybe a possibility..