What is an appropriate dose?

F. Jacobs
Infectious Diseases Clinic
Erasme Hospital
7 April 2011
Appropriate empirical therapy

• **Appropriate**: in vitro effective against most probable pathogens

• **Adequate**: appropriate
  + Intravenous administration
  + Penetration (CSF,...)
  + Delay:
    • first 24 hours!
    • within 1 hr of diagnosis of septic shock and severe sepsis without septic shock
  + Correct dose

*Kumar Crit Care Med 2006; 34,1589*
Impact of appropriate dose

Increased mortality in case of insufficient doses

- **Gram negative bacilli**
  - Cefepime
  - Piperacillin-tazobactam

- **Gram positive cocci**
  - Vancomycine
Cefepime (Maxipim®)

- Systematic review of randomised trials
cefepime × another β-lactam (± another non β-lactam)

- 57 trials included

- Mortality (all causes) at day 30:
  higher for cefepime  + 26%  RR 1.26 (1.08-1.99)

- No specific cause for the increased mortality nor a specific population at risk (except neutropenic pts)

- Usual doses in USA: ≤ 4g/day (1-2 bid)

Yahar Lancet Infect Dis 2007; 7, 338-48
Explanation?

• 2 models showed
  - 1 g bid: 40% probability of T>MIC higher than 50% of time if MIC is 8 (Monte Carlo simulation)
  - With 1g bid: 2%
    2g bid: 21%
    2g tid: 88%

Reese Int J Antimicr Agents 2005; 26, 114-119

So a MIC of 8 shouldn’t mean sensitive if less than 2g tid is used empirically!!
Importance of adequate doses of cefepime in GNB bacteremia

Multivariate analysis:

\[ \text{MIC} \geq 8 \mu g/ml: \text{independent predictor of mortality} \]
\[ (p \leq 0.001; \text{OR} \ 8.2) \]

Bhat AAC 2007;
51, 4390-95
Outcome of bacteremia due to *P. aeruginosa* with reduced susceptibility to PTAZ

Implication on the appropriateness of the breakpoint

**Figure 1.** Thirty-day mortality rate for patients with bacteremia due to *Pseudomonas aeruginosa*, according to piperacillin-tazobactam MIC.

*Tam CID 2008; 46, 862-7*
MRSA: influence of vancomycine MIC on the treatment of MRSA bacteremia

- 414 episodes of MRSA bacteremia in 1 Spanish hospital (1991-2005) with
  - appropriate empirical vancomycin therapy
  - trough concentration ≥ 10 µg/ml
- **MIC 1**: 38 episodes
- **MIC 1.5**: 90 episodes
- **MIC 2**: 40 episodes

→ vancomycin is not an optimal option for strains with MIC>1 if trough levels of 10 are the target

**Multivariate analysis**

Table 5. Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant Staphylococcus aureus bacteremia.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.02 (1.00–1.04)</td>
<td>.013</td>
</tr>
<tr>
<td>Receipt of corticosteroids</td>
<td>1.85 (1.04–3.29)</td>
<td>.034</td>
</tr>
<tr>
<td>Prognosis of underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>1.81 (1.06–3.10)</td>
<td>.029</td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>10.2 (2.85–36.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Source of bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.18 (1.17–4.04)</td>
<td>.014</td>
</tr>
<tr>
<td>High risk</td>
<td>3.60 (1.39–6.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMIC1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VMIC1.5</td>
<td>2.86 (0.87–9.35)</td>
<td>.08</td>
</tr>
<tr>
<td>VMIC2</td>
<td>6.39 (1.68–24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NA</td>
<td>3.62 (1.20–10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shock</td>
<td>7.38 (4.11–13.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
What is different in ICU patients

• More severe infections, high inoculum

• Resistant strains (high MIC)

• Immunosuppression
  - Underlying diseases, immunosuppressive therapy
  - Due to hospitalization: malnutrition, surgery, invasive procedure

• Altered pharmacokinetics
Altered pharmacokinetics in ICU patients

• Due to resuscitation measures
  - Catecholamines, mechanical ventilation

• Polypharmacy
  - Drug-drug interactions
  - Competition for protein binding: only free drug is active

• Due to sepsis
Increased Cardiac index

Increased clearance
261 ICU patients treated with continuous infusion of vancomycin.

**Diagram:**
- **Patients (n):**
  - CRRT: 50
  - <30: 50
  - 30-60: 40
  - 60-80: 25
  - 80-100: 15
  - 100-120: 15
  - 120-150: 15
  - >150: 15

- **Measured creatinine clearance (ml/min*1.73m2):**
  - 100 → 254 ml/min

- **25%**
SEPSIS

- Increased cardiac index
  - Increased clearance
    - Low serum drug concentration
SEPSIS

- Increased Cardiac index
- Increased clearance
- Increased capillary permeability (fluid shift);
  Venous pooling
- Increased volume of distribution
- Low serum drug concentration
Changes in VD in ICU patients

- Mechanical ventilation
- Hypoalbuminemia
- Extracorporeal circuits
- Postsurgical drains
- Significant burn injuries
- Vasopressors
- Sepsis
Changes in VD

Volume of distribution (liters)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Volume (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>healthy volunteers</td>
<td>10</td>
</tr>
<tr>
<td>cystic fibrosis</td>
<td>15</td>
</tr>
<tr>
<td>intra-abdominal</td>
<td>25</td>
</tr>
<tr>
<td>infections</td>
<td>20</td>
</tr>
<tr>
<td>sepsis</td>
<td>25</td>
</tr>
</tbody>
</table>

SEPSIS

- Increased Cardiac index
  - Increased clearance
  - Increased volume of distribution
  - Low serum drug concentration

- Increased capillary permeability (fluid shift); Venous pooling
  - Increased clearance
  - Increased volume of distribution

- Organ dysfunction
  - Decreased clearance
  - High serum drug concentration
PK parameters

- Serum concentration
- Distribution (Vd)
- Elimination, metabolism, degradation

MIC

Injection → Time after injection
Pharmacokinetic characteristics

Hydrophilic antibiotics
- Beta-lactames
  - Penicillins
  - Cephalosporins
  - Carbapenems
- Glycopeptides
- Aminoglycosides

Lipophilic antibiotics
- Macrolides
- Fluoroquinolones
- Rifampicine
- Linezolid
- Tétracyclines

- Low Vd (low intracellular penetration)
  - Predominant renal clearance
- High Vd (good intracellular penetration)
  - Predominant hepatic clearance

Altered in ICU patients
Antibiotics used in ICU

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - Piperacillin - tazobactam

- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxone
  - Ceftazidime
  - Cefepime

- **Carbapenems**
  - Meropenem

- **Aminoglycosides:** amikacin

- **Vancomycin**

**Empirical treatment of nosocomial infections:**
Broad spectrum β-lactam
± aminoglycosides/quinolones

vancomycin if MRSA or SCN are suspected
Several studies in ICU:
- At steady-state (day 2-5)
- After exclusion of very sick patients
- Low serum concentrations in many patients

First 24 hours (first dose)
- Determinant for clinical evolution or prognosis
- Subtherapeutical concentrations can be associated with
  - clinical failure
  - emergence of resistance
Amikacin
Aminoglycosides

Serum concentration

Cmax (peak) → Concentration dependent (Cmax/MIC): aminoglycosides

AUC

MIC

8-10 x MIC

8-10 x MIC

Response Rate %

Maximum Cmax / MIC Ratio

Injection → Time after injection
Aminoglycosides in ICU patients

• In combination for 2-3 days
  - Improves survival and clinical response in severely ill patients
    (Kumar Crit Care Med 2010; 38, 1651-1664)

• Severe sepsis and septic shock
  • Increased Vd → Lower $C_{\text{max}}$
  • Abnormal clearance = accumulation and toxicity

Once a day: 15 mg/kg

HIGHER DOSES: 25-30mg/kg
**First doses of antibiotics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>74</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Men / Women</td>
<td>50 / 24</td>
</tr>
<tr>
<td>BMI</td>
<td>24.7 ± 4.6</td>
</tr>
<tr>
<td>APACHE II</td>
<td>21 [16-26]</td>
</tr>
<tr>
<td>SOFA on admission</td>
<td>8 [5-11]</td>
</tr>
<tr>
<td>Medical / Surgical</td>
<td>50 / 24</td>
</tr>
<tr>
<td>Community / Hospital</td>
<td>22 / 52</td>
</tr>
<tr>
<td>Severe Sepsis / Shock</td>
<td>17 / 56</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>56 (76%)</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>39 (53%)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>14 [5-25]</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>27 (37%)</td>
</tr>
</tbody>
</table>

**St Luc Hospital Brussels**

**St Pierre Hospital Ottignies**

**Universitair Ziekenhuis Brussels**

**Erasme Hospital Brussels**

*Taccone Crit Care 2010; 14, R53*
First dose of amikacin: 25 mg/kg
Median 1750 mg (1125-3000mg)

Clinical breakpoint
P. aeruginosa

Mean pharmacokinetic profile of amikacin

Serum conc. of amikacin (µg/mL)

8-10 x MIC

Times (hr)

Taccone Crit Care 2010; 14, R53
$C_{\text{max}}$ distribution

Number of patients

- Less than 40: 23%
- 40-60: 10%
- 60-80: 35%
- 80-100: 30%
- Greater than 100: 10%
Increased VD

- No correlation between $C_{\text{max}}$ of amikacin and any clinical, hemodynamic or therapeutic variable
First dose of amikacin: **25 mg/kg**
Median 1750 mg (1125-3000mg)

**Mean pharmacokinetic profile of amikacin**

Acute renal failure: 53%
Amikacin in case of CRRT

13 patients in septic shock
25mg/kg (1500-2500mg)

9/13 (69%) peak conc >64µg/ml

Median time to reach concentration <5µg/ml: 34h

Taccone (In Press Inter J Antimicr Agents 2011)
Amikacin in pan-resistant strains

- 2 patients with septic shock despite carbapenem and colistin
- **Amikacin: 3000 to 6000mg**
- Serum creatinine: 2-2.5 mg/dl
- CVVHDF (starting 2 hours after amikacin injection) until blood concentration fall below 5µg/ml
  - To minimize nephrotoxicity
  - To allow daily amikacin administration

**Layeux Antimicr Agents Chemother**
2010, 54: 4939-41
Amikacin in pan-resistant strains
Amikacin in septic shock

25-30 mg/kg
Broad spectrum β-lactams

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - Piperacillin - tazobactam

- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxon
  - Ceftazidime
  - Cefepime

- **Carbapenems**
  - Meropenem

- **Aminoglycosides**: amikacin

- Vancomycine
PK parameters

Serum concentration

Time dependent (Time > MIC): β-lactams
PK/PD parameters of β-lactams

• Concentration > MIC

• Better efficacy if concentration > 4 x MIC


Time-kill curves of *Pseudomonas aeruginosa* with exposure to ticarcillin
**β-lactams: efficacy**

- **PK parameter: T>CMI**
  - Penicillins: 50%
  - Cephalosporins: 70%
  - Carbapenems: 40%

- No post-antibiotic effect (except carbapenems): regrowth when concentrations below MIC

In ICU patients: 100%??
• **First dose** of $\beta$-lactams in patients with severe sepsis or septic shock:

  - Ceftazidime 2g
  - Cefepime 2g
  - Piperacillin-tazobactam 4g
  - Meropenem 1g

Then adapted to renal function
Pharmacokinetic profiles:

- **Ceftazidime (CAZ)**
  - 18 patients

- **Cefepime (CEF)**
  - 19 patients

- **Meropenem (MER)**
  - 16 patients

- **Piperacillin-tazobactam (PTZ)**
  - 27 patients
Volume of distribution

Vd (L/kg)

PTAZ  ceftazidime  cefepime  meropenem

healthy volunteers
sepsis
Adequate concentrations of the four drugs (dose interval adapted to renal function)

<table>
<thead>
<tr>
<th></th>
<th>Meropenem (n=16)</th>
<th>Ceftazidime (n=18)</th>
<th>Cefepime (n=19)</th>
<th>PTAZ (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of adequate PK</td>
<td>75</td>
<td>28</td>
<td>16</td>
<td>44</td>
</tr>
</tbody>
</table>

Target: $T > CMI \times 4$ (CMI of *P. aeruginosa*).

Time Interval
- Penicillins: 50%
- Cephalosporins: > 60-70%
- Carbapenems: 40%
TDM of cefepime in ICU patients

- Daily dose
  - 2g bid if Cl\text{\textsubscript{creat}} ≥ 50ml/ml
  - 2g od if Cl\text{\textsubscript{creat}} < 50ml/min
- 21 consecutive patients with VAP
- PK parameters: trough level > 10µg/ml
- PK/PD parameters: good for MIC up to 4µg/ml

neurological side effects (confusion, flapping tremor)

Chapuis Critical Care 2010; 14, R51
Case report

- 78-y-old man
- Underlying diseases
  - Urothelial carcinoma in generalization
  - Cardiomyopathy
  - Hypertension
  - Surgery for abdominal aortic aneurysm
  - Atrial fibrillation
- Admitted for subdural hematoma requiring drainage
- Neurological improvement
- Lung infection: vancomycin and amoxicillin-clavulanic acid, changed in cefepime
- Neurological degradation $\rightarrow$ coma (GCS 5/15)
- EEG: epilepsy
- Failure of anti-epileptic drugs
- Decision to stop all treatments
- 2 days after: patient wakes up!!
Continuous epileptiform discharges in patients treated with cefepime or meropenem

- Retrospective review of patients treated with meropenem or cefepime in whom EEG has been performed (42 months)

<table>
<thead>
<tr>
<th></th>
<th>Patients treated</th>
<th>EEG performed</th>
<th>Continuous epileptiform discharges</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefepime</td>
<td>1120</td>
<td>59</td>
<td>14</td>
<td>1.25</td>
</tr>
<tr>
<td>meropenem</td>
<td>1572</td>
<td>80</td>
<td>3</td>
<td>0.25</td>
</tr>
</tbody>
</table>

- Blood serum creatinine concentration: elevated in 5/14 pts

Naeije accepted in Arch Neurology
CRRT (continuous renal replacement therapy)

• Clearance from the device
  - Drug (protein binding and molecular weight)
  - Flow
  - Membrane
  - Surface
  - Technique (CVVH vs CVVHDF)
  - Duration

• Clearance from residual renal function

• Clearance other than renal
<table>
<thead>
<tr>
<th>Study</th>
<th>ATB</th>
<th>Dosing</th>
<th>Pts</th>
<th>Membrane</th>
<th>Technique</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumuller 2002</td>
<td>CEFTA</td>
<td>2g q8h</td>
<td>12</td>
<td>PSF</td>
<td>CVVH</td>
<td>MIC 4 OK, MIC 8 NO</td>
</tr>
<tr>
<td>Allaouchich 1997</td>
<td>CEFE</td>
<td>2g q12h</td>
<td>6</td>
<td>AN69</td>
<td>CVVH</td>
<td>MIC 8 = 2/6 PK</td>
</tr>
<tr>
<td>Capellier 1998</td>
<td>PIP</td>
<td>4g q8h</td>
<td>10</td>
<td></td>
<td>CVVH</td>
<td>MIC 16 = OK</td>
</tr>
<tr>
<td>Valtonen 2001</td>
<td>PIP</td>
<td>4g q8h</td>
<td>6</td>
<td>PSF</td>
<td>CVVH/HD</td>
<td>MIC 16 OK</td>
</tr>
<tr>
<td>Valtonen 2000</td>
<td>MERO</td>
<td>0.5g q12h</td>
<td>6</td>
<td>PSF</td>
<td>CVVH/HD</td>
<td>MIC 2 OK</td>
</tr>
<tr>
<td>Krueger 2000</td>
<td>MERO</td>
<td>0.5g q12h, 1g q12h</td>
<td>8</td>
<td>PSF</td>
<td>CVVH</td>
<td>MIC 1 OK, MIC 2 = 5/8</td>
</tr>
<tr>
<td>Robatel 2003</td>
<td>MERO</td>
<td>0.5g q12h, 1g q12h</td>
<td>15</td>
<td>PSF</td>
<td>CVVHDF</td>
<td>MIC 2 = 1g q12h</td>
</tr>
<tr>
<td>Giles 2000</td>
<td>MERO</td>
<td>1g q12h</td>
<td>10</td>
<td>PAN</td>
<td>CVVH/CVVHDF</td>
<td>MIC 2 = OK</td>
</tr>
<tr>
<td>Ververs 2000</td>
<td>MERO</td>
<td>0.5g q12h</td>
<td>5</td>
<td></td>
<td>CVVH</td>
<td>MIC 2 = OK</td>
</tr>
</tbody>
</table>
# Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

Robin L. Trotman, John C. Williamson, D. Matthew Sheemaker, and William L. Salzer

## Table 2. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CVVH</th>
<th>CVVHD or CVVHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoxycholate</td>
<td>0.4–1.0 mg/kg q24h</td>
<td>0.4–1 mg/kg q24h</td>
</tr>
<tr>
<td>Lipid complex</td>
<td>3–5 mg/kg q24h</td>
<td>3–5 mg/kg q24h</td>
</tr>
<tr>
<td>Liposomal</td>
<td>3–5 mg/kg q24h</td>
<td>3–5 mg/kg q24h</td>
</tr>
<tr>
<td>Ayclovir</td>
<td>5–7.6 mg/kg q24h</td>
<td>5–7.6 mg/kg q24h</td>
</tr>
<tr>
<td>Ampicillin-sublactam</td>
<td>3 g q12h</td>
<td>3 g q6h</td>
</tr>
<tr>
<td>Aztreonem</td>
<td>1–2 g q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1–2 g q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1–2 g q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1–2 g q12h</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g q12–24h</td>
<td>2 g q12–24h</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600–900 mg q8h</td>
<td>600–900 mg q8h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>200 mg q12h</td>
<td>200–400 mg q12h</td>
</tr>
<tr>
<td>Colistin</td>
<td>2.5 mg/kg q48h</td>
<td>2.5 mg/kg q48h</td>
</tr>
<tr>
<td>Deptomycin</td>
<td>4 or 6 mg/kg q48h</td>
<td>4 or 6 mg/kg q48h</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200–400 mg q24h</td>
<td>400–800 mg q24h</td>
</tr>
<tr>
<td>Imipenem–cilastatin</td>
<td>250–2500 mg q12h or</td>
<td>500 mg q8h, or</td>
</tr>
<tr>
<td></td>
<td>600 mg q8h</td>
<td>500 mg q8h, or</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>250 mg q24h</td>
<td>250 mg q24h</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg q12h</td>
<td>600 mg q12h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg q24h</td>
<td>400 mg q24h</td>
</tr>
<tr>
<td>Nafcillin or oxacillin</td>
<td>2 g q4–6h</td>
<td>2 g q4–6h</td>
</tr>
<tr>
<td>Pirepoxilin-tazobactam</td>
<td>2.25 g q6h</td>
<td>2.25–3.375 g q6h</td>
</tr>
<tr>
<td>Ticaricillin–clavulanate</td>
<td>2 g q6–8h</td>
<td>3.1 g q6h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g q48h</td>
<td>1 g q48h</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>4 mg/kg po q12h</td>
<td>4 mg/kg po q12h</td>
</tr>
</tbody>
</table>

---

Antibiotic dosing in patients treated with CRRT

Seyler et al 48th Annual ICAAC (Chicago) 2008
CRRT et β-lactames

Seyler et al ICAAC 2008
Probability of target attainment

- 4 times MIC of *Pseudomonas*
- Duration
  - PTAZ 50% of time
  - Cefta-cefepime 70%
  - Mero 40%

<table>
<thead>
<tr>
<th></th>
<th>First 48h</th>
<th>Meropenem</th>
<th>Pip-tazo</th>
<th>Cefepime</th>
<th>Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>71%</td>
<td>66%</td>
<td>0%</td>
<td>38%</td>
</tr>
<tr>
<td>After 48h</td>
<td>87%</td>
<td>78%</td>
<td>0%</td>
<td>71%</td>
<td></td>
</tr>
</tbody>
</table>

Possibility of target for various MIC for at least 75% of the patients (µg/ml)

<table>
<thead>
<tr>
<th></th>
<th>Meropenem</th>
<th>Pip-tazo</th>
<th>Cefepime</th>
<th>Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUCAST clinical breakpoints</td>
<td>2</td>
<td>16</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Recommendations

• Insufficient doses of β-lactams
  - Early phase (first 48h), especially for cephalosporins and PTAZ
  - Late phase (>48h): possible accumulation → TDM

PTAZ 2.25 q6h → 4g qid (EI)
Ceftazidime 2g q12h → 2g q8h
Cefepime 2g q12h → 2g q8h
Meropenem 1g q12h → 1g q8h
Effect of antibiotic prescribed on the need for β-lactam antibiotic dose adjustment at the first therapeutic drug monitoring (TDM) level.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Standard initiation dose</th>
<th>Patients</th>
<th>Dose maintained</th>
<th>Dose increased</th>
<th>Dose decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIP/TAZc</td>
<td>4.5 g q6h</td>
<td>116</td>
<td>27(23%)</td>
<td>57(49%)</td>
<td>32(28%)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g q6h</td>
<td>4</td>
<td>0(0%)</td>
<td>11(25%)</td>
<td>3(75%)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q8h</td>
<td>51</td>
<td>8(16%)</td>
<td>29(57%)</td>
<td>14(27%)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>2.4 g q4h</td>
<td>9</td>
<td>3(33%)</td>
<td>3(33%)</td>
<td>3(33%)</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>2 g q4h</td>
<td>16</td>
<td>1(6%)</td>
<td>15(94%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1 g q8h</td>
<td>6</td>
<td>0(0%)</td>
<td>6(100%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g q12h</td>
<td>33</td>
<td>22(67%)</td>
<td>7(21%)</td>
<td>4(12%)</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>1 g q6h</td>
<td>1</td>
<td>0(0%)</td>
<td>1(100%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>236</td>
<td>61(25.8%)</td>
<td>119(50.4%)</td>
<td>56(23.7%)</td>
</tr>
</tbody>
</table>

Roberts, Int J Antimicrob Agents 2010
Broad spectrum β-lactams

- **Penicillins**
  - Amoxicillin - clavulanate
  - Oxacillin
  - Piperacillin - tazobactam

- **Cephalosporins**
  - Cefuroxime
  - Ceftriaxon
  - Ceftazidime
  - Cefepime

- **Carbapenems**
  - Meropenem

- **Aminoglycosides**: amikacin

- **Vancomycin**
Glycopeptides (vancomycin)

Serum concentration

Both (AUC/MIC = AUIC): Glycopeptides

AUC/MIC: 400
Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

Michael Rybak, Ben Lomaestro, John C. Rotschafer, Robert Moellering Jr., William Craig, Marianne Billeter, Joseph R. Dalovisio, and Donald P. Levine

Am J Health-Syst Pharm. 2009; 66:82-98
TDM vancomycine

- **AUC/MIC 400**
- **Optimal monitoring parameter: trough serum concentration**

**Recommendation**
- > 10 µg/ml
- > 15 if MIC of 1 µg/ml
  - Complicated infections
    - Bacteremia
    - Endocarditis
    - Osteomyelitis
    - Meningitis
    - HAP/VAP
    - min 15 µg/ml
  - If MIC ≥ 2 µg/ml: target not achievable
Vancomycine: CI or II

- Not recommended in IDSA guidelines

- Similar clinical outcome (Wysocki et al. Antimicr Ag Chemother 2001, 2460-7)

- Logistically more convenient

- Achieves target concentrations faster

- Results in less variability in serum concentrations

- Slower onset of nephrotoxicity (Ingram Int J Antimicr Ag 2009)

*Wysocki et al. AAC 2001, 2460-7*
Continuous infusion of vancomycin

- **Loading dose**: 15-30mg/kg
- **Continuous infusion**: 30mg/kg/j

Adapted to the real body weight
Vancomycine CI: retrospective review

- 1 year (January 2008-January 2009)
- 172 patients
  - >18-y-old
  - sepsis
  - Vancomycine >48h
- Target: 20-30µg/ml

Ocampos Martinez et al
Optimal concentrations

Ocampos Martinez et al
Delay for obtaining therapeutic concentrations

- Inadequate concentration

- 25% of the patients
Relationship between vancomycin clearance and creatinine clearance

Fig. 1. Relationship between vancomycin clearance ($\text{CL}_v$) and creatinine clearance ($\text{CL}_{Cr}$): $\text{CL}_v \text{ (L/h)} = 0.0261 \times \text{CL}_{Cr} \text{ (mL/min)} + 1.78$ ($r = 0.83$).
Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100ml/min/1.73m2, followed by administration as a 35 mg/kg per day continuous infusion.

Roberts Antimicr Ag Chemother 2011
The effect of creatinine clearance on vancomycin concentrations administered by continuous infusion (35 mg/kg per day after 35mg/kg loading dose).
Clinical study in ICU patients

- **Loading dose**: 35mg/kg (total body weight) in 4-hours infusion

- **Daily dose**
  calculated Clcreat (Cockroft)

<table>
<thead>
<tr>
<th>Clearance de créatinine</th>
<th>Dose entretien par 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150</td>
<td>45 mg/kg</td>
</tr>
<tr>
<td>120-150</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>80-120</td>
<td>35 mg/kg</td>
</tr>
<tr>
<td>50-80</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>25-50</td>
<td>14 mg/kg</td>
</tr>
<tr>
<td>&lt;25 / Oligurie</td>
<td>7 mg/kg</td>
</tr>
<tr>
<td>Hémofiltration</td>
<td>14 mg/kg</td>
</tr>
</tbody>
</table>

- **40 ICU patients**
  - Loading dose: median **2500mg** (1400-4000mg)
  - Daily dose: median **1600mg** (500-4500mg)
Preliminary results

End of 4-hours infusion

H. Kabtouri, Taccone et al
Nephrotoxicity of high doses of vancomycin

CRITICAL CARE MEDICINE

Influence of Vancomycin on Renal Function in Critically Ill Patients after Cardiac Surgery

Continuous versus Intermittent Infusion

Samata Nath, M.D.; Christina Guo, M.D.; M.M. Zako; Shahnawaz, M.D.; Florian Thathiram, M.D.; Markus Miller, M.D.; and Janna Fischman, M.D.

A Retrospective Analysis of Possible Renal Toxicity Associated with Vancomycin in Patients with Health Care–Associated Methicillin-Resistant Staphylococcus aureus Pneumonia

Meghan N. Jeffres, PharmD; Warren Isakow, MD; Joshua A. Doherty, BS; Scott T. Micek, PharmD; and Marin H. Kollef, MD

Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity

Thomas P. Lodise,1,2 M.D.; Ben Lomaestro,3 and G. L. Drusano3

Albany College of Pharmacy, Albany, New York; Center for Infection Control, Alynh, New York; and Albany Medical College–Hospital, Albany, New York

Received 17 December 2008; accepted 3 January 2009

Journal of Antimicrobial Chemotherapy

doi:10.1093/jac/dkn080

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

Thomas P. Lodise,1,2 Nimish Patel,1 Ben M. Lomaestro,3 Keith A. Rodvold,4 and George L. Drusano3

1Albany College of Pharmacy and Health Sciences; 2Galaxy Research Institute; and 3Albany Medical Center Hospital, Albany, New York; and 4Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago

JAC

Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy

Paul R. Ingram1,2, David C. Lye3, Paul A. Tambyah1,2, Wei P. Goh3, Vincent H. Tam4 and Dale A. Fisher1,2
Conclusions

Era of increasing resistance amongst microorganisms

No new drugs for Gram negative bacilli

Has the era of untreatable infections arrived?

David M. Livermore

Optimal dosage of antibiotic has become important
TDM
Therapeutic drug monitoring
Thanks

St Luc Hospital
Brussels
PF Laterre,
X. Wittebole
I. Delattre
P. Wallemacq

Erasme Hospital
Brussels
F. Taccone
D. De backer
Ocampos Martinez
L. Seyler
B. Layeux
M. Hites
F. Cotton
JL Vincent
F. Jacobs

St Pierre Hospital
Ottignies
T. Dugernier

Universitair
Ziekenhuis
Brussels
H. Spapen