Continuous Renal Replacement Therapy—Therapeutic and Drug Dosing Implications
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November 16th, 2012

Disclosures
• None

Objectives
• Discuss the impact of Acute Kidney Injury in the ICU
• Discuss the different modalities of Continuous Renal Replacement Therapy (CRRT)
• Review how CRRT affects drug elimination
• Identify important drugs that require dose adjustment in a patient receiving CRRT
AKI Classification Systems

**RIFLE**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Serum creatinine increased ≥ 1.5 times of baseline</td>
</tr>
<tr>
<td>Injury</td>
<td>Serum creatinine increased ≥ 3 times of baseline</td>
</tr>
<tr>
<td>Failure</td>
<td>Serum creatinine increased ≥ 5 times of baseline, or urine output &lt; 0.5 mL/kg/h for 24 or 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent acute renal failure, completion of kidney</td>
</tr>
<tr>
<td>End-stage</td>
<td>End-stage renal disease for longer than 3 months</td>
</tr>
</tbody>
</table>

Table 1: RIFLE Classification

Chang et al, Shock 2010

AKI Classification Systems

**AKIN**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine Criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 - 2 x baseline (or rise ≥ 26.4 ( \mu \text{mol/L} ))</td>
<td>&lt; 0.5 mL/kg/hour for &gt; 6 hours</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 2 - 3 x baseline</td>
<td>&lt; 0.5 mL/kg/hour for &gt; 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 3 x baseline (or &gt; 354 ( \mu \text{mol/L} ) with acute rise ≥ 44 ( \mu \text{mol/L} ))</td>
<td>&lt; 0.3 mL/kg/hour for 24 hours or anuria for 12 hours</td>
</tr>
</tbody>
</table>

Patients receiving RRT are Stage 3 regardless of creatinine or urine output

Chang et al, Shock 2010

Acute Kidney Injury in the ICU

- Approximately 30,000 patients from 54 hospitals in 23 countries
- 6% of all ICU admissions developed AKI
  - Approximately 70% required dialysis
- 30% of patients had renal impairment prior to development of AKI
  - 13% of patients were dialysis-dependent at discharge
- CRRT was initial dialysis modality in 80% of patients
- Hospital mortality of 60%
- Cost of around $100,000 (just for RRT therapy)

Uchino et al, JAMA 2005
Rauf et al, J Int Care Med 2008
Sepsis

- Single most common cause for acute kidney injury (AKI) in the critically ill
- Patients have more physiologic disturbance, more severe organ dysfunction, and higher mortality compared to those with nonseptic AKI
- CRRT has become the preferred treatment for AKI in ICUs

Which of the following treatment options has been shown to decrease mortality in patients with AKI in the ICU?

- A. Diuretics
- B. Low dose dopamine
- C. Dialysis
- D. Fenoldopam
- E. None of the above

Proposed Indications for RRT

- Oliguria <200ml/12 hours
- Anuria <50ml/12 hours
- Hyperkalemia >6.5mmol/L
- Severe acidemia pH <7.0
- Uremia >30mmol/L
- Uremic complications
- Dysnatremias >155 or <120mmol/L
- Hyper/hypothermia
- Drug overdose with dialyzable drug

Lameire et al, Lancet 2005
Goals of CRRT

- Mimic the functions and physiology of the native organ
- Qualitative and quantitative blood purification
- Restore and maintain of homeostasis
- Avoid complications and good clinical tolerance
- Provide conditions favoring recovery of renal function

Benefits of CRRT

- Haemodynamic stability => ?? better renal recovery
- Stable and predictable volume control
- Stable and predictable control of chemistry
- Stable intracranial pressure
- Disease modification by cytokine removal (CVVH)?

Cons of CRRT

- Anticoagulation requirements
- Higher potential for filter clotting
- Expense – fluids etc.
- Immobility & Transport issues
- Increased bleeding risk
- High heparin exposure
A. Dialysis depends on diffusion whereas filtration depends on convection
B. Filtration is more effective than dialysis at removing small molecules
C. Filtration is more effective than dialysis at removing cytokines
D. Dialysis is not as effective as filtration at removing water

CRRT Techniques

- SCUF
  - CVVH/CAVH
  - CVVHD/CAVHD
  - CVVHDF/CAVHDF

SCUF

- Slow Continuous Ultrafiltration
  - Fluid overload without uremia or electrolyte imbalance
  - Not suitable for solute clearance
  - High flux membranes
  - Blood flow rate 50–200 ml/min
  - UF rate 2–8 ml/min
**CVVH/CAVH**
- Continuous veno-venous hemofiltration
  - Uremia, severe pH or electrolyte imbalance with or without fluid overload
  - Effective solute removal method via convection
  - Large/middle molecules removed
  - Can maintain a net zero or positive fluid balance
  - Replacement fluid pre or post filter
  - Blood flow 50–200ml/min
  - UF rate 10–60ml/min

**CVVHD/CAVHD**
- Continuous veno-venous hemodialysis
  - Similar to traditional hemodialysis
  - Diffusive solute clearance
  - Effective for removal of small to medium sized molecules
  - Blood flow 50–200ml/min
  - UF rate 1–8ml/min
  - Dialysate flow 15–60ml/min

**CVVHDF/CAVHDF**
- Continuous veno-venous hemodiafiltration
  - Combines diffusion and convection
  - Countercurrent dialysate
  - Replacement fluid as required– net zero or positive balance
  - Blood flow rate 50–200ml/min
  - UF rate 10–60ml/min
  - Dialysate flow 15–30ml/min
  - Replacement 10–30ml/min
Replacement Solutions

- Physician Rx and adjusted based on pt. clinical need.
- Sterile replacement solutions may be:
  - Bicarbonate–based or Lactate–based solutions
  - Electrolyte solutions
  - Must be sterile and labeled for IV Use
  - Higher rates increase convective clearances
  - You are what you replace

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Table 1. Comparison of various modalities of renal replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>CRRT</th>
<th>CAPD</th>
<th>CVVH</th>
<th>CVVHD</th>
<th>CVVHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency per week</td>
<td>3–7 days</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>3–6</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Number of treatments</td>
<td>3–6</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Efficiency</td>
<td>High</td>
<td>Low and variable</td>
<td>Moderate and variable</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Urine output (mL)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dialysis clearance</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Solute removal</td>
<td>Diffusion*</td>
<td>Convection</td>
<td>Diffusion</td>
<td>Convection</td>
<td>Diffusion and convection</td>
<td></td>
</tr>
<tr>
<td>Dialysate (D)</td>
<td>D</td>
<td>RF</td>
<td>D</td>
<td>RF</td>
<td>D</td>
<td>RF + D</td>
</tr>
<tr>
<td>Replacement fluid (RF)</td>
<td>HD</td>
<td>CRRT</td>
<td>CAPD</td>
<td>CVVH</td>
<td>CVVHD</td>
<td>CVVHDF</td>
</tr>
</tbody>
</table>


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Molecular Weights

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
</tr>
<tr>
<td>50,000</td>
</tr>
<tr>
<td>10,000</td>
</tr>
<tr>
<td>5,000</td>
</tr>
<tr>
<td>1,000</td>
</tr>
<tr>
<td>500</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>Lower</td>
</tr>
</tbody>
</table>

"Large" Set

- Urea (5.0 kg)
- Creatinine (1.0 kg)
- BUN (1.0 kg)
- Electrolytes (1.0 kg)
- Vitamin B12 (1.0 kg)

"Middle" Set

- Albumin (250 mg)
- Alumina (250 mg)
- Calcium (250 mg)
- Magnesium (250 mg)
- Phosphorus (250 mg)
- Potassium (250 mg)

"Small" Set

- Insulin (250 mg)
- Dopamine (250 mg)
- Furosamide (250 mg)
Optimal Dose of Effluent Removal

Two large, multicenter, randomized controlled trials
- Investigated the effects of RRT dose on patient outcomes
- ATN—conducted in ICUs throughout the US
- RENAL—conducted in ICUs in Australia and New Zealand

Table 3: Comparison of patient populations in ATN and RENAL Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VA/NHH ATN study</th>
<th>RENAL study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.7</td>
<td>61.0</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>25.1</td>
<td>23.7</td>
</tr>
<tr>
<td>Female (%)</td>
<td>74.9</td>
<td>76.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Serum Na (mEq/L)</td>
<td>143.9</td>
<td>142.9</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Serum Ca (mg/dL)</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Serum Mg (mg/dL)</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Urine Output (mL/day)</td>
<td>124.4</td>
<td>124.4</td>
</tr>
<tr>
<td>Urine Sodium (mEq/L)</td>
<td>32.6</td>
<td>32.6</td>
</tr>
</tbody>
</table>

Table 3 footnote:
- Prowle et al, Nat. Rev. Neph. 2010
Which of the following therapies are used as anticoagulation in CRRT?

- A. Heparin
- B. Aspirin
- C. Citrate
- D. Warfarin
- E. A and C

Anticoagulation

- Heparin
- Regional Citrate
- Low Molecular Weight Heparin
- Direct Thrombin Inhibitors
- None

Anticoagulation

- Clotting cascade activated when blood comes in contact with the non-endothelial surfaces of the tubing and filter
- Prevents circuit from clotting
- Prolongs life of filter
  - Reduced time off therapy, reduced nursing time for filter changes, and reduced cost
- Prescriber must consider relative risks of anticoagulation and choose safest option for the patient
Unfractionated Heparin

- Advantages
  - Monitoring of aPTT generally available
  - Low cost
  - Short half-life

- Disadvantages
  - Systemic bleeding
  - HIT

Citrate

- Regional anticoagulation
- 4% sodium citrate, ACD-A
- Sodium citrate chelates ionized calcium in the circuit

- Advantages
  - Filter may last longer
  - Reduced transfusion requirements

- Disadvantages
  - Infusion of IV calcium required
  - Monitoring of ionized calciums (post filter vs. serum)
  - Hypocalcemia
  - Metabolic alkalosis

Low Molecular Weight Heparin

- Alternative to UFH
- Not shown to be superior to UFH for prolonging filter life
- Advantages
  - Effective anticoagulant
- Disadvantages
  - Systemic bleeding
  - Monitoring of anti-Xa not readily available
  - Pharmacokinetics in renal failure
- Not widely used

Alternative Methods

- Factor Xa inhibitors
- Direct Thrombin Inhibitors
- Predilution
- No anticoagulation
  - Increasing the blood flow may not necessitate anticoagulation
  - Contraindicated: Platelets <50,000, INR >2, actively bleeding, severe hepatic dysfunction

Dosing of Drugs in CRRT
Which of the following drugs need to be dose adjusted during CRRT?

- A. Diazepam
- B. Linezolid
- C. Vancomycin
- D. Moxifloxacin
- E. A and C

Drug Dosing and CRRT

- Removal of drugs due to CRRT depends on mostly three factors:
  - Drug
    - Protein binding, volume of distribution, molecular weight
  - Membrane Permeability
    - Gibbs-Donnan effect–drug charge and membrane interaction
  - CRRT Technique
    - Flow rates, duration

Predicting Drug Removal by Dialysis

- Population Data
- Factors Influencing Dialysis Removal
  - Dialyzer/Filter used: membrane thickness, pore size, surface area
  - Blood flow
  - Duration
  - Ultrafiltrate Rate/Fluid removed
  - Transmembrane pressure
  - Drug: molecular weight and charge
  - Sieving coefficient
- Drug Levels
  - Time relationship to dose and HD
  - Sample site: (Pre->Post filter if removable)
Sieving Coefficient

- Ratio of drug concentration in the UF to the plasma
- Mathematical expression of the ability of a solute to convectively cross a membrane
  \[ SC = \frac{C_{UF}}{C_p} \]
- SC values range from 0–1
  - SC of 1 means that the solute freely crosses the membrane and is removed in the same concentration as in the plasma, while an SC of 0 means that there is no solute removal due either to large molecular size or to extensive protein binding

<table>
<thead>
<tr>
<th>Drug</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>0.9</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.9</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>0.3</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>0.6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.9</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.8</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>0.9</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1</td>
</tr>
<tr>
<td>Levofloxacine</td>
<td>0.8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.8</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.8</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Not that Simple…First Principles

- Convective clearance (CVVH)
  \[ Cl_{CVVH(post)} = Q_f \times S_c \]
  \[ Cl_{CVVH(pred)} = Q_f \times S_c \times \frac{Q_b}{Q_b + Q_{rep}} \]
- Diffusion clearance (CVVHD)
  \[ Cl_{CVVHD} = Q_f \times S_c \]
  \[ Cl_{CVVHD(post)} = clearance \ from \ CVVH \ using \ post-filter \ hemodilution; \ Q_f = ultrafiltrate \ rate; \ Cl_{CVVH} \ (pre) = clearance \ from \ CVVH \ using \ pre-filter \ hemodilution; \ Q_b = blood \ flow \ rate; \ Q_{rep} = predilution replacement \ rate; \ Cl_{CVVHD} = clearance \ from \ CVVHD \]

Choi et al, Blood Purif 2010
But wait....

- Diffusion plus Convection - CVVHDF
- \( CL_{CVVHDF} = (Q_f + Q_d) \times S_d \)
- \( CL_{CVVHDF} \) = clearance from CVVHDF; \( Q_d \) = dialysate flow rate

- Native clearance also taken into account
  - Usually minimal

Choi et al, Blood Purif 2010

Dosing of Drugs in CRRT

Consult the Available Literature
Review of Medline-referenced literature

For drugs with no specific published data with CRRT dosing—used known chemical properties and other clinical data

Most cases—recommended “target” drug concentration corresponds to the upper limit of the MIC range for susceptibility

Goal of recommendations to keep the concentration above the target MIC for an optimal proportion of the dosing interval

Assume an UF rate of 1L/hr, a dialysate flow rate of 1L/hr, and no residual renal function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Type of replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>0.5–1.0 mg/kg</td>
<td>Oral or IV 24 hour infusion</td>
</tr>
<tr>
<td>Lipid complex</td>
<td>3–5 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Enemate</td>
<td>3–5 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Anisole</td>
<td>1g-3g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Anisole solution</td>
<td>3 g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Calcium</td>
<td>1–2 g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Sodium</td>
<td>2–3 g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Calcium</td>
<td>1–2 g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Sodium</td>
<td>2–3 g 12hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>2 g 24 hr</td>
<td>Continuous replacement</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.5–1.0 mg/kg</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.5–1.0 mg/kg</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td>Colistin</td>
<td>2–3 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>4–5 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1–2 mg/kg</td>
<td>24 hour infusion</td>
</tr>
</tbody>
</table>

Loading dose of 500mg with levofloxacin

Loading dose of 15–20mg/kg of vancomycin

Loading dose of 6mg/kg x 2 doses for voriconazole

Medline search from 1986–2010

Clearance determined by nonrenal clearance, residual renal clearance and CRRT dose

Sieving and saturation coefficients are membrane specific but may be altered by changes in protein binding induced by critical illness

Individualized dosing based on first principles may be the most appropriate method of dosing

Excellent reference

Principles of Antibacterial Dosing in CRRT

Blood Purif 2010; 30:195–212
Variability of Antibiotic Concentrations in Critically III Patients Receiving CRRT: A Multicentre Pharmacokinetic Study

**Table 2. Dose regimens administered to the study participants**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>500 mg every 6 hrs</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>500 mg every 12 hrs</td>
<td>1</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>1000 mg every 6 hrs</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1000 mg every 12 hrs</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4000 mg every 6 hrs</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4000 mg every 12 hrs</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1000 mg once daily</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2000 mg every 6 hrs</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2000 mg every 12 hrs</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4000 mg every 6 hrs</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4000 mg every 12 hrs</td>
<td>3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg every 6 hrs</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1000 mg every 12 hrs</td>
<td>2</td>
</tr>
</tbody>
</table>

- 24 critically ill adult patients with acute kidney injury
- Trough blood samples obtained
- Measured antibiotic concentrations

Overall, 15% of dosing intervals did not meet predetermined minimum therapeutic target concentrations
- 40% did not achieve the higher target concentration
- During 10% of the dosing intervals, antibiotic concentrations were excessive
- Empiric dosing failed to achieve target trough concentrations during 25% of dosing intervals

**Figure 1. Vancomycin levels (μg/dl) relative to time since prior administered dose (h). Line indicates therapeutic level threshold.**

We recommend an initial dose of 20 mg/kg of vancomycin, followed by 15 mg/kg every 24 h while a patient is on CVVHD at the Qb and Qd utilized, with monitoring of serum levels every 48 – 72 h. "Dosing by level" in this setting is not recommended as routine practice.

**Table 4. Percentage of dosing intervals (n = 40) achieving the antibiotic therapeutic targets**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Lower Target (%)</th>
<th>Higher Target (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

*The lower therapeutic target was defined as 100x MIC for meropenem and piperacillin, ≤0.5 mg/l for vancomycin, and ≤1 mg/l for ciprofloxacin; the higher therapeutic target was defined as 100x MIC minimum inhibitory concentration for meropenem and piperacillin, ≤20 mg/l for vancomycin, and ≤5 mg/l for ciprofloxacin.*

**Vancomycin levels are frequently subtherapeutic during CVVHD**

*Clinical Nephrology 2012; 77:329–331*
Drug Dosing…other

- Limited case reports on antiepileptics with conflicting information
- Catecholamines are small molecules which are not bound to plasma proteins and pass easily through the membrane
  - Extracorporeal elimination not clinically significant due to short plasma half life and high nonrenal clearance
- Digoxin is significantly eliminated but digitoxin is not
- H2 antagonists are not significantly removed
- PPIs have high nonrenal clearance
  - Administer normal doses

Drug Dosing Summary

- Neither renal failure nor extracorporeal renal replacement therapy requires adjustment of the loading dose which depends solely on Vd.
- Maintenance doses of drugs that undergo considerable renal excretion should be adapted to the reduced renal clearance.
- Should be decided whether this adapted dose needs to be compensated for extracorporeal elimination.
- Large amount of literature devoted to antimicrobials.
- Extracorporeal clearance is calculated taking a low-performance technique with a CrCl of 10ml/min and a high-performance technique with a CrCl of 25ml/min
  - Schetz et al, Intensive Care Med. 1995

Summary

- CRRT is now widely accepted as the most appropriate therapy for vasopressor-dependent patients who require RRT for AKI in the ICU.
- Two large, multicenter, randomized controlled trials have now established that increasing the dose of CRRT above an effluent rate of 25ml/kg/hr is not beneficial.
- Anticoagulation to prolong filter life if warranted.
- Simplest method of drug dosing during CRRT
  - Based on total creatinine clearance
  - VD, protein binding, nonrenal clearance
  - For antibiotics with low toxicity—the consequences of underdosing is more dangerous than the adverse effects of overdosing.
- Use therapeutic drug monitoring
- Use clinical judgment
Questions