Hemofiltration in Sepsis: State of the Art in 2015

1. Seminal Study of Ronco on Dose

2. Large Randomized Studies on Lower Dose CRRT

3. Large Randomized Studies on High Dose CRRT (High Volume) in Sepsis

4. What about High Cut-Off Membranes?

5. Highly Adsorptive Membranes without LPS

6. Highly Adsorptive Membranes with LPS

7. Perspectives - Conclusions

Prof P.M. Honoré, MD, PhD, FCCM Intensivist-Nephrologist
Prof of ICU Medicine, UZB-VUB University, Bxl, Belgium
Frontiers in Hemofiltration in ICU: 2015 Update
14 October 2015 – Veranda VUmc-Amsterdam
Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

Claudio Ronco, Rinaldo Bellomo, Peter Homel, Alessandra Brendolan, Maurizio Dan, Pasquale Piccinni, Giuseppe La Greca

THE LANCET • Vol 356 • July 1, 2000

Survival (%)

Ultrafiltration rate

P < 0.0016
Prospective Randomized Studies & Timing to Start Therapy

The VA/NIH Study

Between 2003 et 2007

1124 patients

CVVH at 17 ml/kg/h + CVVD at 18 ml/kg/h Total = 35 ml/kg/h

CVVH at 10 ml/kg/h + CVVD at 10 ml/kg/h Total = 20 ml/kg/h

561 HIT

563 LIT

Mean ICU Stay Before Randomisation

> 7 Days

> 7 Days

Excluding 3216 patients

Survival at day 60

46.4 %

48.5 %

Sepsis

43.0 %

47.4 %

Predilution

100 %

100 %

Palevsky P et al. NEJM 2008 ; 359:7-20

Ronco C,Honore PM (letter)

Ronco C, Cruz D, Oudemans HM, Honore PM et al. Rev Crit Care 2008;308:EAP
Prospective Randomized Studies & Timing to Start Therapy

RENAL Trial

1500 patients
35 sites
3 years

Randomization

Intensive CRRT
(post-dilution CVVHDF at 40 ml/kg/h of effluent)
750 patients

Conventional CRRT
(post-dilution CVVHDF at 25 ml/kg/h of effluent)
750 patients

The RENAL Study
Kaplan Meier graph of survival time from randomisation to day 90

Logrank p=0.9301

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>721</td>
<td>45% (322)</td>
<td>55% (399)</td>
</tr>
<tr>
<td>Lower</td>
<td>743</td>
<td>45% (332)</td>
<td>55% (411)</td>
</tr>
</tbody>
</table>
CRRT is now widely accepted as the most appropriate therapy for vasopressor-dependent patients who require renal replacement therapy for AKI in the ICU.

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

Olivier Joannes-Boyau
Patrick M. Honoré
Paul Perez
Sean M. Bagshaw
Hubert Grand
Jean-Luc Canivet
Antoine Dewitte
Claire Flamens
Wilfried Pujol
Anne-Sophie Grandoulier
Catherine Fleureau
Rita Jacobs
Christophe Broux
Hervé Floch
Olivier Branchard
Stephane Franck
Hadrien Rozé
Vincent Collin
Willem Boer
Joachim Calderon
Bernard Gauche
Herbert D. Spapen
Gérard Janvier
Alexandre Ouattara

Intensive Care Med 2013;39:1535-1546
Any dose of noradrenaline or > 5µg/kg/min of dopamine

patients with Septic Shock and Acute Kidney Injury

- Oliguria < 0.5 ml/kg/h
- creatinine X 2

RIFLE Injury

Randomization within 24 hours of ICU admission (i.e. early septic shock)

35 ml/kg/h

70 ml/kg/h

Mortality

D28 D90
Recently Completed PRT’s: The IVOIRE Study

GFR Criteria* | Urine Output Criteria
---|---
Increased creatinine $\times 1.5$ or GFR decrease $> 25\%$ | UO $< 0.5$ ml/kg/h $\times 6$ hr
Increased creatinine $\times 2$ or GFR decrease $> 50\%$ | UO $< 0.5$ ml/kg/h $\times 12$ hr
Increased creatinine $\times 3$ or GFR dec $> 75\%$ or creatinine $\geq 4$ mg/dl (Acute rise of $\geq 0.5$ mg/dl) | UO $< 0.3$ ml/kg/h $\times 24$ hr or Anuria $\times 12$ hrs

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

End Stage Renal Disease

90 days survival

Joannes-Boyau O, Honore PM et al. ICM 2013;39:1535-1546

Log-rank $p = 0.94$

Standard Volume

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

Ping Zhang¹, Yi Yang¹, Rong Lv¹, Yuntao Zhang², Wenqing Xie¹ and Jianghua Chen¹

Nephrol Dial Transplant (2012)

with severe Sepsis and AKI

criteria: oliguria (urine output <100 mL in a 6-h period and unresponsive to fluid resuscitation), serum potassium concentration >6.5 mmol/L, severe acidemia (pH < 7.2), serum creatinine (SCr) >250 µmol/L or presence of severe organ edema (e.g. pulmonary edema).
Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: a single-center randomized clinical trial

Ping Zhang¹, Yi Yang¹, Rong Lv¹, Yuntao Zhang², Wenqing Xie¹ and Jianghua Chen¹

Table 1. Baseline characteristics of enrolled patients

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<tr>
<th>Characteristics</th>
<th>EHVHF group</th>
<th>HVHF group</th>
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<tbody>
<tr>
<td>Sepsis shock no. (%)</td>
<td>72 (51.06%)</td>
<td>69 (49.64%)</td>
</tr>
<tr>
<td>Mechanical ventilation before randomization no. (%)</td>
<td>116 (82.3%)</td>
<td>109 (78.4%)</td>
</tr>
<tr>
<td>Vasoactive drugs before randomization no. (%)</td>
<td>75 (53.2%)</td>
<td>78 (56.1%)</td>
</tr>
<tr>
<td>Inotropic support of norepinephrine before randomization no. (%)</td>
<td>50 (35.5%)</td>
<td>60 (43.2%)</td>
</tr>
<tr>
<td>Time in ICU before randomization (days)</td>
<td>5.40 ± 18.50</td>
<td>6.18 ± 14.36</td>
</tr>
<tr>
<td>Time in hospital before randomization (days)</td>
<td>9.33 ± 21.12</td>
<td>13.83 ± 38.79</td>
</tr>
<tr>
<td>APACHE II score before randomization</td>
<td>21.97 ± 8.25</td>
<td>22.60 ± 7.59</td>
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Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: a single-center randomized clinical trial

Ping Zhang¹, Yi Yang¹, Rong Lv¹, Yuntao Zhang², Wenqing Xie¹ and Jianghua Chen¹

Nephrol Dial Transplant (2012)
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<tr>
<th>Study</th>
<th>Mortality</th>
<th>Renal Failure</th>
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<tbody>
<tr>
<td>Hemodiafe study</td>
<td>73%</td>
<td>66%</td>
</tr>
<tr>
<td>ATN study</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Renal study</td>
<td>52%</td>
<td>52%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOFA Cardiovascular Score</th>
<th>Death from any cause by day 60 (n, %)</th>
<th>N Engl J Med 2008</th>
<th>N Engl J Med 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>509 (43.9)</td>
<td>362 (51.5)</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>615 (61.7)</td>
<td></td>
<td>289 (51.5)</td>
</tr>
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<tr>
<td>Yes</td>
<td>247/510 (48.4)</td>
<td></td>
<td>254/546 (46.5)</td>
</tr>
<tr>
<td>No</td>
<td>74/210 (35.2)</td>
<td></td>
<td>75/194 (38.7)</td>
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</table>

Patients with SOFA cardiovascular score of 3 or 4:
- Yes: 247/510 (48.4) vs. 254/546 (46.5)
- No: 74/210 (35.2) vs. 75/194 (38.7)

Patients with criteria for sepsis:
- Yes: 168/359 (46.8) vs. 186/363 (51.2)
- No: 154/362 (42.5) vs. 145/379 (38.3)
To conclude, in septic patients without AKI, hemofiltration with an ultrafiltration rate of 2 L/hr did not limit organ failure.

## Not Only Dose is Important but Also « True » Post-Dilution

<table>
<thead>
<tr>
<th>Author</th>
<th>Population (n)</th>
<th>HVH Regimen</th>
<th>Outcome</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honore et al (CCM 2000)</td>
<td>Refractory septic shock (20)</td>
<td>35L UF/4 hr followed by CVVH</td>
<td>55% “Responders“ + 81% survived</td>
<td>32.4% (4h)</td>
</tr>
<tr>
<td>Ronco et al (Lancet 2000)</td>
<td>Sepsis subgroup 45 ml/kg/h</td>
<td>45 mL/kg/hr Continuous Mb change 24 h</td>
<td>Best Survival Rate (sepsis subgroup) as compared to 20 and 35 ml</td>
<td>27 %</td>
</tr>
<tr>
<td>Joannes-Boyau O,Honore PM et al (ICM 2013)</td>
<td>Septic Shock + AKI 200 patients 140 rand</td>
<td>70 vs 35 mL/kg/hr for continued CVVH Mb change 48 h</td>
<td>No change in Survival at 28, 60 and 90 days.</td>
<td>20.5 % (70)</td>
</tr>
<tr>
<td>Payen D et al (CCM 2009)</td>
<td>Severe Sepsis/Septic Shock/No AKI 76 Rand</td>
<td>25 ml versus control 4 days CVVH (QB 150 ml)</td>
<td>Worsen SOFA score in CVVH group</td>
<td>20.6 %</td>
</tr>
<tr>
<td>Zhang P et al (NDT 2012)</td>
<td>Severe Sepsis + AKI 280 rand</td>
<td>85 vs 50 mL/kg/hr Continuous CVVH</td>
<td>No Change in Survival at 28, 60 and 90 days…</td>
<td>15 % (85)</td>
</tr>
</tbody>
</table>

Honore PM, Constantin JM, Guilbaud J-Ch et al - Blood Purif Abstract 2015
The Concept of «Albumin Detoxification » in CRRT.

- Immunomodulation: Removal of Free Mediators but also to Remove some bounded Mediators ....
- Albumin Detoxification

High-Cut-Off Filters: Why?

100000
- Albumin (55000 – 60000)
- Beta 2 Microglobulin (11800)
- Inulin (5200)

50000
- Vitamin B12 (1355)
- Aluminium/Desforoxamine complex (700)

10000
- Glucose (180)
- Uric Acid (168)
- Creatinine (113)
- Phosphate (80)

5000
- Urea (60)
- Potassium (35)

1000
- Phosphorus (31)

500
- Honore PM et al., Blood Purification, 2012
Recent HPHF Studies in Sepsis: HICOSS

IL-6 Clearance

**Sieving coefficient:**

<table>
<thead>
<tr>
<th></th>
<th>0.0</th>
<th>0.0</th>
<th>0.0</th>
<th>0.9</th>
<th>0.9</th>
<th>0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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), Prof Honoré (Bxl), Prof Clark (Indianapolis)

**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, Clark W et al. 10th Congress of WFSICCM, Florence 2009
Safety: Stable plasma albumin levels with septeX/ HCO compared to standard high flux - CVVHD

N= 81 pts CVVHD

In preparation for publication

Honore PM et al. 10th Congress of WFSICCM Florence 2009
Honore PM et al., Blood Purification, 2012
High-Adsorbing Filter : AN 69-ST

600UI/m² adsorbed heparin

**PEI = PolyEthylene Imine**

Honore PM et al. Annals of intensive Care 2011;1-24
Rationale for Adsorption Therapy: HMGB-1

Riedemann RC. Nat Med 2003;9:517-
Highly Adsorptive Mb for HMGB-1

**FIG. 4.** Time course of high mobility group box 1 protein (HMGB1) levels in the test solution during hemofiltration. Results are shown as mean ± SD of four experiments. The values at time 0 represent 100%. Dotted line shows the tubing data. These two curves are significantly different from each other (*P < 0.01 vs. the tubing). AN69ST, surface-treated polycrylonitrile; HCO, high cut-off membrane of polyarylethersulfone; PMMA, polymethylmethacrylate; PS, polysulphone.

Yumoto M et al. Therap Apheres and Dial 2011; 15: 385-393
HMGB-1 Endokine Elimination

Yumoto et al, Therapeutic Apheresis 2011

(HMGB-1: MW: 26 kDa)
No Saturation Effect for AN69 ST Regarding Adsorption of HMGB-1

Yumoto et al, Therapeutic Apheresis 2011
AN 69-oXiris : High Adsorption + LPS

**PEI=PolyEthylene Imine**

10,000 UI/m² grafted heparin

Honore PM et al. ASAIO J 2013; 59:99-106
Rationale of PMX Therapy for LPS

Endotoxemia

Endotoxin shed from local bacterial infection

Endotoxin translocation from GI Tract

- Every human has 25-30 grams of Endotoxin in their GI tract
- Less than 0.001 grams of Endotoxin is enough to kill a person

Endotoxin Removal – AN69 oXiris

Endotoxin plasma concentration

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

Rimmele T et al., NDT 2009;24:354-357
Hemoperfusion with Polymyxin B Column: Extracorporeal Removal of Endotoxin

Hemoperfusion is performed for 2-3 hrs.

- Blood pump 80-150 ml/min
- Femoral vein
- Anticoagulant Infusion

= Endotoxin
Hybrid Systems: PMX Cartridges (EUPHAS)

64 Post-Surgical Sepsis

Randomization

PMX Treatment for 2 Sess (N=34)

Standard Therapy (N=30)

<table>
<thead>
<tr>
<th></th>
<th>34 PMX Treatment</th>
<th>30 Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA Score</td>
<td>Improved</td>
<td>No Changes (P)</td>
</tr>
<tr>
<td>Hemodynamics (MAP)</td>
<td>Improved</td>
<td>No Improvement (P)</td>
</tr>
<tr>
<td>28 Days Mortality</td>
<td>32%</td>
<td>53% (Significant)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>Decreased</td>
<td>No Changes (T)</td>
</tr>
</tbody>
</table>

Cruz D et al JAMA 2009; 301:2445-2452
AN69 ST – Is Adsorption Superior To Convection in Improving Survival Status?

Hirasawa et Al. Blood Purif 2012;59:99-106

Table 1. Reports of blood purification aiming at the removal of humoral mediators in the patients with septic shock

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<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
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<th>Observed/predicted survival ratio</th>
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<td>Honore et al. [31]</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>
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<tr>
<td>Piccinni et al. [32]</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 et al. [12]</td>
<td>2006</td>
<td>20</td>
<td>26.1 ± 3.1</td>
<td>43.1</td>
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<td>2008</td>
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<tr>
<td>PMX-DHP</td>
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<td></td>
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<td></td>
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<td>Vincent et al. [34]</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>
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<td>Kojika et al. [35]</td>
<td>2006</td>
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<td>16.8 ± 4.1</td>
<td>73.8</td>
<td>87.5</td>
<td>1.19</td>
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<td>Nakamura et al. [36]</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>
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<td>Cruz et al. [2]</td>
<td>2009</td>
<td>34</td>
<td>21 (19–23)</td>
<td>61.1</td>
<td>67.7</td>
<td>1.11</td>
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<tr>
<td>CAH-CHDF</td>
<td></td>
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<tr>
<td>PMMA-CHDF [25]</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>
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<td>2012</td>
<td>34</td>
<td>32.5 ± 10.2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMMA-CHDF [25]</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>2012</td>
<td>34</td>
<td>32.5 ± 10.2</td>
<td>22.7</td>
<td>73.5</td>
<td>3.24</td>
</tr>
</tbody>
</table>

Hirasawa et Al. Blood Purif (published online October 24, 2012)
High-Adsorbing Filter : AN 69-ST

600UI/m² adsorbed Heparin / heparin Coated Membrane

Fig. 3 Kaplan-Meier survival curve for AN69ST (full line) and conventional AN69 filters (dashed line). a For all filters. b For clotted filter only.
## Dosage of Antibiotics & Antifungals During CVVH

<table>
<thead>
<tr>
<th>Antibioticum/Fungicidum</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amikacin</strong></td>
<td>30-35mg/kg</td>
<td>TDM</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>2g</td>
<td>2g over 3h tid</td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td>4g/0.5g</td>
<td>16g/2g (CI)</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>35mg/kg over 4h</td>
<td>30mg/kg (TDM=25-30mg/L)</td>
</tr>
<tr>
<td><strong>Teicoplanin</strong></td>
<td>3x15mg/kg om de 12h</td>
<td>600mg od</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td></td>
<td>600mg tid</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>800mg</td>
<td>400mg tid</td>
</tr>
<tr>
<td><strong>Tigecyclin</strong></td>
<td>150mg</td>
<td>100mg bid</td>
</tr>
<tr>
<td><strong>Colistin</strong></td>
<td>9 MIU</td>
<td>4,5 MIU tid</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td>8 mg/kg bid</td>
<td>6mg/kg bid</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td></td>
<td>600mg bid</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td></td>
<td>2g tid</td>
</tr>
<tr>
<td><strong>Gentamycin</strong></td>
<td></td>
<td>7 mg/kg od</td>
</tr>
<tr>
<td><strong>Bactrim</strong></td>
<td>1200 mg/240 mg (3amp)</td>
<td>800 mg/160 mg (2amp) tid</td>
</tr>
<tr>
<td><strong>Clindamycine</strong></td>
<td></td>
<td>900 mg qid</td>
</tr>
</tbody>
</table>

Honore PM et al. Journal of Translational Internal Medicine 2013
CRRT in Sepsis is Superior to IHD in terms of Morbidity & Renal Recovery in Hemodynamically Unstable Patients (Sepsis)........

Delivered Dose should be at Least 25 ml (so 30-35 prescribed) (Cfr KDIGO Guidelines)

High Volume (Above 35 ml/kg/h) is No Longer Recommended in Septic AKI but Wacht FR in Following Studies...

Do Not Start CRRT in Sepsis Without AKI

Starting at Rifle Injury in Septic AKI could be Better ..... 

Highly Adsorptive Membranes Could Be the Therapy of the Future........

Antibiotic Adaptation is a Key Point during CRRT!