Il moderno laboratorio di farmacologia clinica

Pier Giorgio Cojutti, Federico Pea

Istituto di Farmacologia Clinica
Azienda Sanitaria Universitaria Integrata di Udine
Outline

1. The need for antimicrobial TDM: rationale basis and updates
2. How to perform useful TDM: technical and procedural aspects
3. Patient-oriented antimicrobial dosage optimization: examples in clinical practice
Criteria for rational, selective TDM:

When the right treatment is chosen for the patient, there are several criteria to be considered to be able to rationally perform TDM:

1. a good relationship between drug concentration and pharmacological response

2. a defined target concentration range

3. availability of an accurate and selective bioanalytical assay with a rapid turnaround time

4. large interindividual variability in PK


HOSPITAL-ACQUIRED INFECTIONS DUE TO GRAM-NEGATIVE BACTERIA


MECHANISMS OF RESISTANCE IN GRAM-NEGATIVE BACTERIA AND THE ANTIBIOTICS AFFECTED.

MBL and KPC + Enterobacteriaceae
POSSIBLE STRATEGIES TO DEAL WITH THE PROBLEM OF MDR GRAM-NEGATIVE INFECTIONS IN CRITICALLY ILL PATIENTS

- Empirical combination therapy using a carbapenem with other antibiotic classes should be used first-line in critically ill patients at risk for MDR Gram-negative bacteria.

- Pharmacokinetic/pharmacodynamic optimization of antibiotics with Gram-negative activity can overcome resistance associated with MDR Gram-negative bacteria.

- Strategies to limit antibiotic exposure, such as shorter courses of antibiotics, attenuate the emergence of resistant Gram-negative bacteria.

- Active surveillance of MDR Gram-negative bacteria with isolation should be an active component of infection control bundles to prevent the proliferation of MDR Gram-negative bacteria.
DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

### Table 1. Definitions Used for Pharmacokinetic/Pharmacodynamic and Clinical Endpoints

<table>
<thead>
<tr>
<th>PK/PD Target</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% $fT_{&gt;\text{MIC}}$</td>
<td>Free drug concentration maintained above MIC of the known or suspected pathogen for at least 50% of dosing interval. This was considered to be the most conservative PK/PD target.</td>
</tr>
<tr>
<td>50% $fT_{&gt;4\times\text{MIC}}$</td>
<td>Free drug concentration maintained above a concentration 4-fold higher than the MIC of the known or suspected pathogen for at least 50% of dosing interval.</td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$</td>
<td>Free drug concentration maintained above MIC of the known or suspected pathogen throughout the entire dosing interval.</td>
</tr>
<tr>
<td>100% $fT_{&gt;4\times\text{MIC}}$</td>
<td>Free drug concentration maintained above a concentration 4-fold higher than the MIC of the known or suspected pathogen throughout the entire dosing interval.</td>
</tr>
</tbody>
</table>

**Positive clinical outcome**
Completion of treatment course without change or addition of antibiotic therapy, and with no additional antibiotics commenced with 48 h of cessation. De-escalation to a narrower spectrum antibiotic was permitted but excluded from the clinical outcome analysis.

**Negative clinical outcome**
Any clinical outcome other than positive clinical outcome.

### Table 2. Clinical and Demographic Characteristics of Included Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 361)</th>
<th>Patients Treated for Infection (n = 248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (48–73)</td>
<td>60 (48–74)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 (65–85)</td>
<td>78 (65–86)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18 (13–24)</td>
<td>18 (14–24)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>5 (2–9)</td>
<td>6 (3–9)</td>
</tr>
<tr>
<td>Serum creatinine concentration, μmol/L</td>
<td>77 (53–134)</td>
<td>76 (53–144)</td>
</tr>
<tr>
<td>Calculated creatinine clearance, mL/min</td>
<td>80 (42–125)</td>
<td>82 (44–125)</td>
</tr>
<tr>
<td>Urinary creatinine clearance, mL/min</td>
<td>62 (31–107)</td>
<td>64 (32–103)</td>
</tr>
</tbody>
</table>
Of the 248 patients treated for infection, 16% did not achieve 50% $f_{T>MIC}$ and these patients were 32% less likely to have a positive clinical outcome (odds ratio [OR], 0.68; $P = .009$).

Positive clinical outcome was associated with increasing 50% $f_{T>MIC}$ and 100% $f_{T>MIC}$ ratios (OR, 1.02 and 1.56, respectively; $P < .03$), with significant interaction with sickness severity status.
Pharmacodynamics of carbapenems for the treatment of Pseudomonas aeruginosa VAP: associations with clinical outcome and recurrence

 Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Linezolid (n=35)</th>
<th>Linezolid + rifampicin (n=10)</th>
<th>P value[^d]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (years), mean± SD</td>
<td>49.9±15.2</td>
<td>58.3±16.2</td>
<td>0.149[^b]</td>
</tr>
<tr>
<td>gender (male/female)</td>
<td>19/16</td>
<td>7/3</td>
<td>0.481</td>
</tr>
<tr>
<td>body weight (kg), mean± SD</td>
<td>74.7±15.8</td>
<td>81.1±15.3</td>
<td>0.269[^b]</td>
</tr>
<tr>
<td>serum creatinine (mg/dL) at time of the first TDM, median (IQR)</td>
<td>0.85 (0.72 - 1.0)</td>
<td>0.94 (0.87 - 1.09)</td>
<td>0.149[^c]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid dosage and exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of TDM, median (IQR)</td>
<td>7 (4 - 11)</td>
<td>5 (3 - 7)</td>
<td>0.174[^c]</td>
</tr>
<tr>
<td>patients with dosage adjustments to avoid overexposure, n (%)</td>
<td>14 (40)</td>
<td>0 (0)</td>
<td>0.018</td>
</tr>
<tr>
<td>dose/kg/day, median (IQR)</td>
<td>15.39 (11.21 - 17.91)</td>
<td>14.46 (13.33 - 18.46)</td>
<td>0.500[^c]</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L), median (IQR)</td>
<td>3.71 (1.43 - 6.38)</td>
<td>1.37 (0.67 - 2.55)</td>
<td>&lt;0.001[^c]</td>
</tr>
<tr>
<td>$\text{AUC}_{24}$ (mg/L·h), median (IQR)</td>
<td>212.77 (166.67 - 278.42)</td>
<td>123.33 (97.36 - 187.94)</td>
<td>&lt;0.001[^c]</td>
</tr>
<tr>
<td>Co-treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omeprazole</td>
<td>12 (34.2)</td>
<td>0 (0)</td>
<td>0.042</td>
</tr>
<tr>
<td>amiodarone</td>
<td>3 (8.6)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>amlodipine</td>
<td>2 (5.7)</td>
<td>1 (10)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients

LETTER TO THE EDITORS

Linezolid underexposure in a patient co-treated with venlafaxine

Piergiorgio Cojutti¹ ² • Massimo Crapis³ • Matteo Bassetti³ • William Hope⁴ • Federico Pea¹ ²

Table 1 Pharmacokinetic parameters of linezolid estimated in the described patient compared to those previously reported in healthy adults

<table>
<thead>
<tr>
<th>Patient</th>
<th>AUC⁰–²₄h (mg h/L)</th>
<th>CL/F (L/h)</th>
<th>t₁/₂ (h)</th>
<th>Vd (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with venlafaxine</td>
<td>87.7</td>
<td>13.5</td>
<td>1.66</td>
<td>32.3</td>
</tr>
<tr>
<td>Healthy subjects [2]</td>
<td>282.2</td>
<td>4.7</td>
<td>5.4</td>
<td>36.1</td>
</tr>
</tbody>
</table>

CL/F apparent oral clearance, Vd distribution volume

In conclusion, clinicians should be aware that venlafaxine might cause underexposure to linezolid, and we recommend avoidance of co-administration to prevent therapeutic failure with linezolid and also to avoid the potential occurrence of serotonin syndrome due to synergic anti-MAO activity [10].
HOW TO PERFORM ADEQUATE ANTIMICROBIAL TDM?
### Formulazione richiesta

**Paziente** Prova Prova [16/12/1959]  **Sesso/età** MAS/52a  **Ident./N° con.** 4354725/  **Note**

**Trasporto** A letto  **Inviante**  **Dest. ref.**

**Medico**  **Contratto**  **Causale**  **Priorità**  **Ente Pag.**

**Orien. diag.**  **Testo ques.**  **Indirizz. (Altro - AOU)**

<table>
<thead>
<tr>
<th>Visite</th>
<th>c.Cons</th>
<th>d.Eco</th>
<th>d.Rm</th>
<th>ROUTI</th>
<th>Orm/I</th>
<th>Microb</th>
<th>Infetti</th>
<th>Specia</th>
<th>URGEN</th>
<th>Altre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omocisteina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH Paratormo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatomedin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17alphaDrossipr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH(adrenoc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AldosteroneCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AldosteroneOR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Peptide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eritropoietina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGH/GH/soma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renina CLINO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renina ORTO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liq.Biologici</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lissocitico</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FARMACI (1)**
- Acido valproico
- Amiodarone
- Carbamazepina
- Ciclosporina
- Clonazepam
- Digossina
- Everolimus
- Fenitoina/Dinto
- Fenobartile
- Lamotrigina
- Levofoxicacina
- Litio
- Oxxcarbazepina
- Paracetamolo
- Sirolimus
- Tacrolimus
- Tolazoline

**Autoimm.(2)/Allergologia**
- IgEspec.12Aller...
- IgEspec.1 Aller...
- ANCA(PR3/anti...
- LAC
- anti B2Glicopr...
- anti Cardiolipina
- anti CelluleNeu...
- anti Citrullina
- anti Cure
- anti Endomisio
- anti FattoreIntr...
- anti Gangliosidi
- anti GAD
- anti Gliadin
- anti IA2
- anti InsulaPan...

**Tetano antico...**
- Anti MAG
- Anti Membrana
- Anti Mieloperos...
- Anti Mitochondri...
- Anti MucosaGa...
- Anti MuscoloLis...
- Anti Ovaio
- Anti Piastrine
- AntiPF4Eparina...
- Anti Protrombina
- Anti PR3(protei...
- AntiRec.Acetic...
- AntiRecettoriTSH
- Anti SLA
- Anti Surrone
- Anti TSH

[Aggiungi prescrizione] [Richiedi nella stessa giornata] [Richiedi]
Istituto di Farmacologia Clinica – Azienda Sanitaria Universitaria Integrata di Udine

QUALI SONO I DATI CLINICI

**Modulo di richiesta accertamenti/consulenze**

<table>
<thead>
<tr>
<th>Richiesta</th>
<th>Data</th>
<th>Compilata da</th>
<th>Data di Compilazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predetta</td>
<td>08/02/2011 02:19</td>
<td>Medico</td>
<td>08494</td>
</tr>
<tr>
<td>Priorità</td>
<td>P - Programmati</td>
<td>Referto preso</td>
<td>2° piano, Pad. 1 - Udine</td>
</tr>
<tr>
<td>Accesso</td>
<td>Ricevuta Ordinaria AOU UD</td>
<td>Richiesta n.</td>
<td>5903673</td>
</tr>
</tbody>
</table>

**Dati utente**

- Cognome e nome
- Codice fiscale

**Appuntamento**

- martedì 1º febbraio 2011 06:00
- AOU UD S.M. Misericordia
- UOC Istituto di Farmacologia interno

**Prestazioni**

**Dati accessori**

| a. Diagnosi                      | SEPSI    |
| b. Alterazione                  | 70       |
| c. Peso Kg                      | 70       |
| d. Motivazione della richiesta  | Sospetto di tossicità 350MC |
| e. Dosaggio farmaco e unità di misura | 20/01/2011  |
| f. Data inizio terapia          | 24 h     |
| g. Data e ora ultima somn.ne    | 07.02.2011 H 8:00 |
| h. Via di somn.ne               | Endovenosa |
| i. Terapie concomitanti        | CARVEDILOLO AMLODIPINA ALLOPURINOL ALLOPERIDOL VANCOMICINA MEROPENEM |

**Richiesta laboratorio**

| 50398119 | Firma del Medico |

**Istituto di Farmacologia Clinica – Azienda Sanitaria Universitaria Integrata di Udine**
Personalization of antimicrobial dosing regimens: indicators of performance

Pea F, Cojutti P, Dose L, Furian C, Guarrera G, Furlanut M.

Aim:
to assess the **efficiency** and **effectiveness** of the organizational system of a **Clinical Pharmacological Service** of an Italian tertiary care teaching hospital **in providing advices (CPAs)** to clinicians within timeframes useful for the personalization of antimicrobial dosing regimens in different patients’ populations according to the clinical benefit for patient care.

**Study period:** December 2011 – June 2012

**Classification:**
- **high priority level:** for antimicrobials used to treat acute infections in the critically ill patients;
- **moderate priority level:** for those used to treat cytomegalovirus infections in solid organ transplant recipients;
- **mild priority level:** for those used to treat chronic infections
# Personalization of antimicrobial dosing regimens: indicators of performance


## WEEKLY-BASED SCHEDULE OF CLINICAL PHARMACOLOGICAL ADVICES FOR PERSONALIZED ANTIMICROBIAL THERAPY

<table>
<thead>
<tr>
<th>Drug</th>
<th>TD (h)</th>
<th>TATt of CPA (days)</th>
<th>Drug</th>
<th>TD (h)</th>
<th>TATt of CPA (days)</th>
<th>Drug</th>
<th>TD (h)</th>
<th>TATt of CPA (days)</th>
<th>Drug</th>
<th>TD (h)</th>
<th>TATt of CPA (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>0.5</td>
<td>2</td>
<td>Daptomycin</td>
<td>4.9</td>
<td>4</td>
<td>Ceftazidime</td>
<td>5.5</td>
<td>4</td>
<td>Voriconazole</td>
<td>5.9</td>
<td>5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.5</td>
<td>2</td>
<td>Fluconazole</td>
<td>4.1</td>
<td>4</td>
<td>Ganciclovir</td>
<td>5.2</td>
<td>4</td>
<td>Isoniazid</td>
<td>4.3</td>
<td>11</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>0.5</td>
<td>2</td>
<td>Linezolid</td>
<td>3.4</td>
<td>4</td>
<td>Piperacillin</td>
<td>6.3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.5</td>
<td>2</td>
<td>Meropenem</td>
<td>4.2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>3.3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Istituto di Farmacologia Clinica – Azienda Sanitaria Universitaria Integrata di Udine
Personalization of antimicrobial dosing regimens: indicators of performance

Pea F, Cojutti P, Dose L, Furian C, Guerrera G, Furlanut M. 

Mean ± SD of turnaround time (TAT) of clinical pharmacological advices (CPA) for dosing regimen individualization of those antimicrobials classified at high or moderate priority level, scheduled 3 or 2 times weekly
The Antimicrobial Therapy Puzzle; Could Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients?

Pea F and Viale P. *Clin Infect Dis.* 2006;42(12):1764-71
Clinical Pharmacological Advice (CPA)

EXAMPLE OF CLINICAL PHARMACOLOGICAL ADVICE

DEPARTMENT of INTERNAL MEDICINE

Institute of Clinical Pharmacology

Applicant hospital/ward: .................

Mr.......................... Birth Date: ....... Age: .... yrs Sex: ..... Request no: ........ Request date:.........

Patient Weight
Patient Height
Sampling day and time
MEROPENEM concentration
Day for TDM reassessment

78
178
03.08.2012 h8:00
17.51
Monday 06.08.2012

kg
cm
mg/L

Comment:
Highly efficacious concentration for the treatment of bloodstream infection caused by the identified pathogen (K. pneumoniae with an MIC for meropenem of 0.5 mg/L). According to an estimated creatinine clearance of 0.98 ml/min/kg and to the observed concentration, in order to prevent drug accumulation and to optimize the time-dependent pharmacodynamic activity of meropenem, it is advisable to adjust dosage to 500 mg every 6 h administered by continuous infusion (total daily dose of 2 000 mg) and to reassess TDM on next Monday.

Warning: Meropenem is stable in aqueous solution maximum 6 hours; therefore it is mandatory that the solution is reconstituted every maximum six hours, next to each single administration.
Pharmacokinetics and Pharmacodynamics of Continuous-Infusion Meropenem in Pediatric Hematopoietic Stem Cell Transplant Patients
Individualization of Piperacillin Dosing for Critically Ill Patients: Dosing Software To Optimize Antimicrobial Therapy
Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing

Educational and Organizational Interventions to Improve the Usefulness of Clinical Pharmacological Advice for Personalized Drug Dosing Based on Therapeutic Drug Monitoring

Federico Pea$^{1,2}$, Lucia Dose$^1$, Piergiorgio Cojutti$^{1,2}$, Massimo Baraldo$^{1,2}$, Fabrizio Fontana$^3$, Carlo Favaretti$^4$ and Mario Furlanut$^{1,2}$

Istituto di Farmacologia Clinica – Azienda Sanitaria Universitaria Integrata di Udine
Educational and Organizational Interventions to Improve the Usefulness of Clinical Pharmacological Advice for Personalized Drug Dosing Based on Therapeutic Drug Monitoring


Temporal trends of the number of TDM requests, and of the number and of the percentage of them affected by errors, in relation to the type of applicant unit
A 1 year retrospective audit of quality indicators of clinical pharmacological advice for personalized linezolid dosing: one stone for two birds?

Federico Pea,1,2 Piergiorgio Cojutti,1,2 Lucia Dose1 & Massimo Baraldo1,2

1Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria Della Misericordia, Udine and 2Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Targeting plasma trough concentration ($C_{\text{min}}$) of linezolid between 2 and 7 mg l$^{-1}$ may improve safety outcomes during linezolid therapy while retaining efficacy.
• Therapeutic drug monitoring (TDM) may poorly influence clinicians’ prescribing attitudes whenever it is not supported by appropriate suggestions concerning dosage adjustments.
• Cost benefit analysis may influence stakeholder decisions about implementation of TDM programmes.

Clinical pharmacological advice (CPA)
Total number of CPAs
Applicant units, n (%)
Medical ward 73 (43.5)
Surgical ward 66 (39.3)
ICU 29 (17.2)

Patients’ demographics
Total number of patients 168
Age (years), mean ± SD 62.8 ± 17.1
Gender (male/female) 117/51
Body weight (kg), mean ± SD 75.1 ± 15.5
Indications for linezolid use, n (%)
Bone and joint infections 44 (26.2)
Hospital-acquired pneumonia 35 (20.8)
Severe sepsis/septic shock 31 (18.4)
CNS infections 19 (11.3)
Skin and soft tissue infections 18 (10.7)
Cardiosurgical infections/endocarditis 17 (10.1)
Intra-abdominal infections 2 (1.2)
Nocardiosis 1 (0.6)
MDR-tuberculosis 1 (0.6)
Number of CPAs per patient, median (IQR) 2.0 (1.0–4.0)

Type of CPA suggestions, n (%)
At first TDM
Dose confirmation 86/168 (51.2)
Dose reduction 59/168 (35.2)
Dose increase 23/168 (13.7)
At subsequent TDM
Dose confirmation 270/376 (71.8)
Dose reduction 74/376 (19.7)
Dose increase 32/376 (8.5)

Linezolid daily dosage, n (%)
At first TDM (n = 168)
600 mg every 12 h 168/168 (100)
At subsequent TDM (n = 376)
600 mg every 12 h 127/376 (33.8)
450 mg every 12 h 97/376 (25.8)
450 mg every 24 h 95/376 (25.3)
600 mg every 24 h 22/376 (5.8)
450 mg every 8 h 21/376 (5.6)
600 mg every 8 h 8/376 (2.1)
300 mg every 24 h 6/376 (1.6)

Route of linezolid administration (oral/i.v.) (%) 75.6/24.4
Linezolid $C_{\text{min}}$ (mg l$^{-1}$), median (IQR) 5.0 (2.9–8.0)
Duration of optimized therapy (days), median (IQR) 11.0 (5.0–27.0)
A 1 year retrospective audit of quality indicators of clinical pharmacological advice for personalized linezolid dosing: one stone for two birds?


WHAT THIS STUDY ADDS

- Clinical pharmacological advice (CPA) may enable very high adherence rates by clinicians to dosing recommendations based on TDM of linezolid.
- TDM-based CPA may consistently increase the rate of desired and safe $C_{min}$ (+ 23.4%) during linezolid therapy.
- TDM-based CPA may allow consistent cost saving especially for long term therapy with linezolid.
PATIENT-CENTRED ANTIMICROBIAL DOSAGE OPTIMIZATION
WHICH DOSAGES OF ANTIMICROBIALS ???

250 KG, BMI 81.6 !!!

SCr 4,6 mg/dL

Istituto di Farmacologia Clinica – Azienda Sanitaria Universitaria Integrata di Udine
CONCLUSIONS: Real-time TDM may represent an invaluable approach in optimizing drug exposure with high-dose daptomycin plus continuous infusion meropenem in patients with severe cellulitis, morbid obesity, and changing renal function.
TREATMENT OF CONSECUTIVE EPISODES OF MDR BACTERIAL PLEURISY WITH DIFFERENT ETIOLOGY IN A HEART TRANSPLANT CANDIDATE: PROOF OF CONCEPT OF PK/PD OPTIMIZATION OF ANTIMICROBIAL THERAPY AT THE INFECTION SITE

Pea F, Cojutti P, Merelli M, Crapis M, Bassetti M.

TREATMENT OPTIONS FOR VRE AND MDR *P. aeruginosa* INFECTION

- **VRE** (MIC for Linezolid = 1 mg/L)
  - 600 mg q12h colistin
  - 2 mg/L colistin
  - 16 mg/L ceftazidime
  - >128 mg/L piperacillin/tazobactam
- **MDR *P. aeruginosa***
  - 2 mg/L meropenem
  - 8 mg/L meropenem
estim. CLCr 47.5 mL/min
  - 16 mg/L ceftazidime
  - >128 mg/L piperacillin/tazobactam
  - >16 mg/L amikacin
  - 450 mg q48h
  - 2 mg/L ciprofloxacin

Estimated CLCr 29 mL/min
The Antimicrobial Therapy Puzzle: Could Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients?

Federico Pea and Pierluigi Viale

1Institute of Clinical Pharmacology and 4Infectious Disease, Department of Medical and Morphological Science

Infectious Diseases 2006;42: