RENAL FAILURE: 
UPDATE ON RENAL SUPPORT

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Renal Support in the ICU

- General principles
- How?
- When?
- Special Circumstances
- Emerging Technologies
Renal Support in the ICU: General Principles

1. Renal Support in AKI is different than ESRD

<table>
<thead>
<tr>
<th></th>
<th>AKI</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goals of therapy</strong></td>
<td>Improve OSF</td>
<td>Ameliorate uremia</td>
</tr>
<tr>
<td><strong>Desired Outcome</strong></td>
<td>Survival</td>
<td>Long term survival</td>
</tr>
<tr>
<td></td>
<td>Recovery of renal function</td>
<td>Quality of Life</td>
</tr>
<tr>
<td><strong>Determining Factor</strong></td>
<td>Other Organ Function</td>
<td>Renal Process</td>
</tr>
<tr>
<td><strong>Indication for dialysis</strong></td>
<td>Renal Support</td>
<td>Renal Replacement</td>
</tr>
</tbody>
</table>

## Renal Support in the ICU: General Principles

1. Renal Support in AKI is different than ESRD

<table>
<thead>
<tr>
<th></th>
<th>Renal Replacement</th>
<th>Renal Support</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Replace renal function</td>
<td>Support other organs</td>
</tr>
<tr>
<td><strong>Timing of Intervention</strong></td>
<td>Based on level of biochemical markers</td>
<td>Based on individualized need</td>
</tr>
<tr>
<td><strong>Indications for Dialysis</strong></td>
<td>Narrow</td>
<td>Broad</td>
</tr>
<tr>
<td><strong>Dialysis Dose</strong></td>
<td>Extrapolated from ESRD</td>
<td>Targeted for overall support</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Renal Failure</td>
<td>Renal and Non-renal indications</td>
</tr>
</tbody>
</table>

## Renal Support in the ICU: General Principles

1. Renal Support in AKI is different than ESRD

<table>
<thead>
<tr>
<th>Renal Replacement</th>
<th>Renal Support</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Life Threatening Indications</strong></td>
<td>Hyperkalemia, Acidemia, Pulmonary edema, Uremic complications</td>
</tr>
<tr>
<td><strong>Solute control</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fluid removal</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Regulation of acid-base and electrolyte status</strong></td>
<td></td>
</tr>
</tbody>
</table>

Renal Support in the ICU: General Principles

2. Renal Support should meet patient need

- Patients span spectrum of severity at initial evaluation
- Change in severity of illness is common during the course and predicts outcomes
- Therapeutic Modalities need to support organ function
Renal Support in the ICU: General principles

2. Renal support needs to be comprehensive

**Therapeutic Targets for RRT**
- Solute Homeostasis
- Fluid Regulation
- Biologic effects
  - Hemodynamics
  - Cytokines
  - Cell function
  - Metabolic control
  - Apoptosis

**Operational Characteristics of RRT**
- Solute clearance
  - Electrolytes
  - Acid Base Balance
  - Amino acid removal
- Fluid regulation
  - Space
  - Pressor support
- Modulation of Mediators
  - Removal of hepatotoxic factors
  - Adsorption
- Thermal Control
  - Hemodynamic support
  - Cerebral Edema
Renal Support in the ICU

- General principles
- How?
Extracorporeal Therapies

- **What is processed**
  - Blood
    - Dialysis systems
    - ECMO
    - ECCOR
    - Hemoperfusion
  - Plasma
    - Plasmapheresis
      - (Centrifugal, membrane separation)
  - Ultrafiltrate
    - Renal and hepatic support devices
  - Cellular elements
    - BMT
    - Chemotherapy

- **Basic Processes**
  - Separation and removal
    - Dialysis systems (fluid, solute)
    - Plasmapheresis
  - Separation and regeneration
    - Sorbent based dialysis
  - Separation and replacement
    - Hemofiltration
    - Plasmapheresis
  - Selective removal
    - Hemoperfusion
    - Endotoxin, Lipid, IgG columns
  - Addition of substances
    - ECMO
    - Chemotherapy
IHD Operational Characteristics

Diffusion
- Concentration Gradient based transfer
- Small mol wt (<500 Daltons) are transferred more efficiently

Convection
- Movement of water carries solute across the membrane
- Middle molecules are removed more efficiently

Adsorption
- Solute removal by binding to membrane
- Process influenced by membrane structure and charge
PD Operational Characteristics

**Solutes**
- Concentration Gradient based transfer facilitated by dextrose containing dialysate
- Small mol wt (<500 Daltons) are transferred more efficiently

**Fluids**
- Oncotic pressure from high percentage dextrose removes water and solute through ultrafiltration across the membrane by convective transport

**Adsorption**
- Minimal in PD
CRRT Operational Characteristics

- CVVHDF
- CVVHD
- CVVH

Dialysate:
Diffusive clearance

Ultrafiltrate:
Convective Clearance

Effluent:
Total fluid in waste bag at end of a time period.
Effluent Sieving Coefficient = UF/Plasma concentration of solute (1 = freely permeable, 0+ not permeable).

Dialysate Diffusive clearance

Ultrafiltrate Convective Clearance

Clearance in CRRT = SC or equivalent x effluent volume (UF, dialysate, UF + dialysate) + membrane adsorption

Dialyzer and blood clearance differ based on solute and membrane characteristics.
# Renal Support in the ICU: How?

## Solute Control

<table>
<thead>
<tr>
<th></th>
<th>IHD</th>
<th>SLED/EDD</th>
<th>CVVHD</th>
<th>CVVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow Rate (mL/min)</td>
<td>200-300</td>
<td>100-300</td>
<td>150-200</td>
<td>150-300</td>
</tr>
<tr>
<td>Dialysate Flow Rate (mL/min)</td>
<td>500-800</td>
<td>100</td>
<td>20-40</td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration Rate (mL/min)</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>20-40</td>
</tr>
<tr>
<td>% Saturation</td>
<td>15-40</td>
<td>60-70</td>
<td>85-100</td>
<td>100</td>
</tr>
<tr>
<td>Daily Kt/V*</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>EKR urea (mL/min)#</td>
<td>variable</td>
<td>~25</td>
<td>20-40</td>
<td>20-40</td>
</tr>
</tbody>
</table>

*Assumes V = 36 L

*EKR = \( \frac{G}{C} \)

Schlaeper *et al.*, Kidney Int 1999
Renal Support in the ICU: How? Solute Control

Azotemia control profiles in CVVH, daily HD, and SLED

Liao, Z et al Kinetic Comparison of Different Acute Dialysis Therapies. Artificial Organs 2003, 27 (9), 802-807
Renal Support in the ICU: How?

Solute Control

Mehta et al: Kidney Int 2001; 60:1154
Fluid Removal on Dialysis

Refill Rate

Interstitial Space

Capillary Membrane interface for NDF

Vascular Space

Dialyzer

UF

Mitra S et al Am J of Kid Dis, 40, 2002
Renal Support in the ICU: General Principles

2. Renal Support needs to be comprehensive

Changes in Fluid Balance in Intermittent Dialysis

Schematic representation of the bi-diurnal variation of fluid status in chronic hemodialysis patients. Between the 2 subsequent dialysis treatment sessions, usually 44 hours apart, the patient’s interdialytic weight gain reflects fluid retention between 2 consecutive hemodialysis treatments, which will then be removed rather quickly via dialysis ultrafiltration (UF) during a 4-hour dialysis treatment. DryWt indicates dry weight; PreWt, predialysis weight; and n Lit, magnitude of ultrafiltered fluid in liter.

Effect of Daily Hemodialysis on Blood Volume and Weight

**IHD 3/week**

![Graph showing weekly blood volume and body weight changes for IHD 3/week.](image)

*Fig. 7. Weekly blood volume and body weight changes in a standard haemodialysis schedule (three sessions per week). The figure clearly shows both the intradialytic blood volume in-bounds and the post-dialysis blood volume rebounds (these are followed by a further slow blood volume recovery up to the following session).*

**IHD 6/week**

![Graph showing weekly blood volume and body weight changes for IHD 6/week.](image)

*Fig. 8. Weekly blood volume and body weight changes in a daily haemodialysis schedule (six sessions per week). Intradialytic blood volume in-bounds are less steep and deep than those in Figure 7. Furthermore, post-dialysis blood volume recoveries are slowly progressive and do not show any acute rebound phases.*

Modified from Santoro et al NDT, UC San Diego.
Principles For Fluid Removal with Dialysis

Removal
Fluid is primarily removed from intravascular compartment

Refill
Plasma refilling rates from interstitial compartment determine rate of change of intravascular blood volume

Balance
If ultrafiltration rate exceeds plasma refilling rate decreased blood volume ensues and contributes to hemodynamic instability
Principles For Fluid Management With Intermittent Hemodialysis

- Fluid is removed by ultrafiltration governed by transmembrane pressure
- Volume of fluid removed is precisely regulated by volumetric balance chambers in machine
- Rate of fluid removal dictated by prescription
- Maximum fluid removal rate per hour dictated by machine limits (generally 2 L/hr)
- Fluid replacement generally not required

Since time is rate limiting factor, goal is to find maximally tolerated ultrafiltration rate
Principles For Fluid Management With Continuous Dialysis

- Fluid is removed by ultrafiltration governed by transmembrane pressure.
- Volume of fluid removed is precisely regulated by Gravimetric scales outside the machine (Prisma, Prismaflex, Aquarius, B. Braun) or Volumetric balancing chamber inside the machine (NxStage).
- Rate of fluid removal is dictated by prescription and operational characteristics.
- Maximum fluid removal rate per hour is dictated by machine limits (2-12 L/hr).
- Fluid replacement is required.

As procedure is continuous, goal is to target ultrafiltration to achieve fluid balance over time.
### Comparisons of Fluid Management Capability

<table>
<thead>
<tr>
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<th>Normal Kidney</th>
<th>Intermittent HD*</th>
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<td>120</td>
<td>34</td>
<td>14</td>
<td>100</td>
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<tr>
<td><strong>Volume of Filtrate /day (L)</strong></td>
<td>173</td>
<td>8</td>
<td>14</td>
<td>144</td>
</tr>
<tr>
<td><strong>Volume removed /Day (L)</strong></td>
<td>0.1-1.5</td>
<td>0-8</td>
<td>0-14</td>
<td>0-100</td>
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**Net Ultrafiltration capacity**

![Graph showing net ultrafiltration capacity for different CRRT modalities](image)
## Comparisons of Fluid Management Capability

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<td>0-100</td>
</tr>
<tr>
<td><strong>Regulatory mechanism</strong></td>
<td>GFR Control</td>
<td>UFR Control</td>
<td>UFR control</td>
<td>UFR Control</td>
</tr>
<tr>
<td></td>
<td>Reabsorption</td>
<td>-</td>
<td>-</td>
<td>Replacement Fluid</td>
</tr>
<tr>
<td><strong>Sensing mechanism</strong></td>
<td>Hemodynamic</td>
<td>-</td>
<td>-</td>
<td>- ? hemodynamic</td>
</tr>
<tr>
<td></td>
<td>Volume status</td>
<td>-</td>
<td>-</td>
<td>? volume status</td>
</tr>
</tbody>
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* 4 hours /day

# High volume HF 6L/hr
# Fluid Management Comparisons

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<tr>
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<th>Fluid Regulation</th>
</tr>
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<tr>
<td>Normal Kidney</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>IHD</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>CRRT</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Influence of Modality on Fluid Overload

Days

Mean percentage fluid overload

Days

UC San Diego
SCHOOL of MEDICINE
CRRT Operational Characteristics

- CVVHDF
- CVVHD
- CVVH

- Dialysate
  - Diffusive clearance

- Ultrafiltrate
  - Convective Clearance

- Effluent
  - Total fluid in waste bag at end of a time period.
Fluid Management in CRRT

Principles
- Substitution fluid
- Dialysate

Site
- Pre-filter
  - Dilution
- Post-Filter
  - Replacement
Principles of Fluid Management in CRRT

**Ultrafiltrate**
- UF is used to remove fluid and UF rate can be controlled.
- UF removes fluid with composition close to plasma water.
- Solutes removed to varying degrees depending upon membrane characteristics.

**Replacement**
- Replacement fluid may be used to replace varying amounts of the fluid removed.
- Composition of the replacement fluid can be varied.

**CRRT Fluid Balance**
- Fluid balance for the CRRT device is computed as the difference between UF removed and replacement fluid given for any given period of time.

**Patient Fluid Balance**
- Depends on the difference between all intakes and outputs including CRRT for any given period of time.
Principles of Fluid Management in CRRT

CRRT Fluid Balance
- Provides a mechanism for achieving the patient fluid balance goals
- Two approaches
  - Fluid removal
  - Fluid regulation

Patient Fluid Balance
- Depends on goals for patient
- Goals may range from removing fluid, keeping even or giving fluid.
- Fluid balance goals require adjustment frequently and will often determine the operational parameters.
Optimizing Renal Support for Fluid Management

- Desired fluid balance
- Fluid management strategy (removal, even, positive balance)
- Adjustments: Frequency
- Goals of Therapy

Goals of therapy
- Short term
- Long term

CRRT Operational Parameters
- Effluent volume
- Pump settings
- Solutions rate
- Measurements

Patient Assessment
Fluid Management in CRRT

Key Decisions

- How much UF volume is required to provide solute clearance
- How much UF is needed to achieve fluid balance
- What fluid composition is needed to replace fluid removed

Practical Issues

- Prescription
- Implementing fluid management with different pumped systems
- Monitoring and charting
- Roles and responsibilities
Operational Characteristics of RRT Applicable for Renal Support

- **Parameters**
  - Solute clearance
    - Electrolytes
    - Acid Base Balance
    - Amino acid removal
  - Fluid regulation
    - Space
    - Pressor support
  - Modulation of Mediators
    - Removal of hepatotoxic factors
    - Adsorption
  - Thermal Control
    - Hemodynamic support
    - Cerebral Edema

- **RRT attributes**
  - Solute concentration can be manipulated independent of fluid balance
  - Plasma composition can be altered by changing composition of dialysate and substitution fluid
  - Fluid regulation can occur concurrently with solute removal to maintain patient fluid balance desired
  - Core temperature regulation can be achieved
Renal Support in the ICU

- General principles
- How?
- When?
Timing of RRT in AKI: The Dilemma

Patient with AKI

Early RRT
- Recover without RRT

Late RRT
- Benefit
- Harm
- Die without RRT because of futility
Timing of RRT in AKI: Early vs Late

What is Early?
- Clock start
- Retrospective assessment
- Prospective evaluation

What is Evidence?
- Retrospective studies
- Analysis of existing datasets
- Prospective studies

Areas of Concern
- Criteria for Start
- Consequences
- What’s needed
Timing of RRT in AKI: Early vs Late

What is Early?

- Clock start
- Retrospective assessment
- Prospective evaluation
Timing of RRT in AKI: Early vs Late

What is Early?
• When does clock start

Time from hospitalization
Time from ICU admission
Start of AKI
Oliguria
Max severity of AKI
Other clinical parameters
Timing of RRT in AKI: Early vs Late

What is Early?
- When does clock start?
- Retrospective Studies

Retrospective analysis of demographic and physiologic data of 1,847 patients who received RRT for AKI in 22 ICUs in UK and Germany between 1989 - 1999.

Parameters at time of RRT

<table>
<thead>
<tr>
<th>Interval between ICU admission and RRT</th>
<th>ALIVE</th>
<th>DEA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 days</td>
<td>657 (77.5%)</td>
<td>679 (68%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-5 days</td>
<td>97 (11.4%)</td>
<td>159 (15.9%)</td>
<td>&lt;3 days vs ≥ 3 days</td>
</tr>
<tr>
<td>6-10 days</td>
<td>73 (8.6%)</td>
<td>101 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>21 (2.5%)</td>
<td>60 (6.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Days between biochemical diagnosis of AKI III and RRT

<table>
<thead>
<tr>
<th>Days between biochemical diagnosis of AKI III and RRT</th>
<th>ALIVE</th>
<th>DEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same day or before</td>
<td>1,568 (84.9%)</td>
<td>832 (53.1%)</td>
</tr>
<tr>
<td>1-2 days later</td>
<td>67 (3.6%)</td>
<td>44 (65.7%)</td>
</tr>
<tr>
<td>3-5 days later</td>
<td>37 (2.0%)</td>
<td>24 (64.9%)</td>
</tr>
<tr>
<td>6-10 days later</td>
<td>69 (3.7%)</td>
<td>32 (46.4%)</td>
</tr>
</tbody>
</table>

Survivors shorter interval to start dialysis from ICU admission and Biochemical abnormalities

Osterman et al: Critical Care 2009, 13:R175
Timing of RRT in AKI: Early vs Late

**What is Early?**
- Clock start
- Retrospective assessment
- Prospective evaluation

**What is Evidence?**
- Retrospective studies
- Analysis of existing datasets
- Prospective studies
Timing of RRT in AKI: Early vs Late

What is Evidence?

- Epidemiologic studies
- Delayed Start?

PICARD 1999-2001

- 622 pts with AKI in ICU with nephrology consultation
- 384 dialyzed
  - IHD
  - CRRT
  - Combined

Process of care
Reasons for dialysis
Nephrologist initiating dialysis

Prospective 3 yr study at 5 centers in USA
Detailed data collection through hospital discharge

Outcomes
- ICU and Hospital mortality
- Renal functional recovery
- LOS in ICU
- Economics
Renal Support in the ICU: When? Dialysis is Initiated late

Dialyzed Patients eGFR – Day of First Dialysis

IHD  CRRT

PICARD Database N= 384

US and European guidelines for starting dialysis in ESRD recommend dialysis initiation when symptomatic or at GFR < 10-15 ml/min.
Renal Support in the ICU?
Choice of modality is dependent on clinical severity

PICARD Database N= 384
Timing of RRT in AKI: Early vs Late

Retrospective analysis of demographic and physiologic data of 1,847 patients who received RRT for AKI in 22 ICUs in UK and Germany between 1989 - 1999.

What is Evidence?
• Epidemiologic studies
• Delayed Start?

Survivors shorter interval to start dialysis from ICU admission and biochemical abnormalities

Osterman et al: Critical Care 2009, 13:R175
Timing of RRT in AKI: Early vs Late

Retrospective analysis of demographic and physiologic data of 1,847 patients who received RRT for AKI in 22 ICUs in UK and Germany between 1989 - 1999.

ALIVE n=848
DEAD n =999

What is Evidence?
- Epidemiologic studies
- Delayed Start?

Survivors had more organ failures, had a greater % oliguric and were more hemodynamically compromised at start of RRT

Osterman et al: Critical Care 2009, 13:R175
Timing of RRT in AKI: Early vs Late

What is Evidence?

• Epidemiologic studies
• Improved Outcomes?

Retrospective analysis of demographic and physiologic data of 1,847 patients who received RRT for AKI in 22 ICUs in UK and Germany between 1989 - 1999.

Timing of RRT in relation to onset of AKI III

Patients who received RRT before they met the creatinine criteria for AKI stage III (serum creatinine ≥ 354 μmol/L (≥ 4.0 mg/dL) or a rise in serum creatinine by more than 300% from baseline) had a significantly lower ICU mortality than patients who were started on RRT on the day when they met the AKI stage III criteria (49.8% versus 64.6%; P < 0.0001).

This group also had a better ICU outcome compared with patients in whom RRT was initiated after the AKI criteria were fulfilled (49.8% versus 56.3%) but this difference did not reach statistical significance (P = 0.05).

Osterman et al: Critical Care 2009, 13:R175
Timing of RRT in AKI: Early vs Late

What is Evidence?

- Prospective studies
- Improved Outcomes?

Timing of RRT in AKI: Early vs Late

What is Evidence?
• Improved Outcomes?

80 patients with acute liver failure and AKI requiring RRT after major abdominal surgery analyzed with respect to timing of start.

Early or late dialysis considered based on arbitrary BUN cut off of 80mg/dl at start of RRT

Wu et al J Am Coll Surgeons 2007

![Chart showing survival rates for early and late dialysis]
Timing of RRT in AKI: Early vs Late

What is Evidence?

- Improved Outcomes?

- 370 patients with sepsis and AKI requiring RRT in surgical intensive care units were enrolled between January 2002 and October 2009. The patients were divided into early (sRIFLE-0 or -Risk) or late (sRIFLE-Injury or -Failure) initiation of RRT by sRIFLE criteria. Cox proportional hazard ratios for in hospital mortality were determined to assess the impact of timing of RRT.

- 190 underwent early RRT

Chou et al Critical Care 2011, 15:R134
Timing of RRT in AKI: Early vs Late

What is Early?
- Clock start
- Retrospective assessment
- Prospective evaluation

What is Evidence?
- Retrospective studies
- Analysis of existing datasets
- Prospective studies

Areas for Concern
- Criteria for Start
- Delayed start reduces likelihood of success
Areas of concern: criteria for start have not been defined

Criteria for Start
- Urine Output and Biochemical markers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Higher-Intensity CRRT (N=722)</th>
<th>Lower-Intensity CRRT (N=743)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliguria (urine, &lt;400 ml/day)</td>
<td>430/722 (59.6)</td>
<td>444/743 (59.8)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>68/722 (9.4)</td>
<td>45/743 (6.1)</td>
</tr>
<tr>
<td>Severe acidemia</td>
<td>257/722 (35.6)</td>
<td>264/743 (35.5)</td>
</tr>
<tr>
<td>BUN &gt;70 mg/dl (plasma urea &gt;25 mmol/liter)</td>
<td>315/722 (43.6)</td>
<td>286/743 (38.5)</td>
</tr>
<tr>
<td>Creatinine &gt;3.4 mg/dl (300 µmol/liter)</td>
<td>349/722 (48.3)</td>
<td>343/743 (38.5)</td>
</tr>
<tr>
<td>Severe organ edema associated with acute kidney disease</td>
<td>323/722 (44.7)</td>
<td>319/743 (42.9)</td>
</tr>
<tr>
<td>BUN — mmol/liter**</td>
<td>24.2±13.3</td>
<td>22.8±12.2</td>
</tr>
<tr>
<td>Creatinine before randomization — µmol/liter††</td>
<td>338±192</td>
<td>330±197</td>
</tr>
<tr>
<td>pH</td>
<td>7.3±0.1</td>
<td>7.3±0.1</td>
</tr>
<tr>
<td>Bicarbonate — mmol/liter</td>
<td>18.1±5.7</td>
<td>18.5±5.9</td>
</tr>
<tr>
<td>Base excess — mmol/liter</td>
<td>−8.3±7</td>
<td>−8.2±7</td>
</tr>
</tbody>
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Bellomo et al: RENAL Study NEJM 2009
Areas of concern: criteria for start have not been defined

Criteria for Start
- Urine Output and Biochemical markers

Non-oliguric patients have late start of dialysis

Areas of concern: criteria for start have not been defined

### Criteria for Start
- Urine Output and Biochemical markers

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<tr>
<th></th>
<th>Survivors (n=17)</th>
<th>Non-survivors (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of initial nephrology consult</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>76±49</td>
<td>42±32</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>4.3±2.5</td>
<td>2.3±1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>At time of initiation of dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOF score</td>
<td>1.7±0.8</td>
<td>2.7±1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to initiation of dialysis (days)</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Urine volume (L/day)</td>
<td>0.7±0.8</td>
<td>1.5±1.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Non-oliguric patients have late start of dialysis

Areas of concern: criteria for start have not been defined

Criteria for Start
• Biomarkers

RRT incidence in 10 studies was 4.3%:
NGAL prediction of RRT:
Diagnostic Odds Ratio, 12.9 [95% CI, 4.9-33.9]
Sample size-weighted AUC-ROC, 0.782
[95% CI, 0.648-0.917]
Hierarchical summary receiver operating characteristic (HSROC) plot depicts the combined sensitivity and specificity (95% CI) weighted for sample size

Overall Positive predictive value of NGAL in ICU RRT was 0.12

Areas of concern: criteria for start have not been defined

Criteria for Start
• Severity of Organ dysfunction

28-Day Survival

- **EHV**: 74.3%
- **ELV**: 68.8%
- **LLV**: 75.0%

Treatment Group

- **EHV**
  - *n=35*
  - SOFA: 10.3±2.8

- **ELV**
  - *n=35*
  - SOFA: 10.1±2.2

- **LLV**
  - *n=36*
  - SOFA: 10.6±1.9

Areas of Concern: Delayed start reduces likelihood of success

Late start of Dialysis and Adverse Outcomes

- Organ recruitment
- Fluid overload
- Reduced renal recovery
- Delineation of futility
- Mortality
Nephrology Consultation in Acute Renal Failure: Does Timing Matter?

Table 3. Associations between Time to Nephrology Consultation (from Time of Admission to Intensive Care Unit) and Mortality or Combined Outcome of Mortality or Nonrecovery of Renal Function

<table>
<thead>
<tr>
<th>Days to Consultation*</th>
<th>Odds Ratio (95% Confidence Interval) for Mortality</th>
<th>Odds Ratio (95% Confidence Interval) for Mortality or Nonrecovery of Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 (n = 121)</td>
<td>2.1 (1.2–3.6)</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>≥2 (n = 61)</td>
<td>3.1 (1.7–5.8)</td>
<td>2.0 (1.0–3.9)</td>
</tr>
<tr>
<td>≥4 (n = 31)</td>
<td>4.7 (1.9–11.4)</td>
<td>2.6 (1.0–6.5)</td>
</tr>
</tbody>
</table>

* Note that these categories are not mutually exclusive.
† Adjusted for age, sex, urine output, liver failure, hematologic failure, heart rate, and serum creatinine and blood urea nitrogen levels.

Organ system failure in early (filled bars) and delayed (empty bars) consultation left, \( P = 0.26 \) and at the time of nephrology consultation (right, \( P = 0.006 \)).
Fluid Balance and AKI

Areas of Concern: Delayed Start reduces likelihood of success

Late start of Dialysis and Adverse Outcomes
- Organ recruitment
- Fluid overload
- Reduced renal recovery
- Delineation of futility
- Mortality

- Adjusted OR for death with % FO >10% at dialysis initiation:
  2.07 (95% CI 1.27-3.37)

Bouchard et al Kidney Int. 2009
Dialysis Decisions for AKI

Issues

Variation in the utilization of dialysis
- Timing of initiation
- Stopping dialysis
- Modality
- Dose

Perceived Benefits vs. Risks
- Benefits: Volume, solute, organ support
- Risks: catheter placement, dialysis procedure, effect on renal recovery

Limited information
- How decisions are made
- Factors affecting decisions
Renal Replacement in the ICU Early vs late Start: Summary

Renal Replacement

- Renal support is more appropriate conceptual framework
- Organ support in the ICU requires adequate kidney function
- Dialysis should be offered when kidney function cannot meet the demand

Early vs Late

- Early vs late concepts should be reassessed as difficult to standardize time clock starts
- Better to consider timely vs delayed initiation based on individual patient need

What’s Needed?

- Standardized criteria that are patient specific and dynamic to define patient need for RRT
- Prospective studies to validate concepts of timeliness
Renal Support in the ICU

- General principles
- How?
- When?
- Special Circumstances
RRT using an in-line hemofilter during extracorporeal membrane oxygenation (ECMO).
RRT using a CRRT machine during extracorporeal membrane oxygenation (ECMO).
CRRT machines with ECMO

- Access Pressure on CRRT may be positive
  - Some Dialysis Machines can allow for alarms to be adjusted during ECMO
  - Clamps can be used to avoid these alarms
    - Increases Hemolysis

- Circuit prime
  - Can use either a saline prime or blood prime
  - Careful with heparin rinse
What type of modality is used

Fleming G, et al for the KIDMO Study Group
ASAIO in press, 2012
## Differences between RRT methods

<table>
<thead>
<tr>
<th></th>
<th>In Line Hemofilter</th>
<th>CRRT machine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration control</td>
<td>IV pump controlled</td>
<td>CRRT machine controlled</td>
</tr>
<tr>
<td>Metabolic Control</td>
<td>NOT if only using SCUF</td>
<td>YES</td>
</tr>
<tr>
<td>ECMO Flow</td>
<td>Blood Shunt</td>
<td>NO systemic changes</td>
</tr>
<tr>
<td></td>
<td>- decrease ECMO flow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- decreased PaO2</td>
<td></td>
</tr>
<tr>
<td>Complexity</td>
<td>Less People</td>
<td>More People</td>
</tr>
</tbody>
</table>
ELSO registry

Askenazi et al. Pediatric Critical Care Medicine 2011
Survival in AKI/ RRT subjects

Askenazi et al. Pediatric Critical Care Medicine 2011
Demirozu ZT et al: Results of HeartMate II left ventricular assist device implantation on renal function in patients requiring post-implant RRT. J Heart and Lung Transplant 2009

Renal function in 15/107 heart failure patients supported by the HeartMate II continuous-flow LVAD who required RRT by CVVHD or IHD, or both.

Indications for RRT included oliguria (urine 400 ml/day) unresponsive to diuretic therapy for 24 hours with a creatinine level 2.0 mg/dl or 1.5 X that of the pre-implant creatinine level, severe acidemia, and volume overload.
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## Extracorporeal Therapies
### Biologic Effects

<table>
<thead>
<tr>
<th>Disease Modification</th>
<th>Organ Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Removal of inflammatory mediators</td>
<td>• Renal</td>
</tr>
<tr>
<td>• Immunomodulation</td>
<td>• Cardiac</td>
</tr>
<tr>
<td></td>
<td>• Respiratory</td>
</tr>
<tr>
<td></td>
<td>• Neurological</td>
</tr>
<tr>
<td></td>
<td>• Nutrition</td>
</tr>
<tr>
<td></td>
<td>• Thermal regulation</td>
</tr>
</tbody>
</table>
Extracorporeal Therapies
Disease Modification in Sepsis

Removal of Inflammatory mediators

- Rationale based on targeting removal of inflammatory molecules as molecular weight of most cytokines (e.g. TNF) ranges from 17-50K
## Cytokine removal

### Pro-inflammatory

<table>
<thead>
<tr>
<th>Molecular Weight (Kd)</th>
<th>Cytokines/Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Endotoxin fragments (± 100Kd)</td>
</tr>
<tr>
<td>60</td>
<td>TNFα (T) (T=51 Kd)</td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td><strong>cut-off point</strong></td>
</tr>
<tr>
<td></td>
<td>IL6 (26 Kd)</td>
</tr>
<tr>
<td>20</td>
<td>TNFα ((M) (M:17.5 Kd) IL-1b (17 Kd))</td>
</tr>
<tr>
<td>10</td>
<td>MIF (13Kd) complement activation products IL-8 (8 Kd) (±10 Kd)</td>
</tr>
<tr>
<td>5</td>
<td>Kinin activation products ± 1 Kd Bradykinin</td>
</tr>
<tr>
<td>1</td>
<td>Autacoids (PAF) (&lt; 1 Kd) Endothelin I (&lt;1Kd) Arachidonic acid metabolites - Eicosanoid components (&lt; 1 Kd)</td>
</tr>
</tbody>
</table>

### Anti-inflammatory

<table>
<thead>
<tr>
<th>Cytokines/Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 soluble receptor (65Kd)</td>
</tr>
<tr>
<td>IL-1 soluble receptor (50Kd)</td>
</tr>
<tr>
<td>IL-10 (40 Kd)</td>
</tr>
<tr>
<td>S-TNFR-II (33 Kd)</td>
</tr>
<tr>
<td>S-TNFR-I (30 Kd)</td>
</tr>
<tr>
<td>IL-1ra (22 Kd)</td>
</tr>
</tbody>
</table>
Extracorporeal Therapies
Disease Modification in Sepsis

Removal of Inflammatory mediators

• Cytokine removal is variable and depends on operational characteristics
Extracorporeal Therapies
Disease Modification in Sepsis

Removal of Inflammatory mediators

- Removal can be enhanced by
  - Increasing permeability of membrane (High Cut Off membranes, plasma filtration)
Solute Classes by Molecular Weight

Daltons

- Albumin (55,000 - 60,000)
- Inflammatory Mediators (1,200-50,000)
- Myoglobin (17,800)
- Beta 2 Microglobulin (11,800)
- Inulin (5,200)
- Vitamin B12 (1,355)
- Aluminium/Desferoxamine Complex (700)
- Glucose (180)
- Uric Acid (168)
- Creatinine (113)
- Phosphate (80)
- Urea (60)
- Potassium (35)
- Phosphorus (31)
- Sodium (23)

“large”

“middle”

“small”
Variation of membrane pore sizes

Electron micrographs of inner membrane surface

- $\varnothing < 0,01 \, \mu m$
- $\varnothing < 0,02 \, \mu m$
- $\varnothing \approx 0,09 \, \mu m$
- $\varnothing \approx 0,30 \, \mu m$

- high flux
- high cut-off*
- plasma separation membrane
- protein separation membrane

*high cut-off
Effect of Membrane Permeability on Solute Removal

**Figure 1.** Asymmetric, polysulfone membranes (Filtron Technology Corp.) having MWCO of 30, 50 and 100 kD are compared using polydisperse (MW) dextran.²
### High Permeability Membranes for RRT

#### Sieving coefficients of large pore membranes and conventional pore membranes

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Operating characteristics</th>
<th>IL-8 (MW = 8 kDa)</th>
<th>TNFα (MW = 17 kDa)</th>
<th>IL-1 (MW = 17 kDa)</th>
<th>IL-10 (MW = 17 kDa)</th>
<th>IL-6 (MW = 26 kDa)</th>
<th>Albumin (MW = 69 kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 kDa polyamide [20]</td>
<td>1 l/h</td>
<td>0.31</td>
<td>0.27</td>
<td>0.81</td>
<td>0.56</td>
<td>0.73</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>6 l/h</td>
<td>0.19</td>
<td>0.09</td>
<td>0.75</td>
<td>0.56</td>
<td>0.32</td>
<td>0.0</td>
</tr>
<tr>
<td>Polyamide* [21]</td>
<td>Variable</td>
<td>0.25</td>
<td>0</td>
<td>0.18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Polysulfone* [22]</td>
<td></td>
<td>0.12</td>
<td>0.22</td>
<td>0.42</td>
<td>0</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>AN69** [23]</td>
<td></td>
<td>0.08</td>
<td>0.16</td>
<td>0.22</td>
<td>0</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

TNFα, tumor necrosis factor alpha; MW, molecular weight. Mean molecular weight cut-off (MWCO) of 30 kDa is shown in the table by the sign * and the MWCO of 50 kDa is shown in the table by the sign **.
Extracorporeal Therapies
Disease Modification in Sepsis

Removal of Inflammatory mediators

- Removal can be enhanced by
  - Increasing convection (HVHF, Pulse HVHF)
High Volume Hemo-Filtration (HVHF)

<table>
<thead>
<tr>
<th>CATEGORIES (4)</th>
<th>UF VOLUME INDEXED TO BODY SIZE</th>
<th>EQUIVALENCE FOR HUMAN BEING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very low volume hemofiltration</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>VLVHF</strong></td>
<td>35 ml/kg/h 2.6 l/h</td>
<td></td>
</tr>
<tr>
<td><strong>Low volume hemofiltration</strong></td>
<td>35</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>LVHF</strong></td>
<td>50 ml/kg/h 3.75 l/h</td>
<td></td>
</tr>
<tr>
<td><strong>High volume hemofiltration</strong></td>
<td>50</td>
<td>3.75</td>
</tr>
<tr>
<td><strong>HVHF</strong></td>
<td>100 ml/kg/h 7.5 l/h</td>
<td></td>
</tr>
<tr>
<td><strong>Very high volume HF</strong></td>
<td>100</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>VHVHF</strong></td>
<td>120 ml/kg/h 9 l/h</td>
<td></td>
</tr>
<tr>
<td><strong>Very high volume HF</strong></td>
<td>150</td>
<td>11.25</td>
</tr>
<tr>
<td><strong>VHVHF</strong></td>
<td>215 ml/kg/h 16.125 l/h</td>
<td></td>
</tr>
</tbody>
</table>

(20) Honoré PM et al. First International Symposium on Critical Care Nephrology – Melbourne November 2001
Randomised multicentre international therapeutic trial assessing the impact of high-volume continuous veno-venous (CVVH) hemofiltration (HVCVVH) in early treatment of the patient with septic shock complicated by acute kidney injury

→ Should define the adequate « Septic Dose » of CRRT
patients with Septic Shock and Acute Renal Failure

Any dose of vasopressors (Noradrenaline)
Or $> 5\mu g/kg/m$ of Dopamine

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

RIFLE Injury

Randomization within 24 hours of ICU admission (! Early septic shock)

Mortality

D28

D90
167 patients assessed for eligibility

27 Excluded
- 14 Refused participation
- 2 Obesity > 150 kg
- 11 Met exclusion criteria

140 Randomized

2 patients excluded
- 1 Withdraw consent
- 1 Acute leukemia

66 patients analyzed

1 patient excluded
- 1 Withdraw consent

71 patients analyzed
Extracorporeal Therapies
Disease Modification in Sepsis

Removal of Inflammatory mediators

- Removal can be enhanced by
- Utilizing adsorption (PMMA CHDF, Polymixin, Osiris Membrane)
CORRELATION BETWEEN CLEARANCE AND BLOOD LEVEL OF CYTOKINES IN CRITICALLY ILL PATIENTS TREATED WITH PMMA-CHDF

**TNF (MW:17000)**

\[ y = 22.1 \log x - 14.0 \]

\[ r = 0.77 \quad P < 0.01 \]

\( n = 12 \)

**IL-6 (MW:21000)**

\[ y = 9.91 \log x - 22.4 \]

\[ r = 0.56 \quad P < 0.01 \]

\( n = 27 \)

**IL-8 (MW:8000)**

\[ y = 22.4 \log x - 48.2 \]

\[ r = 0.63 \quad P < 0.01 \]

\( n = 12 \)

<table>
<thead>
<tr>
<th>Blood Level (pg/mL)</th>
<th>Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

3 hrs after the change to a new filter

24 hrs after the change to a new filter
CHANGES IN SYSTOLIC BLOOD PRESSURE AND CATECHOLAMINE INDEX IN THE TREATMENT OF SEPTIC SHOCK PATIENTS WITH ACUTE RENAL FAILURE

CUMULATIVE URINE VOLUME IN THE TREATMENT OF SEPTIC SHOCK PATIENTS WITH ACUTE RENAL FAILURE

CHDF

PMMA-CHDF
(n=10)

PAN-CHDF
(n=16)

Cumulative Urine Volume (mL)

CHDF (mean ± SD)

0
2
4
6
8
10
12
14
16
18
20
22
24 (hr)

1620 ± 1500 (mL)

610 ± 700 (mL)
COMPARISON OF CUMULATIVE SURVIVAL OF SEPTIC SHOCK PATIENTS WITH ACUTE RENAL FAILURE BETWEEN PAN-CHDF GROUP AND PMMA-CHDF GROUP

Logrank (Mantel-Cox) p<0.05

PAN-CHDF (n=16) 80%

PMMA-CHDF (n=10) 25%

Cumulative Survival (%)
Interaction between LPS and Polymyxin-B

Strong affinity between LPS and PMX is governed by 2 types of bonds:

1. IONIC: major factor in binding

2. HYDROPHOBIC: alter the spatial structure of the acyclic chains of LPS, neutralizing its toxicity.

Lipid A of LPS

Polymyxin unsuitable for systemic use because of neuro- and nephrotoxicity
Polymyxin B Immobilized Fiber Column:
No systemic side effects since PMX does not enter circulation
Hemoperfusion with Polymyxin B Column: Extracorporeal Removal of Endotoxin

Blood pump 80-150 ml/min

Femoral vein

Anticoagulant Infusion

Hemoperfusion is performed for 2-3 hrs.

● = Endotoxin
28 studies, 7 countries, Total of 1,425 patients

This systematic review of the published literature found positive effects of PMX-F:
- Able to reduce endotoxin levels
- ↑ MAP
- ↓ dopamine/dobutamine use
- ↑ PaO₂/FiO₂ ratio
- ↓ Mortality

Limited ability to make conclusions
- Suboptimal quality of available studies
- Heterogenous study populations

These putative benefits remain to be determined definitively in a prospective trial.
Extracorporeal Therapies
Disease Modification in Sepsis

- Strategies include
  - Anticoagulant based strategies
  - Citrate enabled selective cytophoretic device (SCD)
A Biomimetic Membrane Device That Modulates the Excessive Inflammatory Response to Sepsis

Feng Ding¹, Joon Ho Song², Ju Young Jung³, Liandi Lou⁴, Min Wang⁴, Linda Charles⁴, Angela Westover⁴, Peter L. Smith⁴, Christopher J. Pino⁴, Deborah A. Buffington⁴, H. David Humes⁴,⁵*

¹Division of Nephrology, Huashan Hospital, Fudan University, Shanghai, China, ²Department of Internal Medicine, Center for Advanced Medical Education by BK21 Project, Inha University School of Medicine, Incheon, Korea, ³Chungnam National University, Daejeon, Korea, ⁴Innovative BioTherapies, Inc., Ann Arbor, Michigan, United States of America, ⁵Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States of America

PLoS ONE April 2011 Vol 6 Issue 4 e18584
Pre-Clinical Studies

Figure 6. Leukocyte adherence to outer surfaces of hollow fibers. Light micrographs stained with H&E from three animals show leukocyte adherence to surfaces of the SCD. Panel A: Low-power micrograph showing adherent cells around each hollow fiber (160×). Panels B and C: High power micrographs demonstrating cluster of leukocytes along the outer surface of hollow fibers (400×). Panel D: High-power micrograph display predominant polymorphonuclear cells along with mononuclear cells in the adherent cell clusters (1600×).

do:10.1371/journal.pone.0018584.g006
PRECLINICAL STUDIES

ACTIVATED LEUKOCYTES - LUNG TISSUE

Control

Treated
Working Hypothesis of Mechanism for SCD Influence on SIRS

1. Primed
   - patient blood
   - PMN
   - monocyte

2. Activation
   - UF

3. Adherence
   - Citrate and Ca i↓

4. Inhibition
One-Pump System
U.S. Pilot IDE Multicenter Trial

**Design**

- 35 patients treated with SCD for up to 7 sequential 24 hour treatments with CRRT.
- Safety and early efficacy endpoints:
  - 28 and 60 day mortality and dialysis dependency

**Results**

- Demographics (35 patients):
  - Age: 56 years
  - SOFA score: 11.5
  - Sepsis: 80%
  - Ventilator: 90%
- No SAE’s related to the SCD; average Rx time of 4 days

Pivotal IDE presented to the FDA with 35 patient monitored data
- 28 day mortality: 20%; 60 day mortality: 30%
- At 60 days, no surviving patient was dialysis dependent
Renal Support in the ICU

Summary

- RRT techniques are at a key point in development and application worldwide
- Advances in the field need to focus on standardizing the therapy with a focus on patient support through the continuum of illness
  - Early intervention
    - Concept of renal support
  - Flexibility
    - Variation according to need
  - Multidisciplinary approach
    - Interaction to define goals
    - Trial of therapy
- Innovative use of technology to target therapy for specific diseases and provide renal support will continue.
What is the Future of RRT for AKI?

- Technology Advances x Targeted Therapy x Timing x Therapy Delivery = Therapeutic Success
Acknowledgments

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Rolando Claure-Del Granado
Sharon Soroko
Guillermo Sanz-Berney
Rakesh Malhotra
Sam Kuo
Yang Luo
Jiandong Wei

PICARD group

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Research supported through the NIH-NIDDK O’Brien Center
THE 18th INTERNATIONAL CONFERENCE ON CONTINUOUS RENAL REPLACEMENT THERAPIES

CRRT 2013

Acute Kidney Injury: Controversies, Challenges and Solutions

Endorsed by the
INTERNATIONAL SOCIETY OF NEPHROLOGY
AND ACUTE KIDNEY INJURY NETWORK

SAN DIEGO, CALIFORNIA
HILTON SAN DIEGO BAYFRONT
FEBRUARY 12-15, 2013

Abstract Deadline:
Dec. 7, 2012

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