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Vila Franca Xira Hospital

Acute kidney injury

Dosing of antibiotics

“You’re only given a little spark of madness. You mustn’t lose it.”

Robin Williams
Renal failure is common:

- 6% in multi-international study (BEST)

Mortality rate 60%

Uchino JAMA. 2005;294:813-818

Sepsis (and antibiotic therapy) is common in acute renal failure ~ 50%

Organ dysfunction and Dosing

Implications of MODS in Antibiotic PK

- GI dysfunction
  - Decreased absorption of enterally administered medication
- Tissue hypoperfusion
  - Decreased antibiotic tissue concentration
- Hepatic dysfunction
  - Decreased protein binding of highly-bound drugs
  - Decreased metabolism of lipophilic drugs
- Renal dysfunction
  - Decreased elimination of hydrophilic drugs

UNDERDOSING

OVERDOSING

Uldemollins, Chest 2011; 139:1210
Antibiotics Pharmacokinetics

**Healthy**

- **Vd**: Volume of Distribution
- **Cl**: Clearance
- **C<sub>max</sub>**: Peak Concentration
- **AUC**: Area Under the Curve
- **T>MIC**: Time above the Minimum Inhibitory Concentration

**Organ Failure**

**Sepsis**

- **Increased Vd**
- **Decreased Cl**

Gonçalves-Pereira. Crit Care 2011, 15:R206
### Recommended dosing regimens in MODS

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>PD Parameter Associated With Maximal Activity</th>
<th>LD in Patients With Increased Vd</th>
<th>MD in Acute Kidney Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Lactams</strong></td>
<td>$fT &gt; MIC$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Dose decreases preferred to increased time between intervals</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>$C_{max}/MIC$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Increased time intervals preferred to dose decreases, titrate dosing according to TDM results</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td>$AUC_{0.2}/MIC$</td>
<td>Administer high LD on day 1, as Vd will be significantly increased</td>
<td>Titrate dosing according to TDM results</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>$AUC_{0.2}/MIC$ and $C_{max}/MIC$</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction and principal organ system responsible for clearance</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
<td>$AUC_{0.2}/MIC$ and $fT &gt; MIC$</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction</td>
</tr>
</tbody>
</table>

Avoid underdosing and failure. Avoid accumulation and toxic effects.

Uldemollins, Chest 2011; 139:1210
Pharmacokinetics / Pharmacodynamics

First dose of Aminoglycosides

Gentamicin
- 7.4mg/kg. Peak target 16 mg/L
- N=32; Vd=0.41l/kg

Amikacin
- 25mg/kg. Peak target 64 mg/L
- N=74; Vd=0.41l/kg

No relationship with age, organ failure, SOFA or sepsis severity
First Dose of Antibiotics

Antibiotic
250 mg

Antibiotic
500 mg

Organ Failure
### Recommended dosing regimens

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Increased</th>
<th>Normal</th>
<th>Moderately impaired</th>
<th>Severely impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Piperacillin/tazobatam</strong></td>
<td>16/2 g q24h CI</td>
<td>4/0.5 g q6h</td>
<td>3/0.375 g q6h</td>
<td>2/0.25 g q6h</td>
</tr>
<tr>
<td><strong>Cefotaxime</strong></td>
<td>4 to 6 g q24h CI</td>
<td>2 g q6-8h</td>
<td>1 g q6-8h</td>
<td>2 g q4-6h</td>
</tr>
<tr>
<td><strong>Ceftazidime</strong></td>
<td>4 to 6 g q24h CI</td>
<td>2 g q8h</td>
<td>1 g q8-12h</td>
<td>0.5 to 1 g q24h</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td>4 to 6 g q24h CI</td>
<td>2 g q8h</td>
<td>2 g q12h</td>
<td>1 g q24h</td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>500 mg q4h</td>
<td>500 mg q6h</td>
<td>250 mg q6h</td>
<td>250 mg q12h</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>1 g q6h over 6 hours</td>
<td>500 mg q6h</td>
<td>250 mg q6h</td>
<td>250 mg q12h</td>
</tr>
<tr>
<td><strong>Ertapenem</strong></td>
<td>ND</td>
<td>1 g q24h</td>
<td>1 g q24h</td>
<td>500 mg q24h</td>
</tr>
<tr>
<td><strong>Gentamycin</strong></td>
<td>9 to 10 mg/kg q24h</td>
<td>7 mg/kg q24h</td>
<td>7 mg/kg q36-48h</td>
<td>7 mg/kg q48-96h</td>
</tr>
<tr>
<td><strong>Tobramycin</strong></td>
<td>9 to 10 mg/kg q24h</td>
<td>7 mg/kg q24h</td>
<td>7 mg/kg q36-48h</td>
<td>7 mg/kg q48-96h</td>
</tr>
<tr>
<td><strong>Amikacin</strong></td>
<td>20 mg/kg q24h</td>
<td>15 mg/kg q24h</td>
<td>15 mg/kg q36-48h</td>
<td>15 mg/kg q48-96h</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>600 mg q12h</td>
<td>400 mg q12h</td>
<td>400 mg q12h</td>
<td>400 mg q24h</td>
</tr>
<tr>
<td><strong>Levofloxacin</strong></td>
<td>500 mg q12h</td>
<td>750 mg q24h</td>
<td>500 mg q24h</td>
<td>500 mg q48h</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>30 mg/kg q24h CI</td>
<td>500 mg q6h</td>
<td>500 mg q12h</td>
<td>500 mg q24-72h</td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
<td>ND</td>
<td>6 mg/kg q24h</td>
<td>6 mg/kg q24h</td>
<td>6 mg/kg q48h</td>
</tr>
</tbody>
</table>

Pea Crit Care 2009; 13. 214
Accumulation and Toxicity

**Ceftriaxone 2 g/d**

**Accumulation in renal failure**

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>&gt;50 mL/min</th>
<th>&lt;50 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>19.5 μg/mL</td>
<td>46.5 μg/mL</td>
</tr>
<tr>
<td>Day 7</td>
<td>38.5 μg/mL</td>
<td>125 μg/mL</td>
</tr>
</tbody>
</table>

Heinemeyer Int Care Med 1990; 16; 448

**Betalactamin-induced central nervous side effects** include confusion, disturbances of behaviour, hallucinations, asterixis, myoclonic jerks, and generalised convulsive or nonconvulsive seizures. Those are probably underreported but may contribute to morbidity and mortality.

Chatellier Int Care Med 2002; 28. 214
Renal Replacement Therapy

**Hemofiltration**
- **Convection** based on a pressure gradient
- ‘Transmembrane pressure gradient’
  - Difference between plasma oncotic pressure and hydrostatic pressure

**Dialysis**
- **Diffusion** based on a concentration gradient
Determinants of Drug Removal by CRRT

- **Hemofiltration**
  - **Convection** based on a pressure gradient

- **Dialysis**
  - **Diffusion** based on a concentration gradient

- Pressure
- Sieving coefficient
- Flow and UF rate
- Blood flow
- Dialysate
- Time

\[ QB = 150 \text{ ml/min} \quad \text{and} \quad QD = 1000-2500 \text{ ml/h} \]
The capacity of a drug to pass through the hemofilter membrane is given by the Sieving Coefficient (SC):

$$SC = \frac{C_{uf}}{C_p}$$

- **Protein binding**: Only unbound drug passes through the filter.
- **Protein binding changes in critical illness**
- **Drug membrane interactions**: Not clinically relevant.
- **Adsorption of proteins and blood onto filter**: Related to filter age, decreased efficiency of filter.
### Sieving Coefficient (SC)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Predicted</th>
<th>Measured</th>
<th>Condition</th>
<th>Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0.95</td>
<td>0.88</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>0.10</td>
<td>0.40</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.80</td>
<td>0.69</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.62</td>
<td>0.51</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>0.30</td>
<td>0.30</td>
<td>in vitro</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.90</td>
<td>0.90</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.10</td>
<td>0.71</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.66</td>
<td>0.59</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.40</td>
<td>0.98</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.30</td>
<td>0.37</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.95</td>
<td>0.81</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.80</td>
<td>0.86</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>0.68</td>
<td>0.68</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>N-acetylprocainamide</td>
<td>0.90</td>
<td>0.92</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>0.20</td>
<td>0.54</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.05</td>
<td>0.02</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
</tbody>
</table>

### Sieving Coefficient

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Predicted</th>
<th>Measured</th>
<th>Condition</th>
<th>Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>0.95</td>
<td>0.78</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td></td>
<td>0.90</td>
<td></td>
<td>in vitro</td>
<td>PS(^a)</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td></td>
<td>in vitro</td>
<td>PS(^b)</td>
</tr>
<tr>
<td></td>
<td>0.59</td>
<td></td>
<td>in vitro</td>
<td>AN69(^c)</td>
</tr>
<tr>
<td></td>
<td>0.76</td>
<td></td>
<td>in vitro</td>
<td>PA(^d)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.90</td>
<td>0.76</td>
<td>in vivo</td>
<td>PS(^a)</td>
</tr>
<tr>
<td></td>
<td>0.60</td>
<td></td>
<td>in vitro</td>
<td>PS(^a)</td>
</tr>
<tr>
<td></td>
<td>0.71</td>
<td></td>
<td>in vitro</td>
<td>PS(^b)</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td></td>
<td>in vitro</td>
<td>AN69(^c)</td>
</tr>
<tr>
<td></td>
<td>0.58</td>
<td></td>
<td>in vitro</td>
<td>PA(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Amicon diafilter (polysulfone)
\(^b\) Renal System (polysulfone)
\(^c\) Hospal (AN69)
\(^d\) Gambro (polyamide)
Determinants of Drug Removal by CRRT

Pore Size

<table>
<thead>
<tr>
<th>Filter material</th>
<th>PAN</th>
<th>Polyamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpirome Sieving coefficient</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Ceftriaxone**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sieving coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kroh</td>
<td>0.69</td>
</tr>
<tr>
<td>Matzka</td>
<td>0.48 - AN69</td>
</tr>
<tr>
<td></td>
<td>0.82 - PS</td>
</tr>
<tr>
<td></td>
<td>0.86 - PMMA</td>
</tr>
</tbody>
</table>

Matzka *Pharmacotherapy* 2000 20:635

Phillips *J Clin Pharm Ther* 2002; 23: 353
Determinants of Antibiotic Clearance

- Ultrafiltration rate $R^2 = 0.89$
- Membrane area $R^2 = 0.3$
- Blood flow $R^2 = 0.18$

Approach to Dose during CRRT

Scarce information in patients with sepsis/shock and RRT

A clinical update from Kidney Disease: Improving Global Outcomes

- **Aggressive Loading Dose** (up to 25-50% greater than normal)
  
  Vd is usually significantly increased in acute kidney injury

- **Maintenance dose**: Initiate at normal (or near-normal) dosage regimens for 24-48h
  
  Need to take into account nonrenal clearance

- **Therapeutic drug monitoring** whenever possible
  
  Check for eventual toxic effects

Kidney International 2011;80:1122-37
Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy.

Conclusions: In septic patients receiving CRRT, recommended doses of β-lactams for Pseudomonas aeruginosa are adequate for MEM but not for TZP, FEP and CAZ; for these latter drugs, higher doses and/or extended infusions should be used to optimise serum concentrations.

Accumulation after the first 48h of therapy may not be uncommon.
Approach to Dose during CRRT

Maintenance dose

CRRT

- **Method 1**: Dose as if the CrCl ~ 20-50 ml/min

- **Method 2**: Divide hourly ultrafiltrate rate by 60 to get estimated CrCl
  - eg, 3000 ml/hour divided by 60 = 50 ml/min

SLEDD (Sustained low efficient daily dialysis)

- **Method 1**
  - If SLEDD lasts for 6-12 hours/day: dose for CRRT, namely an estimated CrCl ~10-50 ml/min
  - Antibiotics dosed every 24 hours: give after SLEDD daily
  - Antibiotics dosed every 12 hours: give after SLEDD and 12 hours later
    
    Clin Inf Dis 2009;433-7

- **Method 2**
  - For blood flow rate 200 ml/min and dialysate flow rate 100 ml/min, dose antibiotics for estimated CrCl 60 ml/min while on SLEDD and 10 ml/min while off SLEDD
    
    Crit Care Med 2011;39:560-70
Dose during intermittent hemodialysis

Aminoglycosides

Conclusions: In clinical situations where gentamicin is used as the primary therapy in a patient receiving hemodialysis with a CAHP hemodialyzer, conventional doses after each dialysis session are not as efficient at achieving treatment targets as predialysis dosing with larger doses.


Considerer TDM and PK calculation. Enlarge intervals and dose to ensure adequate peak concentration and low troughs.
Dose during intermittent hemodialysis

Beta-Lactams

Time –dependent antibiotics

Continuous infusion? (easy to dose)

Initial loading dose

Reload (80%)  Reload (80%)

Days

Dialysis  Dialysis

Concentration

MIC

Bugge Best Practice & Research, 2004; 18:175-87
Approach to Dose during CRRT

1. **Loading dose** = desired concentration (table 1) \( \times \) Vd (table 3)

2. Calculate CRRT clearance based on mode of CRRT, formulae in text and values from table 3

3. **Total clearance** (\( C_{\text{tot}} \)) = calculated CRRT clearance + non-CRRT clearance

4. **Pharmacokinetic target?**
   - \( C_{\text{max}} : \text{MIC} \) and \( \text{AUC}_{24} : \text{MIC} \)
   - **Time above threshold concentration**
   - **C_{\text{max}} : \text{MIC} \) ratio

5. **Calculate target mean concentration** = target \( \text{AUC}_{24} / 24 \)

6. **Calculate dosing interval** = dose / [(Cp \( \times \) \( C_{\text{tot}} \))]

7. Repeat loading dose at calculated dosing interval

8. **Calculate half-life** = \( 0.693 \times \text{Vd} / C_{\text{tot}} \)

9. **Calculate time to reach target trough concentration**

10. **Calculate elimination rate** = concentration \( \times \) \( C_{\text{tot}} \)

11. **Maintenance infusion rate** = elimination rate

12. Repeat loading dose at calculated time

“What’s most depressing is the realization that everything we believe will be disproved in a few years.”

Facing with the choice between changing one’s mind and proving there is no need to do so, almost everyone gets busy on the proof.

John Kenneth Galbraith