Drug Dosing During Renal Replacement Therapy

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Outline

- Overview of the processes involved in solute (including drug) & fluid removal during renal replacement therapy:
  - HD, CAPD, SCUF, CAVH, CVVH, CVVHDF
- Factors influencing drug removal during renal replacement therapy
- Use various medications (prototypes) to illustrate drug removal
- Review PK calculations to determine clearance
- Guidelines for determining dosing adjustments in renal patients undergoing hemodialysis or hemofiltration
Hemodialysis
Procedure
Vascular Access
Countercurrent Flow
Dialyzers
Types of Dialyzers

Hollow-fiber dialyzer

Parallel-plate dialyzer
Conventional Hemodialysis
Hemodialysis

Blood

Dialysate

Dialyzer

Dialysate

Dialysate
Ultrafiltration

Dialysate

Dialyzer

Dialysate

Waste

Waste

Pressure
# Dialysate Components

<table>
<thead>
<tr>
<th>mEq/L</th>
<th>Acute HD</th>
<th>Chronic HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>145</td>
<td>135-145</td>
</tr>
<tr>
<td>K</td>
<td>3.5 varies</td>
<td>2.5 varies</td>
</tr>
<tr>
<td>Ca</td>
<td>3.5</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Mg</td>
<td>0.75</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>PO$_4$</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dextrose mg/dl</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>HCO$_3$</td>
<td>25</td>
<td>35 + acetate 4</td>
</tr>
</tbody>
</table>
Factors Affecting Drug Removal during Hemodialysis

- Concentration gradient
- Molecular weight
  - Related to speed and size
- Membrane thickness
- Pore size
- Degree of protein binding
Characteristics of Drugs Likely to be Removed by Hemodialysis

- Small molecular weight
- Low volume of distribution
- Non-protein bound or low protein binding
- Water soluble
- Renal excretion is the main mode of drug elimination
High Flux Dialysis

• Highly permeable membrane
  – Thinner membrane
  – Larger pores
• Greater removal of middle molecules (evil humours)
• Convection & diffusion are optimized
High Flux Hemodialysis
Example

• Vancomycin
  – HD
    • No replacement doses are needed
  – High flux HD
    • Significant vancomycin removal has been reported (range: 39-92%)
    • Replacement doses may be needed
    • Eg. Vancomycin 250 mg IV after high flux HD

  » Ref: AJKD 1995;26(3):469-74
  » Kidney Int 1994;45:232-7
  » AAC 1992;36(7):1424-6
Vancomycin Removal by Hi-Flux HD

• N = 8 critically ill patients
• Age 39 – 72 years
• Purpose
  – Define PK during high-flux HD
  – Characterize rebound phenomenon
Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanco MD</td>
<td>HD</td>
</tr>
<tr>
<td>HD</td>
<td>Interdialytic</td>
</tr>
<tr>
<td>Intradialytic</td>
<td></td>
</tr>
<tr>
<td>Intradialytic</td>
<td></td>
</tr>
</tbody>
</table>

Graph:
- Concentration vs. Time
- Vanco IV x 1 p HD
- 6-hr
- 20-hr
PK Calculations

- **Intradialytic $t_{1/2}$**
- **Data to use**: pre- and post-
  - HD levels
- $k_{\text{intradialytic}} = \ln \left( \frac{\text{pre HD level}}{\text{post HD level}} \right) \frac{\text{delta } t}{\text{delta } t}$
- $t_{1/2 \text{ intradialytic}} = 0.693/k$
PK Calculations

• **Intradialytic clearance**

• **Data to use:**
  
  – Arterial samples - $\text{AUC}_{0\text{-end of dialysis}}$
  
  – Dialysate samples - amount of drug in dialysate ($R$)
    
    • $R = \text{dialysate concentration} \times \text{volume of dialysate}$
    
  – $\text{Cl}_{\text{intradialytic}} = \frac{R}{\text{AUC}_{0\text{-end of dialysis}}}$
PK Calculations

- Interdialytic $t_{1/2}$
- Data to use: 6-hr & 20-hr post-dose levels
- $k_{\text{interdialytic}} = \ln \left( \frac{\text{6-hr level}}{\text{20-hr level}} \right)$
  $\Delta t$
- $t_{1/2 \text{ interdialytic}} = 0.693/k$
PK Calculations

• % rebound

• Data to use:
  – $C_{mr}$ = maximum drug concentration during rebound phase
  – $C_{end}$ = drug concentration at the end of HD
  – % rebound = \( \frac{(C_{mr} - C_{end})}{C_{end}} \times 100 \)
## Results

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>F-80 (n=5)</th>
<th>F60 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interdialytic $t_{1/2}$ (hrs)</td>
<td>162.3 ± 69.8</td>
<td>211.0 ± 166.8</td>
</tr>
<tr>
<td>Intradialytic $t_{1/2}$ (hrs)</td>
<td>4.7 ± 1.3</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>Intradialytic CL (ml/min)</td>
<td>108.5 ± 16.3</td>
<td>100.6 ± 18.3</td>
</tr>
<tr>
<td>Vancomycin Recovered (mg)</td>
<td>238 ± 55</td>
<td>252 ± 79</td>
</tr>
<tr>
<td>% Rebound</td>
<td>Range:15-38%</td>
<td></td>
</tr>
</tbody>
</table>
Guidelines

• “Supplemental vancomycin doses should be given after high-flux HD (approx 250 mg) in addition to the patient’s regular dose or baseline requirement.”
  – Reflects amount recovered in dialysate
• “True” trough levels should be obtained at least 6 hours following dialysis.
  – The rebound effect occurred 2-6 hours following high-flux HD
Vancomycin Dosing in HD

- Simplified, proposed method
- LD 15 mg/kg x 1
- MD 10 mg/kg last 1 hr of each HD

Continuous Ambulatory Peritoneal Dialysis (CAPD)
Continuous Ambulatory Peritoneal Dialysis (CAPD)

- Uses the peritoneal membrane for exchange of fluid and solutes
  - Parietal: underlies the abdominal wall
  - Visceral: overlies the abdominal organs
  - Both are highly vascularized
Figure 46.10. Schematic diagram of the placement of a peritoneal dialysis catheter through the abdominal wall into the peritoneal cavity.
(Reproduced from Ref. 24, p. 126, with permission from WB Saunders Company, Orlando, FL.)
CAPD Process

- Dialysate flows into the peritoneal cavity by gravity (15 min.) and allowed to dwell (approx. 4 hours)
- At the end of dwell time, the empty dialysate bag is placed in a dependent position
- Tube is unclamped & dialysate (effluent) flows into bag, detached, discarded
- New bag is attached & process is repeated
Y-Set System

- Pre-attached bags
- Double-bag
- “Flush-before-fill”
- Fresh dialysis solution flows into the Y-tubing and into the drainage bag
- Flushes out air, bacteria
Y-Set System

- Fresh solution flows into the rinsed tubing
CAPD Components

• Standard volumes 2, 2.5 liters (1.5, 2.0, 2.25, 2.5, or 3 L)
• Dextrose concentrations 1.5, 2.5, 4.25%
## CAPD Components

<table>
<thead>
<tr>
<th></th>
<th>3 Standard Formulations (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na</strong></td>
<td>132</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Cl</strong></td>
<td>102</td>
</tr>
<tr>
<td><strong>Mg</strong></td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Ca</strong></td>
<td>3.5</td>
</tr>
<tr>
<td>Lactate</td>
<td>35</td>
</tr>
</tbody>
</table>
Intraperitoneal Drug Therapy

• 3 main drug classes
  – Antibiotics
  – Insulin
  – Heparin
Peritonitis

• Incidence varies
  – Related to patient’s technique and ability to perform an exchange

• Caused by a variety of microorganisms
  – Gram-positive organisms, eg. *Staph aureus* & *Staph epidermidis* are most common

• Many treatment regimens exist. No single regimen has proven to be the most efficacious
Initial treatment of peritonitis

Abdominal Pain +/- Cloudy Fluid +/- Unexplained Fever

Cell Count/Differential Gram’s Stain, Culture

Initiate Empiric Antibiotic Therapy
Cefazolin or Cephalothin & Ceftazidime

# Empiric Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intermittent Dose in 1 Exchange/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Residual Urine Output (&lt;100 ml/d)</td>
</tr>
<tr>
<td></td>
<td>Residual Urine Output (&gt;100 ml/d)</td>
</tr>
<tr>
<td>Cefazolin or cephalothin</td>
<td>1 g/bag QD or 15 mg/kg/bag QD</td>
</tr>
<tr>
<td></td>
<td>20 mg/kg/bag QD</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 g/bag QD</td>
</tr>
<tr>
<td></td>
<td>20 mg/kg/bag QD</td>
</tr>
<tr>
<td>Gentamicin or tobramycin</td>
<td>0.6 mg/kg/bag QD</td>
</tr>
<tr>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2 mg/kg/bag QD</td>
</tr>
<tr>
<td></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

See ISPD guidelines for further therapy.
Treatment of Exit Site Infection


Purulent Discharge from Exit Site

Gram Stain Culture

Gram Positive Organism
- Penicillinase Resistant PCN po eg. dicloxacillin or 1st generation cephalosporin
- 1 week
  - If no improvement, add rifampin 600 mg/d po

Gram Negative Organism
- Ciprofloxacin 500 mg po bid (Adults only)
- If Pseudomonas and no improvement, add ceftazidime
Exit Site Infections

Purulent Discharge from Exit Site

Gram’s Stain, Culture

Gram Positive Organism

Penicillinase Resistant PCN po or 1st generation cephalosporin po

1 week, no improvement
add 1 week of rifampin 600 mg/d po
Exit Site Infections

Purulent Discharge from Exit Site

Gram’s Stain, Culture

Gram Negative Organism

Ciprofloxacin 250-500 mg po BID or ofloxacin 400 mg po 1st day, then 200 mg po QD;

Stagger doses to avoid chelation reactions
Intraperitoneal Drug Therapy

• Heparin
  – CAPD patients can secrete fibrinogen into the peritoneal cavity resulting in fibrin formation
  – Can lead to:
    • Intraperitoneal adhesions
    • Outflow obstruction
  – Heparin 500 – 1000 u/L is added to the dialysis solution
    • Not absorbed thru peritoneum
    • Minimal systemic anticoagulation effects
Intraperitoneal Drug Therapy

• Regular insulin is used for IP administration
• Insulin IP is 2-3 x insulin SQ
  – Incomplete absorption of insulin IP (F = 25-30%)
  – Adsorption of insulin to the PVC bag and administration set
• Advantages:
  – Convenient
  – Avoids SQ injection site complications
AVOID

• *Certain* oral hypoglycemics
  – Glyburide (DiaBeta, Micronase, Glynase)
  – Tolazamide (Tolinase)
  – Acetohehexamide (Dymelor)
  – Chlorpropamide (Diabinese)
  – Why?
    – Excreted to a large extent in urine
    – Half-life may be greatly prolonged
    – Use may result in severe & prolonged hypoglycemia
Slow Continuous Renal Replacement Therapy (CRRT)
From Arteriovenous to Venovenous

• Arteriovenous
  – A systolic BP of 50-70 mm Hg is necessary to produce ultrafiltrate
  – Efficiency of hemofiltration depends on arterial pressure...low or unstable in ICU patients
  – Low blood flow - frequent clotting
  – Leak in the circuit - rapid blood loss

• Venovenous
  – Made possible by development of double lumen catheters and blood pumps
Vascular Access

- Example of PermCath
- Percutaneously inserted into the right internal jugular vein
  - “right IJ”
Vascular Access

- Example of double lumen catheter
- Inserted into left femoral vein

Fig. 8. Double polyurethane catheter (25 cm length) inserted in the left femoral vein.
Slow Continuous Ultrafiltration (SCUF)

- Arteriovenous or venovenous
- Highly permeable filter
- Ultrafiltrate not replaced
- Used only for fluid control/removal
Hemofilter
Prisma
Continuous Hemofiltration (CVVH or CAVH)

- Features
- Arteriovenous or venovenous
- Highly permeable filter
- Ultrafiltration > weight/volume loss & replacement fluid is needed
- Solute CL is by convection
Continuous Hemodiafiltration (CVVHDF or CAVHDF)

- **Features**
- Arteriovenous or venovenous
- Highly permeable filter
- **Includes dialysate**
- Ultrafiltration > weight/volume loss & replacement fluid is needed
- Solute CL is by convection & diffusion
CVVHDF
HD vs CVVHD

- **HD**
  - Low permeable filter
  - Efficiency is limited to small molecules
    - MW 500–2000 daltons
  - No replacement fluid

- **CVVHDF**
  - Highly permeable filter
  - Efficiency is extended to larger molecules
    - MW 20000 daltons
  - Replacement fluid
  - Sterile dialysate
CVVH or CVVHDF Orders

- Blood flow rate
- 150 ml/min
- Range 100-180 ml/min
CVVH or CVVHDF Orders

- **Bicarbonate solution**
  - 500 ml bottle of NaHCO₃ (300 mEq/500 ml)
  - Starting rate: 50 ml/hr
  - Titrate to maintain serum HCO₃ between 18 – 28 mEq/L and pH 7.32-7.44
CVVH or CVVHDF Orders

• Replacement fluid
  – 3 L bags
  – NaCl 110 mEq/L (careful D5W). Add:
    • KCl 2 - 4 mEq/L
    • MgSO₄ 2 mEq/L
    • CaCl₂ 2 mEq/L per iCa for heparin anticoag only
  – Rate 0-2000 ml/hr
  – Eg. Adjust to maintain a NET LOSS of _____ ml/hr (0-100 ml/hr)
  – If the patient’s BP declines eg. MAP < 60, set at zero balance
Fluid Removal Rate

• Fluid removal rate
  – \((\text{HCO}_3^+) + (\text{Replacement fluid & IV’s}) + \text{(net loss)}\)

• Example
  – Initial HCO\(_3\) rate = 100 ml/hr
  – Replacement fluid rate = 1000 ml/hr
  – All IV’s = 300 ml/hr
  – Net loss = 100 ml/hr
    • “net negative balance” 100 ml/hr

• Fluid removal rate = 100 + 1000 + 300 + 100 ml/hr

• = 1500 ml/hr = output
• Input = 100 + 1000 + 300 ml/hr = 1400 ml/hr
CVVH or CVVHDF Orders

- Heparin
- Minimum infusion rate: 500 U/hr for PTT 50 – 80
- Or “if ACT < 170 increase rate 5%. If ACT > 200 decrease rate 5%.”
CVVHDF Orders

- Dialysate
- 5 L bags with:
  - _____ KCl
- Rate: 500-2500 ml/hr
CVVH & CVVHDF

• Labs
  – Before procedure: Tx panel, ionized Ca, PO₄, Mg, PT, PTT, post filter ACT, CBC
  – Na, K, HCO₃, Ca, PO₄, Mg, PT, PTT/ACT, q 4 h until stable, then q 8-12 h or after any event

• Adjustments:
  – Mg: 1.8–2.4 mEq/L w/ 1-2 g MgSO₄ over 30-60 min.
  – Ionized Ca: 1.12-1.25 mEq/L w/ 1 amp CaCl₂ (1g) over 60 min.
  – PO₄: 2.2-4.6 mEq/L with NaPO₄ at 5 mM per hr (15 or 20 mM)
  – K: 4.0-4.8 with central KCl
Drug Removal by CVVH/DF Estimation

• Sieving Coefficient (SC)
  – Quantitative index of a drug’s ability to traverse the hemofilter membrane
  – Ratio of the drug concentration in the ultrafiltrate ($C_{uf}$) to the drug concentration in the arterial line
  – Similar to the fraction unbound to plasma proteins ($f_{up}$) for many drugs
Evidence

• Phenytoin
  – Ther Drug Monit 1994;16:53

• N=2 ICU patients
  – 36 yo, phenytoin 100 mg IV q 8 h
  – 17 yo, phenytoin 300 mg IV qd

• On CAVH
  – Polysulfone hollow fiber filter
  – Replacement fluid = LR or TPN
  – UFR 100 – 200 ml/hr
## Results

<table>
<thead>
<tr>
<th>Pt.</th>
<th>[Phenytoin] mg/L</th>
<th>[Free Phenytoin] mg/L</th>
<th>% Free Phenytoin</th>
<th>Total Protein g/L</th>
<th>Serum Albumin g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial</td>
<td>Ultra-filtrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11.3</td>
<td>4.2</td>
<td></td>
<td>4.6</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>9.9</td>
<td>4.0</td>
<td></td>
<td>4.6</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>3.4</td>
<td>3.3</td>
<td>44</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>6.3</td>
<td>1.7</td>
<td>1.8</td>
<td>28.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Drug Removal by CVVH/DF Estimation

- Clearance by convection $CL_{\text{convection}}$
  - $CL_{\text{convection}} = Q_f \times SC$, where $Q_f =$ ultrafiltration rate
  - OR $CL_{\text{convection}} = Q_f \times f_{up}$

- If CVVHDF:
  - $CL_{\text{diffusion}} = Q_{\text{dialysis}} \times f_{up}$, where $Q_{\text{dialysis}} =$ dialysate flow rate

- $CL_{\text{CVVHDF}} = CL_{\text{convection}} + CL_{\text{diffusion}}$
Drug Removal by CVVH/DF Estimation

- $\text{CL}_{\text{total}} = \text{CL}_{\text{CVVHDF}} + \text{CL}_{\text{residual}}$
  - $\text{CL}_{\text{residual}}$ is from published literature
- Recall, $\text{Dose/tau} = (C_{pss})(\text{CL})/\text{S F}$
Published Guidelines

• Can serve as a point of reference when drug concentration monitoring is not available

• For continuous renal replacement therapy (CRRT), clearances achieved simulate GFR in the range of 10 – 50 ml/min

• Therefore, when specific drug information is unavailable, drug doses may be initiated as if the patient had a GFR of 10 – 50 ml/min
Example

• Ultrafiltration rate (UFR)
  – URF 2000 ml/hr x 60 min/hr = 33 ml/min
  – UFR 1800 ml/hr x 60 min/hr = 30 ml/min
Imipenem-Cilastatin Removal During CVVH

- **N=12 ICU patients**
- **CVVH:**
  - Polyacrylonitrile hemofilter (AN69 HF)
  - Blood flow rate: 150 – 170 ml/min
  - Replacement fluids: 1000 ml/hr
  - UFR: 1200-1200 ml/hr
  - Balance: 100-200 ml/hr
- **Imipenem-cilastatin 500 mg IV q 6-8 h**
  - Ref: AAC 1997;41(12)2640-5
Imipenem-Cilastatin Removal During CVVH

- $\text{CL}_{\text{CVVH}} = \text{CL}_{\text{convection}} = Q_f \times SC$
  
- $\text{CL}_{\text{CVVH}} = 1100 \text{ ml/hr} \times 1.2 = 1320 \text{ ml/hr}$ or 22 ml/min
  
  - Reported $\text{CL}_{\text{CVVH}} = 19.7 \pm 5.7 \text{ ml/min}$

- Determined $\text{CL}_{\text{total}} = \text{Dose}/\text{AUC}_{0-\text{inf}} = 122.2 \pm 28.6 \text{ ml/min} = 7.3 \text{ L/hr}$
  
  - $\text{AUC}_{0-\text{inf}}$ determined from serial samples thru arterial line
Clearance

• Recall,

• $CL_{total} = CL_{Renal} + CL_{nonrenal}$

• $CL_{total} = CL_{CVVHDF} + CL_{nonrenal}$
  – $CL_{nonrenal}$ can be calculated
    • $CL_{total} - CL_{CVVHDF}$
  
  – $\frac{CL_{nonrenal}}{ml/min} = 122.2 - 22.0 \text{ ml/min} = 100.2 \text{ ml/min}$
  
    • Represents metabolism or nonspecific plasma hydrolysis
Imipenem Dose During CVVH

• Recall, Dose/tau = (C_{ssaver})(CL)/S F
• Dose/tau = (12 mg/L)(7.3 L/hr) = 87.6 mg/hr
  – Target imipenem C_{ssaver} was chosen to ensure that the plasma concentration remained above the MIC_{90} for intermediately resistant \textit{Pseudomonas aeruginosa} for the majority of the dosing interval
• Daily dose = 87.6 mg/hr x 24 hrs = 2100 mg
• Typically dosed q 6 h, therefore recommended dose during CVVH = 500 mg IV q 6h.
  – Corresponds to the recommended dose for GFR 10 – 50 ml/min
PK and PD of Imipenem-Cilastatin Removal During CRRT

- N=12 ICU patients
  - n=6 CVVH; n=6CVVHDF
- CRRT:
  - Polyacrylonitrile hemofilter (AN69 HF)
  - Blood flow rate: 150 – 200 ml/min
  - Replacement fluids: 1000 ml/hr
  - UFR: 19 ml/min
  - CVVHD dialysate rate 973 ml/hr
- Imipenem-cilastatin 1 – 2 g per day IV
  - Ref: AAC 2005;49(6)2421-8
Similar PK results as in previous study
Imipenem PD

- Time above the MIC (T > MIC) should be at least 40 – 50% of the dosing interval for maximum killing effects.
- Imipenem usually displays MICs ≤ 2 mcg/ml against most Gm (-) aerobic pathogens.

\[
T > MIC = \ln \frac{C_{\text{max,free}}}{MIC + k} \\
\%
T > MIC = \frac{T > MIC}{\tau \text{au}} \times 100
\]
## Median % (Range) T > MIC

<table>
<thead>
<tr>
<th>MIC</th>
<th>CVVH n = 2</th>
<th>CVVHDF n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC ≤ 1 mcg/mL</td>
<td>(100)</td>
<td>74 (68-100)</td>
</tr>
<tr>
<td>MIC = 2 mcg/mL</td>
<td>(78-92)</td>
<td>56 (51-93)</td>
</tr>
<tr>
<td>MIC = 4 mcg/mL</td>
<td>(53-58)</td>
<td>38 (34-54)</td>
</tr>
<tr>
<td>MIC = 8 mcg/mL</td>
<td>(24-28)</td>
<td>16 (15-19)</td>
</tr>
</tbody>
</table>

Time above the MIC (T > MIC) should be at least 40 – 50% of the dosing interval.
### Median % (Range) T > MIC

<table>
<thead>
<tr>
<th>MIC</th>
<th>CVVH n = 3</th>
<th>CVVHDF n = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC ≤ 1 mcg/mL</td>
<td>62 (46-100)</td>
<td>64 (56-100)</td>
</tr>
<tr>
<td>MIC = 2 mcg/mL</td>
<td>46 (35-92)</td>
<td>47 (40-99)</td>
</tr>
<tr>
<td>MIC = 4 mcg/mL</td>
<td>35 (31-53)</td>
<td>29 (26-53)</td>
</tr>
<tr>
<td>MIC = 8 mcg/mL</td>
<td>14 (14-22)</td>
<td>11 (6-12)</td>
</tr>
</tbody>
</table>

Time above the MIC (T > MIC) should be at least 40 – 50% of the dosing interval

**Imipenem 0.5 g IV Q 12 h**
Conclusions

• Imipenem should be dosed at 1.0 to 1.5 g/day due to susceptible pathogens with a MIC ≤ 2 mcg/mL

• Imipenem 2.0 g/day appears to be required for pathogens such as *Pseudomonas aeruginosa* with potentially higher MICs (4-8 mcg/mL) or for empiric therapy of serious nosocomial infections in patients undergoing CRRT
CVVH vs CVVHDF

- What is the effect of different modalities on drug clearance?
- What is the effect of increasing dialysate flow rate on drug clearance during CVVHDF?
Fluconazole Removal During CVVH/DF

- N = 6 ARF patients
- Polysulfone filter
  - (Fresenius AV400)
- Pump flow = 100 ml/min
- Day 1: CVVH
- Day 2: CVVHDF
  - Dialysate flow rate: 1L/hr
- Day 3: CVVHDF
  - Dialysate flow rate: 2 L/hr
- Fluconazole 200 mg IV qd
  - J Antimicrob Chemother 1997;40:695-700
Fluconazole Removal During CVVH/DF

<table>
<thead>
<tr>
<th>Patient</th>
<th>$CL_{CVVH}$ ml/min</th>
<th>$CL_{CVVHDF}$ ml/min Dialysate 1L/hr</th>
<th>$CL_{CVVHDF}$ ml/min Dialysate 2L/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.71</td>
<td>21.76</td>
<td>28.24</td>
</tr>
<tr>
<td>2</td>
<td>5.64</td>
<td>31.02</td>
<td>31.40</td>
</tr>
<tr>
<td>3</td>
<td>9.38</td>
<td>25.88</td>
<td>26.00</td>
</tr>
<tr>
<td>4</td>
<td>6.72</td>
<td>19.44</td>
<td>32.96</td>
</tr>
<tr>
<td>5</td>
<td>11.95</td>
<td>26.98</td>
<td>31.54</td>
</tr>
<tr>
<td>6</td>
<td>11.23</td>
<td>24.84</td>
<td>34.42</td>
</tr>
<tr>
<td>Mean±SD</td>
<td><strong>8.61 ± 2.40</strong></td>
<td><strong>24.99 ± 3.71</strong></td>
<td><strong>30.76 ± 2.84</strong></td>
</tr>
</tbody>
</table>
Fluconazole Removal During CVVH/DF

- $\text{CL}_{\text{CVVHDF}}$ significantly different ($p < 0.05$) from $\text{CL}_{\text{CVVH}}$
- Observe greater CL as dialysate flow rate is increased
- Characteristics:
  - MW 306 daltons
  - Small $V_D = 0.7$ L/kg
  - Low plasma protein binding
Cefpirome PK During CVVH

- N=8 anuric ICU patients
- CVVH:
  - High-flux polysulfone capillary hemofilter (Diafilter 30, Amicon)
  - Blood flow rate: 150ml/min
  - UFR: 47 ± 12 ml/min
  - Zero balance
  - Bicarb-based replacement fluid
- Cefpirome 2 g IV q 8 h
Cefpirome

- Semisynthetic 4\textsuperscript{th} generation cephalosporin
- Extended spectrum against gram (-) & (+) pathogens including strains resistant to 3\textsuperscript{rd} generation cephalosporins
- MW 512 daltons
- Small $V_D$
- Protein binding < 10%
- Renal elimination
Is cefpirome likely to be removed during CRRT?

Yes.
Cefpirome Pharmacodynamics

- Killing is time-dependent
  - [Drug] needs to exceed the MIC for at least 25-40% of dosing interval
  - [Drug] 4x – 8x MIC are required

- MIC$_{90}$ of cefpirome against *Enterobacteriaceae* 0.5 – 2 mcg/ml
- MIC$_{90}$ of cefpirome against GPC 1 – 2 mcg/ml
- MIC$_{90}$ of cefpirome against *P. aeruginosa* 8 mcg/ml
Cefpirome

- Plasma [cefpirome] remained above 4 mcg/ml 62% of the dosing interval
- Plasma [cefpirome] remained above 8 mcg/ml 25% of the dosing interval
- Cefpirome [trough] 3.1 ± 0.8 mg/ml
Dosing Recommendation

• Cefpirome 2 g IV q 8 h for gram (-) & (+) pathogens MIC<sub>90</sub> 0.5 – 2 mcg/ml
  – vs usual adult dose in patients with normal renal function: cefpirome 1-2 g IV q 12 h

• “Higher doses are required to cover severe infections caused by P aeruginosa.”

• Can cefpirome 2 g IV q 12 achieve the same targets for gram (-) & (+) pathogens MIC<sub>90</sub> 0.5 – 2 mcg/ml?
### Double Check

<table>
<thead>
<tr>
<th>t1/2 (h)</th>
<th>k (h⁻¹)</th>
<th>V_D (L)</th>
<th>CL (L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.36</td>
<td>0.31</td>
<td>118</td>
<td>589.1 ml/min = 35.35 L/hr</td>
</tr>
</tbody>
</table>

Mean data reported
Target

• Recall, killing is time-dependent
  – [Drug] need to exceed the MIC for at least 25-40% of dosing interval
  – [Drug] 4x – 8x MIC are required \( \text{MIC}_{90} \) of 0.5 – 2 mcg/ml for gram (-) & (+) pathogens
Short IV Infusions

\[
C_{\text{max1}} = \frac{\text{dose} / t}{V_D k} \left(1 - e^{-kt}\right) \text{OR} \frac{\text{dose} / t}{CL} \left(1 - e^{-kt}\right)
\]

\[
C_{\text{min1}} = C_{\text{max1}} e^{-k(\tau-t)}
\]

\[
C_{\text{max,ss}} = \left(\frac{\text{dose} / t}{CL} \left(1 - e^{-kt}\right)\right) \left(\frac{1}{1-e^{-k\tau}}\right)
\]

\[
C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(\tau-t)}
\]

- small \( t = t \) = infusion time
- \( \tau \) = dosing interval
Short IV Infusions

- Recall,
- dose/t = rate of drug infusion
- $1 - e^{-kt} =$ fraction of SS achieved by time $t$ OR fraction of drug lost during time $t$
- $e^{-k(\tau-t)} =$ fraction of drug remaining at end of dosing interval
- $\tau =$ time tau minus $t$
- $R_{ac} =$ accumulation factor
PK Calculations

\[ C_{\text{max}} = \frac{(dose / t)(1 - e^{-kt})}{(V_D)(k)(1 - e^{-k\tau})} \]

\[ C_{\text{max}} = \frac{(2000\text{mg} / 0.5\text{hr})(1 - e^{(-0.208hr^{-1})(0.5\text{hr})})}{(158.2\text{L})(0.208hr^{-1})(1 - e^{(-0.208hr^{-1})(12\text{hr})})} \]

\[ C_{\text{max}} = 13\text{mg} / \text{L} \]

- \( V_D \) & k determined from mean \( C_{\text{max}} \) 14.8 & \( C_{\text{min}} \) 3.1 for cefpirome 2g IV q8h
What is $C_{\text{min}}$?

$$C_{\text{min}} = C_{\text{max}} e^{(-k)(\tau - t)}$$

$$C_{\text{min}} = 13 \text{mg} / Le^{(-0.208 \text{hr}^{-1})(12-0.5\text{hr})}$$

$$C_{\text{min}} = 1.2 \text{mg} / L$$
Cefpirome C vs time

Cefpirome 2 g IV q 8: $C_{\text{max}}$ 14.8 mg/L; $C_{\text{min}}$ 3.1 mg/L
Cefpirome 2 g IV q 12h: $C_{\text{max}}$ 13 mg/L; $C_{\text{min}}$ 1.2 mg/L
Are there differences in drug clearance between filters?
Ceftriaxone

- MW 556 daltons
- $V_D = 0.16 \text{ L/kg (range 0.10-0.22 L/kg)}$
- 40% excreted unchanged
- Protein binding
  - $f_{up} \ 0.08 \ - \ 0.87$
  - concentration dependent
    - ceftriaxone $C_p \ 115 \text{ mg/L} \ -> \ f_{up} \ 0.37 \ + \ 0.20$
    - ceftriaxone $C_p \ 65 \text{ mg/L} \ -> \ f_{up} \ 0.28 \ + \ 0.18$
      - Ref: Pharmacotherapy 2000;20(6):635-642
Ceftriaxone CL by CVVH & CVVHD

- N=8 chronic HD patients
- 12-hr CVVH, CVVHD via 3 filters:
  - AN 69, Hospal Multiflow 60, CGH Medical
  - PMMA, Filtryzer B1-2.1U, Toray Industries
  - PS (Polysulfone) hemofilter, Fresenius F40
- Ceftriaxone 1 g IV over 1h
  - Ref: Pharmacotherapy 2000;20(6):635-642
Effect of Blood Flow Rate on CL

- **Constant:**
  - dialysate flow rate 33.3 ml/min
  - UFR 0 ml/min
- **Increasing blood flow rate at hourly intervals**
  - 75 ml/min
  - 125 ml/min
  - 150 ml/min
  - 250 ml/min
Effect of Blood Flow Rate on CL

• “Clearances were essentially constant at all blood flow rates for all 3 filters.”
Effect of Dialysate Flow Rate on CL

- **Constant:**
  - blood flow rate 100 ml/min
  - UFR 0 ml/min
- **Increasing dialysate flow rate at hourly intervals**
  - 8.3 ml/min
  - 16.7 ml/min
  - 25.0 ml/min
  - 33.3 ml/min
Ceftriaxone Clearance in Relation to Dialysate Flow Rate

Open: Total ceftriaxone
Solid: Unbound ceftriaxone
Slopes of Unbound Ceftriaxone and Dialysate Flow Rate

- **PMMA**
  - Slope 1.00, $r^2 = 0.901$
- **PS**
  - Slope 1.04, $r^2 = 0.953$
- **AN 69**
  - Slope 0.48, $r^2 = 0.883$
- “Analysis of slopes for total ceftriaxone were similar”.
  - Data not reported
Sieving Coefficients (SC)

- **Constant:**
  - Blood flow rate 100 ml/min
  - Dialysate flow rate 0 ml/min
- **Sieving coefficient (SC)**
  - $SC = \frac{C_{UF}}{C_{plasma}}$
  - for total & unbound ceftriaxone
### Sieving Coefficients (SC)

<table>
<thead>
<tr>
<th>Filter</th>
<th>$f_{up}$</th>
<th>SC of unbound ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS (PS, Amicon)</td>
<td>$0.16 \pm 0.07^*$</td>
<td>$0.82 \pm 0.22$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$0.60 \pm 0.39$</td>
</tr>
<tr>
<td>AN 69</td>
<td>$0.30 \pm 0.17^*$</td>
<td>$0.48 \pm 0.13^{**}$</td>
</tr>
<tr>
<td>PMMA</td>
<td>$0.27 \pm 0.12$</td>
<td>$0.86 \pm 0.33$</td>
</tr>
</tbody>
</table>

SC of total ceftriaxone was less than SC of unbound ceftriaxone for all filters (data not reported).
Sieving Coefficients (SC)

• Observed SC of unbound ceftriaxone was 2-3 fold higher than $f_{up}$
• ? Passage through the extracorporeal circuit may alter the fraction of drug available for transport across the filter membrane.
• Suggests ceftriaxone may be weakly bound to plasma proteins
Recall

- \( CL_{CVVH} = CL_{convection} \)
  - \( CL_{convection} = Q_f \times SC \), where \( Q_f = \) ultrafiltration rate
  - OR \( CL_{convection} = Q_f \times f_{up} \)

- If CVVHDF:
  - \( CL_{CVVHDF} = CL_{convection} + CL_{diffusion} \)
  - \( CL_{diffusion} = Q_{dialysis} \times f_{up} \), where \( Q_{dialysis} = \) dialysate flow rate
For Ceftriaxone SC $= f_{up}$

- Concentration dependent protein binding
- Large degree of interpatient variability in protein binding
- Therefore, cannot use a mean value of $f_{up}$ as a predictor of CVVH/DF CL
CVVHD & CVVH CL

- **Constant:**
  - Blood flow rate 100 ml/min
  - Dialysate flow rate 0 ml/min

- **UFR = 500 ml/hr (low); 1000ml/hr (high)**

- **CVVHD & CVVH CL**
  - $\text{CL} = \frac{\text{UFR} \times C_{UF}}{C_{\text{pmidpoint}}}$
  - UFR = ultrafiltration rate
  - $C_{UF} = \text{concentration in ultrafiltrate}$
  - $C_{\text{pmidpoint}} = \text{concentration in the plasma at the midpoint of the collection period (6-hours)}$
  - urea,total & unbound ceftriaxone
Convective Clearance of Unbound Ceftriaxone

Lo (500 L/hr) and Hi (1000 L/hr) UFR
No significant increase with AN69 filter
Comparison of Membranes

• Clearance of unbound ceftriaxone with all 3 filters increased when UFR was doubled from low 500 ml/hr to high 1000 ml/h.

• SC and convective CL of unbound ceftriaxone were significantly lower with the AN69 than the PS & PMMA filters at low and high UFR (p=0.0001).
  – Speculate may be due to adsorption onto filter or a repulsive interaction between the membrane surface and drug that limit membrane transport.
Urea Clearance

Recall, \( y = mx + b \)

or ceftriaxone \( \text{CL} = m[Cl_{\text{urea}}] + b \), where \( b = 0 \)
# Empiric Ceftriaxone Dosing Recommendations/Increments

<table>
<thead>
<tr>
<th>ARF no CRRT (CrCl ≤ 10 ml/min):</th>
<th>ceftriaxone 125-175 mg IV q 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVH:</td>
<td>ceftriaxone 30 mg IV q 12 h for each 0.5 L/hr UFR</td>
</tr>
<tr>
<td>CVVHD:</td>
<td>Dialysate ceftriaxone IV</td>
</tr>
<tr>
<td>PMMA &amp; PS</td>
<td>1 L/hr 80 mg IV q 12 h</td>
</tr>
<tr>
<td></td>
<td>2 L/hr 115 mg IV q 12 h</td>
</tr>
<tr>
<td>AN69</td>
<td>1-2 L/h 50 mg IV q 12 h</td>
</tr>
</tbody>
</table>
Ceftriaxone Dose Individualization

• Recall, \( \text{Cl}_{\text{total}} = \text{Cl}_{\text{renal}} + \text{Cl}_{\text{nonrenal}} \)

• Eg. PMMA
  – \( \text{Cl}_{\text{renal}} = \text{CL}=0.90[\text{Cl}_{\text{urea}}] + \text{residual renal function} \)
    • eg residual renal function GFR 20 ml/min

• \( \text{Cl}_{\text{nonrenal}} \) approximately 30 ml/min in patients with ARF longer than 7-10 days
  – \( \text{Cl}_{\text{nonrenal}} = 93 \text{ ml/min in patients with normal renal function} \)
  – \( \text{Cl}_{\text{nonrenal}} \) reduced by up to 67% in patients w/ARF of longer than 7-10 days; \( \text{Cl}_{\text{nonrenal}} \) ARF approx 32 ml/min
PK Calculations

\[ C_{\text{max}} = \frac{(dose / t)(1 - e^{-kt})}{(CL)(1 - e^{-k\tau})} \]

Solve for dose:

\[ Dose / t = \frac{(C_{\text{max}})(CL)(1 - e^{-k\tau})}{(1 - e^{-kt})(1 - e^{-k\tau})} \]

\[ C_{\text{min}} = e^{(-k)(\tau - t)} \]
Drug Prescribing in Renal Failure
Palm OS