Antimicrobial Pharmacokinetics/dynamics
Bedside Applications in the Critically Ill

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Treatment of ICU patients with antibiotics from a clinical perspective

Bacterial infection

Best antibiotic

Optimum effect

Bacterial eradication & clinical efficacy

Avoid toxicity & adverse effects
Inappropriate therapy and VAP mortality

Celis R Chest. 1988 Feb;93(2):318-24
Kollef MH Chest. 1998 Feb;113(2):412-20
Timing of adequate antibiotics in septic shock

Kumar. Crit Care Med 2006;34:1589-1596
Antibiotic dosing strategies in renal failure in ICU

- Underdosing
- Toxicity
- Resistance
- Severe infections
- Reduced elimination
- Immunocompromised host
- Nosocomial pathogens
- CRRT
- Clinical data
Antibiotics, PK in wards and ICU

**Hydrophilic antibiotics**
- Low Vd
- Predominant renal Cl
- Low intracellular penetration

**Lipophilic antibiotics**
- High Vd
- Predominant hepatic Cl
- Good intracellular penetration

**General PK**
- Beta-lactams
- Aminoglycosides
- Glycopeptides
- Linezolid
- Colistin

**Altered ICU PK**
- Vd largely unchanged
- Cl higher or lower dependent on renal function

**Examples**
- Fluoroquinolones
- Macrolides
- Lincoamides
- Tigecycline
Sepsis

Increased Cardiac Output
- Increased CI
  - Low plasma concentrations

Leaky Capillaries &/or altered protein binding
- Increased Vd
  - Normal plasma concentrations

Normal organ function
- Unchanged Vd
  - Normal plasma concentrations

End Organ Dysfunction (e.g. renal or hepatic)
- Decreased CI
  - High plasma concentrations

Roberts. Crit Care Med;37:840-851
Antibiotics changes in Half-life

- Increased renal perfusion
- Decreased renal perfusion
- Renal failure
- Capillary leakage

- Gold-standard: creatinine clearance (2-hours CL?)

- Hypalbuminemia
  - (e.g. ceftriaxone 95% albumin bound in normal subjects)

\[
T_{1/2} = \frac{0.693 \times Vd}{Cl}
\]

Roberts. Crit Care Med;37:840-851
Continuous Renal Replacement Therapy

SCUF  CVVH  CVVHD  CVVHDF
Convective Elimination during CVVH

Sieving Coefficient (SC)

\[ \text{SC} = \frac{[\text{UF}]}{[\text{Blood}]} \]

\[ \text{Cl}_{\text{CVVH}} = \text{SC} \times \frac{Q_{\text{UF}}}{Q} \]
Basic principles

Extracorporeal clearance ($Cl_{EC}$) is usually considered clinically significant only if its contribution to total body clearance exceeds 25 - 30%.

\[
Fr_{EC} = \frac{Cl_{EC}}{Cl_{EC} + Cl_{R} + Cl_{NR}}
\]

$Fr_{EC} = \text{fractional extracorporeal clearance}$

Not relevant for drugs with high non-renal clearance.

Only drug not bound to plasma proteins can be removed by extracorporeal procedures (unbound protein of a drug $Fup$)

Schetz. Curr Opin crit Care 2007;13:645-51
Loading dose

- Mainly depends on Vd, not elimination
- Reflection of volume to dissolve drug
- No adjustment in renal failure or CVVH

- Vd affected by:
  - Total body water
  - Tissue perfusion
  - Protein binding
  - Lipid solubility
  - pH gradients
  - Active transport mechanisms

- Increased loading dose may be required in critically ill
Efficacy and Pharmacodynamics

- Poor activity
- Efficacy
- Pharmacodynamics
- Time after taking drug
- Drug level in blood
- Unacceptable toxicity
- T_max
- Peak
- Peak
- C_max
- C_min
- MIC
- AUC
- IC_90
- IC_50
- Poor activity
Pharmacodynamic Indices predictive for efficacy

<table>
<thead>
<tr>
<th>T &gt; MIC</th>
<th>Cmax / MIC</th>
<th>AUC_{0-24} / MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-dependent</td>
<td>Concentration-dependent</td>
<td>Concentration-dependent with time-dependent</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Fluoroquinolones</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Metronidazole</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Monobactams</td>
<td>Daptomycin</td>
<td>Quinupristin</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Lincoamides</td>
<td>Glycopeptides</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Tetracyclines</td>
<td></td>
</tr>
</tbody>
</table>
Use of ciprofloxacin in the critical care setting

- Frequently used in critical care setting

- Especially in patients with renal failure (relative aminoglycoside contra-indication)

- Used for gram-negative infections with coverage of *P. aeruginosa* infections

- MIC levels for gram-negative pathogens can vary markedly

- Dosages of 400 mg bid IV are recommended for severe infections
Ciprofloxacin serum concentrations after single bolus IV

Tmax
Cmax
C > MIC
MIC
AUC

Quinolones: AUC/MIC > 125

- AUC above MIC
- Cmax/MIC (>10)
- AUC24/MIC
- Ciprofloxacin: 100-125

Volume of distribution (Vd) of ciprofloxacin 400 mg bid IV in 32 critically ill patients

AUC 1-24 ciprofloxacin 2 x 400 mg IV in 32 critically ill
AUC/MIC > 100 for different MIC levels

Pseudomonas aeruginosa isolates

Risk subtherapeutic dosing with 400 mg bid

Eucast wild type MIC distribution for ciprofloxacin
Simulated fractional attainment of $\text{AUC}_{1-24}/\text{MIC}$ ratio of 125 at MIC 0.25, 0.5, 1.0 and 2.0 mg/l for ciprofloxacin dosages ranging from 800-3200 mg/day based on ICU patient population pharmacokinetics obtained at 800 mg/day.
β-lactam Pk/Pd

Time above MIC
- How long?
- For all bacteria?
- For all β-lactams?
- Influence pharmacokinetics?
β-lactam static effects: streptococci

Severe infection immunocompromised host

> 20% static

> 60% maximum effect

$R^2 = 89\%$

Antimicrob Agents Chemother 2008;52:3492-6
\( \beta \)-lactam specific pharmacodynamics: \( T > \text{MIC} \)
More antibiotic specific: $T > MIC$ for static effect

<table>
<thead>
<tr>
<th>T&gt;MIC static effect</th>
<th>Enterobacteriaciae % $T &gt; MIC$</th>
<th>S. Pneumoniae % $T &gt; MIC$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxon</td>
<td>38 (34-42)</td>
<td>39 (37-41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38 (36-40)</td>
<td>38 (36-40)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>36 (27-42)</td>
<td>39 (35-42)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>22 (18-28)</td>
<td>-</td>
</tr>
<tr>
<td>Imipenem</td>
<td>24 (17-28)</td>
<td>-</td>
</tr>
</tbody>
</table>

Ways to prolong duration of β-lactam concentrations over MIC

1. Use another drug (e.g., probenecid) that interferes with its elimination.
2. Dose frequently.
3. Increase the dose of the antibiotic.
4. Replace it with another therapeutically equivalent antibiotic with a longer serum half-life ($T_{1/2}$).
5. Administer it by constant infusion.
Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy

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Department of Intensive Care, 1Department of Pulmonology, 2Department of Microbiology and 3Department of Pharmacy, Gelderse Vallei Hospital, Ede, and 4Department of Intensive Care, VU Medical Centre, Amsterdam, the Netherlands

Randomised, prospective, open single centre study in 93 COPD patients

suspected or proven pulmonary infection: cefotaxime continuous infusion: 1 gr loading dose iv, 2 gr/24 hr vs. intermittent infusion: 3 x 1 gr = equivalent

More optimal drug levels at the end of dosing interval during continuous infusion
Pharmacokinetics of cefotaxime in 44 ICU patients

cefotaxime continuous infusion: 1 gr loading dose iv, 2 gr/24 hr vs. intermittent infusion: 3 x 1 gr = equivalent in T > MIC although 1 gram lower daily dose

ARH van Zanten et al, submitted for publication
Systematic review on clinical benefits of continuous administration of beta-lactan antibiotics

- Systematic review 14 RCTs (from 59 studies)
- No difference in clinical cure rate
- No difference in mortality
- All studies except one used higher dosages in the bolus group potentially favouring this treatment arm

- The limited data available suggest that CI leads to the same clinical results as higher dosed bolus administration in hospitalized patients

The jury is still out on continuous infusion of beta-lactam antibiotics in critically ill patients

Advantages

- Lower drug acquisition costs
- Reduction of work load
- TDM more easy

Disadvantages

- Adequate drug levels later (loading dose)
- Stability of the antibiotic
- High MIC, all drug levels subtherapeutic

A well-designed large prospective study on potential advantages of continuous administration of beta-lactam antibiotics in ICU patients is warranted

Van Zanten ARH. Crit Care Med 2009; 37:2137-2138
## Total costs of intravenous antibiotic administration using different methods of administration

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time required (SD) (min:s)</th>
<th>Hourly wages (€)</th>
<th>Time costs (€)</th>
<th>Materials costs (€)</th>
<th>Total costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumetric pump</td>
<td>5:04 (2:29)</td>
<td>21.90</td>
<td>01.85</td>
<td>02.06</td>
<td>03.91</td>
</tr>
<tr>
<td>Syringe pump</td>
<td>4:56 (2:03)</td>
<td>21.58</td>
<td>01.78</td>
<td>01.45</td>
<td>03.23</td>
</tr>
<tr>
<td>Bolus injection</td>
<td>9:21 (2:16)</td>
<td>74.09</td>
<td>11.59</td>
<td>00.10</td>
<td>11.69</td>
</tr>
<tr>
<td>Piggyback infusion</td>
<td>5:51 (3:33)</td>
<td>19.75</td>
<td>01.93</td>
<td>03.47</td>
<td>05.40</td>
</tr>
<tr>
<td>Insertion of IV catheter</td>
<td>10:15 (6:31)</td>
<td>23.51</td>
<td>04.02</td>
<td>04.30</td>
<td>08.32</td>
</tr>
<tr>
<td>Removal of IV catheter</td>
<td>02:22 (0:36)</td>
<td>19.41</td>
<td>00.74</td>
<td>01.00</td>
<td>01.74</td>
</tr>
</tbody>
</table>

Importance of nondrug costs of intravenous antibiotic therapy.
Daily costs of six antibiotics intravenously administered by syringe pump

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose (mg)</th>
<th>Dosages (n)</th>
<th>Drug costs (€) (A)</th>
<th>Average time (min:s)</th>
<th>Staff costs (€) (B)</th>
<th>Material costs (€) (C)</th>
<th>Administration costs (€) (B+C)</th>
<th>Total daily costs (€) (A+B+C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>1000 / 200</td>
<td>3</td>
<td>07.35</td>
<td>12:21</td>
<td>03.99</td>
<td>04.35</td>
<td>08.34</td>
<td>15.69</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1000</td>
<td>4</td>
<td>49.40</td>
<td>18:48</td>
<td>06.08</td>
<td>05.80</td>
<td>11.88</td>
<td>61.28</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1000</td>
<td>4</td>
<td>54.44</td>
<td>36:44</td>
<td>11.88</td>
<td>05.80</td>
<td>17.68</td>
<td>72.12</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>320</td>
<td>1</td>
<td>20.34</td>
<td>03:39</td>
<td>01.18</td>
<td>01.45</td>
<td>02.63</td>
<td>22.97*</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>2250</td>
<td>3</td>
<td>43.14</td>
<td>16:31</td>
<td>05.40</td>
<td>04.35</td>
<td>09.75</td>
<td>52.89</td>
</tr>
</tbody>
</table>

Data presented are the medication costs, the time expenditure required, the staff wage and the disposable material costs for each of the antibiotics per day administrated via syringe pump. The figures quoted refer to the total time for preparation and administration of each medication per day, averaged over wards and indications studied. Costs are based on list prices provided by Dutch health care authorities. *If therapeutic drug monitoring costs for gentamicin based on 24-hourly intervals would be included, the total costs would be €58.97 per day.
The jury is still out on continuous infusion of beta-lactam antibiotics in critically ill patients

Advantages

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Van Zanten ARH. Crit Care Med 2009; 37:2137-2138
How to dose in renal failure and CVVH?

Creatinine clearance

- Risk of overdosing in drugs with tubular excretion and underdosing for drugs with tubular reabsorption (e.g. fuconazole)
- Estimations of poor quality

Normal Dose (anuric) => Dose clearance and $Cl_{CVVH}$

Anuric Dose => adjustment using maintenance dose multiplication factor

$$Dose_{CVVH} = \frac{Dose_{normal} \times Cl_{nonrenal} + Cl_{CVVH}}{Cl_{normal}}$$

$$MDMF = \frac{1}{1 - Fr_{CVVH}}$$
**Table 2** Pharmacokinetic data of antibiotics for 70 kg patient receiving CVVH 35 ml/kg per hour

<table>
<thead>
<tr>
<th>Drug</th>
<th>PB %</th>
<th>$V_d$ (l/kg)</th>
<th>$C_{l_{\text{total}}}$ (ml/min)</th>
<th>$F_{R}$ (%)</th>
<th>$C_{l_{\text{NR}}}$ (ml/min)</th>
<th>$C_{l_{\text{CVVH}}}$ (ml/min)</th>
<th>$F_{R_{CVVH}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>15</td>
<td>0.69</td>
<td>405</td>
<td>75</td>
<td>101</td>
<td>35</td>
<td>0.26</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt;10</td>
<td>0.27</td>
<td>91</td>
<td>98</td>
<td>2</td>
<td>39</td>
<td>0.95</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>&gt;90</td>
<td>0.76</td>
<td>35</td>
<td>2.5</td>
<td>31</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>18</td>
<td>0.21</td>
<td>180</td>
<td>86</td>
<td>25</td>
<td>34</td>
<td>0.57</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>36</td>
<td>0.23</td>
<td>260</td>
<td>50</td>
<td>130</td>
<td>26</td>
<td>0.17</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>21</td>
<td>0.23</td>
<td>125</td>
<td>84</td>
<td>20</td>
<td>32</td>
<td>0.62</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>90−95</td>
<td>0.16</td>
<td>17</td>
<td>46</td>
<td>9</td>
<td>4</td>
<td>0.31</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>33</td>
<td>0.19</td>
<td>110</td>
<td>96</td>
<td>3</td>
<td>27</td>
<td>0.87</td>
</tr>
<tr>
<td>Gilstatin</td>
<td>30</td>
<td>0.24</td>
<td>230</td>
<td>98</td>
<td>3</td>
<td>29</td>
<td>0.91</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>40</td>
<td>1.5</td>
<td>420</td>
<td>65</td>
<td>147</td>
<td>25</td>
<td>0.14</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>9</td>
<td>0.21</td>
<td>252</td>
<td>43</td>
<td>143</td>
<td>37</td>
<td>0.21</td>
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<tr>
<td>Clindamycin</td>
<td>93</td>
<td>1.1</td>
<td>329</td>
<td>13</td>
<td>286</td>
<td>3</td>
<td>0.01</td>
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<tr>
<td>Erythromycin</td>
<td>84</td>
<td>0.78</td>
<td>637</td>
<td>12</td>
<td>75</td>
<td>7</td>
<td>0.01</td>
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<tr>
<td>Fluconazole</td>
<td>12</td>
<td>0.7</td>
<td>21</td>
<td>75</td>
<td>5</td>
<td>36</td>
<td>0.87</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>&lt;5</td>
<td>0.6</td>
<td>300</td>
<td>90</td>
<td>30</td>
<td>39</td>
<td>0.56</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>&lt;10</td>
<td>0.25</td>
<td>95</td>
<td>&gt;90</td>
<td>4</td>
<td>37</td>
<td>0.90</td>
</tr>
<tr>
<td>Imipenem</td>
<td>10</td>
<td>0.31</td>
<td>245</td>
<td>52</td>
<td>116</td>
<td>37</td>
<td>0.24</td>
</tr>
<tr>
<td>Itroconazole</td>
<td>99</td>
<td>11</td>
<td>300</td>
<td>&lt;1</td>
<td>300</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Linezolid [19]</td>
<td>30</td>
<td>0.8</td>
<td>123</td>
<td>35</td>
<td>80</td>
<td>29</td>
<td>0.27</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>0.2−0.3</td>
<td>280</td>
<td>0.65−0.8</td>
<td>77</td>
<td>40</td>
<td>0.34</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>10</td>
<td>0.74</td>
<td>91</td>
<td>10</td>
<td>82</td>
<td>37</td>
<td>0.31</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>10</td>
<td>2</td>
<td>250</td>
<td>86</td>
<td>35</td>
<td>37</td>
<td>0.51</td>
</tr>
<tr>
<td>Penicillin</td>
<td>60</td>
<td>0.3</td>
<td>205</td>
<td>85</td>
<td>30</td>
<td>16</td>
<td>0.35</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>16</td>
<td>0.18</td>
<td>180</td>
<td>71</td>
<td>52</td>
<td>34</td>
<td>0.40</td>
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<tr>
<td>Rifampicin</td>
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<td>245</td>
<td>7</td>
<td>229</td>
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<td>Sulfamethoxazole</td>
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<td>22</td>
<td>14</td>
<td>19</td>
<td>16</td>
<td>0.45</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>90</td>
<td>0.8</td>
<td>18</td>
<td>66</td>
<td>6</td>
<td>4</td>
<td>0.41</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt;10</td>
<td>0.33</td>
<td>90</td>
<td>&gt;90</td>
<td>4</td>
<td>37</td>
<td>0.90</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>44</td>
<td>1.8</td>
<td>154</td>
<td>69</td>
<td>48</td>
<td>23</td>
<td>0.32</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30</td>
<td>0.39</td>
<td>95</td>
<td>80</td>
<td>19</td>
<td>29</td>
<td>0.60</td>
</tr>
</tbody>
</table>

The pharmacokinetic parameters are taken from [20], unless otherwise indicated. $C_{l_{\text{CVVH}}}$, CVVH clearance; $C_{l_{\text{NR}}}$, nonrenal clearance; $C_{l_{\text{total}}}$, total body clearance; CVVH, continuous veno-venous hemofiltration; $F_{R}$, fraction unchanged by the kidney; $F_{R_{CVVH}}$, fractional CVVH clearance; PB, protein binding; $V_d$, volume of distribution.
Antimicrobial Pk/Pd: Bedside Applications in the Critically Ill with Renal Failure

- Pharmacokinetics in critically ill patients are highly variable
- Loading as normal, consider higher dose in high Vd
- Continuous infusion is a cost-effective, work-load reducing administration strategy
- Continuous infusion of beta-lactam antibiotics is feasible for several antibiotics such as:
  - Cefotaxime
  - Ceftazidime
  - Amoxicillin
  - Penicillin
  - Piperacillin/tazobactam
- During continuous infusion of beta-lactam antibiotics lower total daily dosages may be adequate due to more optimal pharmacodynamics
Risk of underdosing

- Hydrophylic antibiotic
- Low protein binding (Fup high)
- Large Vd, capillary leakage
- High MIC pathogen (nosocomial infections)
- High dose CVVH
- Antibiotic with high tubular reabsorption

How to increase dose?
- Increase dose in dose dependent killing antibiotics
- More frequent dosing or continuous in time dependent antibiotics
Antimicrobial Pk/Pd: Bedside Applications in the Critically Ill with Renal Failure

- In many infections in ICU patients higher ciprofloxacin dosages should be used even in renal failure or alternative antibiotics should be considered
- Therapeutic drug monitoring may be used to optimize antibiotic therapy
- TDM during continuous infusion does require fewer serum samples
- During therapeutic hypothermia cefotaxime levels are 2 times higher compared to normothermia
- ICU Pk/Pd data are scarce

- During CVVH: calculate maintenance dose multiplication factor or TDM
- Clinical failure could be due to underdosing
- TDM maybe also for non-toxic antibiotics
- Know or measure MICs for common pathogens in hospital ICU
- For nontoxic antibiotics overdosing is preferable to underdosing
Thank you!

“What the? ... This is lemonade! Where’s my culture of amoebic dysentery?”

Arthur van Zanten
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