DETERMINANTS OF TARGET NON-ATTAINMENT IN CRITICALLY ILL PATIENTS RECEIVING β-LACTAMS

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Disclosures

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Introduction

Focus in antibiotic therapy on

• Spectrum
• Timing
• Dose – one size fits all
Target attainment determined by

- **Microorganism**
  - Susceptibility

- **Drug**
  - Pharmaco-dynamics

- **Host**
  - Pharmaco-kinetics
PK variability determinants

Volume of distribution

Protein binding

Drug clearance
Hypoalbuminemia
<table>
<thead>
<tr>
<th>Highly bound (&gt;70%)</th>
<th>Moderately bound (70–30%)</th>
<th>Minimally bound (&lt;30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Cefoxitin (80–50%)</td>
<td>Cefazolin (75–93%)</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Cefoperazone (90%)</td>
<td>Cefonicid (98%)</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Cefotaxime (33–50%)</td>
<td>Cefotiamine (10–15%)</td>
</tr>
<tr>
<td>Cefazolin (75–93%)</td>
<td>Cephalothin (55–75%)</td>
<td>Cefazidine (17%)</td>
</tr>
<tr>
<td>Cloxacillin (94%)</td>
<td>Ciprofloxacin (20–40%)</td>
<td>Cefotobiprole (22%)</td>
</tr>
<tr>
<td>Clindamycin (90% bound to α₁-acid glycoprotein)</td>
<td>Clarithromycin (42–50%)</td>
<td>Cetpirome (9%)</td>
</tr>
<tr>
<td>Daptomycin (90–93%, 30% to α₁-acid glycoprotein)</td>
<td>Chloramphenicol (60%)</td>
<td>Colistin (&lt;10%)</td>
</tr>
<tr>
<td>Dalbavancin (93%)</td>
<td>Levofloxacin (50%)</td>
<td>Doripenem (8%)</td>
</tr>
<tr>
<td>Doxycycline (93%)</td>
<td>Linezolid (31%)</td>
<td>Ethambutol (20–30%)</td>
</tr>
<tr>
<td>Ertapenem (85–95%)</td>
<td>Moxifloxacin (30–50%)</td>
<td>Fluconazole (11–12%)</td>
</tr>
<tr>
<td>Erythromycin (73–81%)</td>
<td>Nitrofurantoin (40%)</td>
<td>Fosfomycin (0%)</td>
</tr>
<tr>
<td>Faropenem (96–99%)</td>
<td>Benzylpenicillin [penicillin-G] (65%)</td>
<td>Gentamycin (&lt;30%)</td>
</tr>
<tr>
<td>Flucloxacin (95%)</td>
<td>Piperacillin (30%)</td>
<td>Imipenem (20%)</td>
</tr>
<tr>
<td>Fusidic acid (95–97%)</td>
<td>Sulfamethoxazole (68%)</td>
<td>Isoniazide (0–10%)</td>
</tr>
<tr>
<td>Iclaprim (93%)</td>
<td>Ticarcillin (55%)</td>
<td>Meropenem (2%)</td>
</tr>
<tr>
<td>Itraconazole (99.8%)</td>
<td>Trimethoprim (45%)</td>
<td>Metronidazole (&lt;20%)</td>
</tr>
<tr>
<td>Lincomycin (80–90%)</td>
<td>Vancomycin (30–60%)</td>
<td>Norfloxacin (10–15%)</td>
</tr>
<tr>
<td>Minocycline (75%)</td>
<td>Voriconazole (58%)</td>
<td>Polymyxin B (&lt;10%)</td>
</tr>
<tr>
<td>Natamycin (90%)</td>
<td></td>
<td>Quinupristin/dalfopristin (11–26%)</td>
</tr>
<tr>
<td>Oxacillin (93%)</td>
<td></td>
<td>Tobramycin (&lt;30%)</td>
</tr>
<tr>
<td>Posaconazole (&gt;97%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin [rifampin] (80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadoxazole (92%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin (90–95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telavancin (92–94%)</td>
<td></td>
<td></td>
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<tr>
<td>Tigecycline (71–89%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vd changes in the critically ill

Goncalves-Pereira, J. Crit Care 2011 5:R206
Elimination of antibiotics

“Augmented renal clearance”
• AKA hyperfiltration
• Increased elimination of solutes compared to baseline

• Cut off 130mL/min
• eGFR not suited, calculated clearance better – 8 or 24h
Pathophysiology of ARC

- Systemic inflammation
  - Intravenous fluids
  - Increased organ blood flow
  - Vasoactive medications
  - Renal reserve
  - Increased GFR
    - Altered tubular function
      - Augmented renal clearance

Udy, AA. Nat Rev Nephrol 2011 9:539-543
Incidence of ARC – Ghent data

599 patientdays - 128 patients who were treated with antibiotics

- Median CLcr 97mL/min
- 52% had 1 or more ARC episodes
- 18% permanent ARC
- ARC patients had more therapeutic failure: 27% vs. 13%, \( p = .04 \)

Claus, BO. J Crit Care 2013 5:695-700
ARC risk profile

- Age
- Trauma patients
- Post surgery
- Sepsis
- Febrile neutropenia - hematological patients
- Burns
- SOFA score 0-4
AB concentrations and ARC

AB trough conc

CrCL

Udy, AA. Chest 2011
Antibiotic dosing in the ICU

- Micro-organism
  - Susceptibility

- Host
  - Pharmaco-kinetics

- Drug
  - Pharmaco-dynamics
PKPD targets

PKPD targets

T>MIC

- Cephalosporins: >60%
- Penicillins: >50%
- Carbapenems: >40%
- ICU infections: >100%
- ? Up to 100% T>4xMIC for maximal bacterial killing
Antibiotic dosing in the ICU

- Microorganism
  - Susceptibility

- Drug
  - Pharmacodynamics

- Host
  - Pharmacokinetics
The micro-organism

- MIC important determinant
- Higher MICs = higher probability of AB treatment failure
- Clinical data available
  - MRSA and vancomycin
  - Pseudomonas and piperacillin
Meropenem / Pseudomonas aeruginosa
EUCAST MIC Distribution - Reference Database 2013-09-29

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)

% microorganisms

Epidemiological cut-off: WT ≤ 2 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

57505 observations (73 data sources)
Antibiotic dosing in the ICU

Microorganism
• Susceptibility

Drug
• Pharmaco-dynamics

Host
• Pharmaco-kinetics

WHY IS THIS IMPORTANT?
Why is this important?

Potential consequences of underdosing

- Therapeutic failure
- Need for multiple antibiotic courses
- Selection of resistant micro-organisms
- Resistance development
Antibiotic dosing in the ICU

**Microorganism**
- Sensitivity

**Drug**
- Pharmacodynamics

**Host**
- Pharmacokinetics

**DALI study**
Disclosures

• This study has been funded in part by:
  – ESICM ECCRN
  – Royal Brisbane and Women’s Hospital Research Foundation, Australia
Aims – The DALI Study

• Primary – to describe the PK of beta-lactam and glycopeptide antibiotics in ICU patients and whether contemporary dosing achieves PK/PD targets
Methods

• Multi-national DALI PK study
• 68 ICUs in 10 countries throughout Europe.
• Point-prevalence PK study
  – Patients were recruited on a single day with PK sampling during that week
  – 9 countries – September 2011
  – France – April 2012
• Antibiotics of interest: beta-lactams; glycopeptides and triazoles and echinocandins
Methods – Sample Collection

• 2 blood samples

• Sample A at 30mins post end of infusion; sample B at 50% of dose interval, and then sample C within 30 minutes preceding the next scheduled dose).

• Continuous infusion – two samples taken at least 6 hours apart.

• Samples couriered from participating centre to Burns Trauma and Critical Care Research Centre, Australia for analysis
Data Collection

• Demographic data
  – age, gender, height, weight

• Clinical data
  – admission diagnosis,
  – APACHE II, SOFA, PIRO scores
  – presence of extracorporeal circuits, procalcitonin (where available),
  – presence/absence of surgery within previous 24 hours

• Organ function data

• Dosing data

• Infection data
  – known or presumed pathogen, known or likely MIC
PK & PK/PD Methods

- Non-compartmental PK analysis of unbound concentrations
- Demographic and clinical data collection
- Actual or EUCAST MIC values
- Individual patient results were compared with outcome and pharmacodynamic targets.
  - 50% $T_{>\text{MIC}}$, 50% $T_{>4\times\text{MIC}}$, 100% $T_{>\text{MIC}}$, 100% $T_{>4\times\text{MIC}}$
Results - patients

- Total n = 450 (includes antibacterials and antifungals)
  - Amoxycillin: n=71
  - Ampicillin: n=18
  - Cefazolin: n=14
  - Cefepime: n=14
  - Ceftriaxone: n=33
  - Doripenem: n=13
  - Piperacillin: n=109
  - Meropenem: n=89
  - Vancomycin: n=43
  - Teicoplanin: n=13
Demographic and Clinical Results

- Results described as Median (IQR)
  - Age: 61 (47-74) years
  - Weight: 75 (65-85) kg
  - APACHE II score: 18 (13-25)
  - SOFA Score: 5 (2-8)
  - PIRO Score: 1 (1-2)
Results – AB concentrations

Mid-dose

End-of-dose
PK/PD results – Beta-Lactams

• Target attainment
  • 50% $T_{\text{MIC}}$
    • 50% $T_{\text{MIC}}$ target achieved by 80.0% patients
    • 50% $T_{4\times\text{MIC}}$ target achieved by 50.2% patients
  • 100% $T_{\text{MIC}}$
    • 100% $T_{\text{MIC}}$ target achieved by 59.3% patients
    • 100% $T_{4\times\text{MIC}}$ target achieved by 31.2% patients
Results – clinical outcome
Acknowledgements

• Contributors
Antibiotic dosing in the ICU

Microorganism
- Sensitivity

Drug
- Pharmacodynamics

Host
- Pharmacokinetics

HOW TO SOLVE THIS?
Practical approach

**PKPD optimization**

- Front-loading
- Beta-lactams: extended/continuous infusion
Loading dose simulation

- Plasma concentration (mg/L) over time (h)
  - Mean
  - Mean + SD
  - Mean - SD

Breakpoint: Pseudomonas aeruginosa
Improving target attainment

Dose (6-hourly)

- 1000mg
- 750mg
- 500mg
- 250mg

Lamoth, F. Antimicrob Agents Chemother 2009 2:785-787
Improving target attainment

Dosing frequency

4 hourly
6 hourly
8 hourly

Lamoth, F. Antimicrob Agents Chemother 2009 2:785-787
Improving target attainment

![Graph showing the relationship between GFR (mL/min) and percent with trough > 1 mg/L for different infusion times: 120 min, 60 min, and 30 min.]
Practical approach

PKPD optimization: prolonged infusion

Piperacillin 4g/6h
Meropenem 1g/8h

T>breakpoint
58% (IQR 41-92%) ➞ 98% (IQR 75-100%)

T>breakpoint
50% (IQR 47-57%) ➞ 81% (IQR 69-88%)
Tissue vs. plasma concentrations

**FIG. 2.** Concentration-time profiles of meropenem in plasma (black) and ELF (gray) as calculated from the mean parameter vector. L, liter.
Variability over time

Carlier M et al, IJAA 2014 in press
MODS

- Risk of underdosing according to disease severity (if using standard dosing)

SOFA <4 | SOFA 4-10 | SOFA >10

Disease severity
Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial

Abstract Purpose: There is variability in the pharmacokinetics (PK) of antibiotics (AB) in critically ill patients. Therapeutic drug monitoring (TDM) could overcome this variability and improve PK target attainment. 100 % $fT_{>AMIC}$ was achieved in 21 % of the PTZ patients and in none of the MEM patients; 100 % $fT_{>MIC}$ was achieved in 71 % of the PTZ patients and 46 % of the MEM patients. Of the patients in the intervention group...
Target attainment using TDM

De Waele, JJ. Intensive Care Med 2014 in press
Conclusions

- Optimal dosing determined by interplay between host, drug and micro-organism
- Antibiotic PK significantly changed in critically ill - confirmed in DALI study
- No single patient characteristic is indicative of underdosing – ARC most important though
- Extended and continuous infusion improves exposure to beta-lactam antibiotics