Optimizing antimicrobial therapy in the elderly

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Dosing should be such that the level of antmicrobial activity is associated with a high likelihood of therapeutic success.

DOSE

Dose Finding - The Past
Efficacy of the drug

Potency of a drug (MIC)

Exposure to the bug
In vivo (PK)

ACTIVITY
in vitro (MIC)

CONCENTRATIONS
in vivo (PK)

DOSING
regimen

ANTMICROBIAL EFFICACY
(Microbiological Cure)

CLINICAL EFFICACY
(Clinical Cure)

MIC
Measure of Potency – antibacterial activity

Lowest concentration with no visible growth after 18 hour incubation

MIC = 2 mg/L
Pharmacokinetic parameters: Measures of Exposure

AUC is usually linearly related to Dose

Dose $\times 2 = \text{AUC} \times 2$

Dose $\times 4 = \text{AUC} \times 4$

Lowest concentration with no visible growth after 18 hour incubation

MIC

$X$-acin 500 mg

$\text{MIC} = 2 \text{ mg/L}$
Pharmacokinetic Parameter (and Dose)

• Thus, we have to:
  – Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
  – Determine which dosing regimens are optimal for Treatment in relation to the MIC

Pharmacokinetic Parameter (and Dose)

• EXPOSURE RESPONSE RELATIONSHIP

Probability of cure after treatment with fluconazole
Oral candidiasis n=132

Treatment with fluconazole
Doses 50 – 800 mg

⇒ Individual AUC

⇒ Culture-results with MIC-values

⇒ MIC-values per individual

⇒ Microbiological outcome (candida cured)

⇒ Clinical outcome

Determine AUC/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis  n=132

- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value.

NOTE: MICs by EUCAST method

Rodriguez-Tudela et al, AAC 2007

Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis  n=132

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Pharmacodynamic Target

NOTE: MICs by EUCAST method

Rodriguez-Tudela et al, AAC 2007
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

- If Dose is known because of the standard dose e.g. 400 mg ~ 400 mg.h/L
- And an Dose/MIC of 100 is required
- It follows that the breakpoint is 400/100 = 4 mg/L

Rodriguez-Tudela et al, AAC 2007

Susceptible (S)
A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with an uncertain therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.

Resistant (R)
Bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.

LAB REPORT

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)
121 patients with *S. pneumo­niae* respiratory infection

- **fAUC/MIC cut-off ~34**

- Relationship between fAUC/MIC ratio & microbiological response from a total 121 patients with respiratory tract infection involving *S. pneumoniae*.
  - fAUC/MIC > 34 had 92.6% response rate.
  - fAUC/MIC < 34 had 66.7% response rate.

**Pharmacokinetic parameters: Measures of Exposure**

- PEAK
- AUC
- MIC
- T > MIC
**Ceftazidime in patients with nosocomial pneumonia**

- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime

N=390 patients included

N=170 with MIC

N=154 with MIC and PK-estimates

16 without PK estimates

220 without Gram negatives in cultures

Muller et al, JAC 2013 68:900-906

**Clinical phase 3 study**

- PK-data
- PK population model
- Individual PK parameters
- Culture-results with MIC-values
- MIC-values per individual
- Individual exposure to CAZ %T>MIC

**Microbiological outcome**

**Clinical outcome**

**Time > MIC dependent on dose frequency**

Total daily dose similar

- 12.5 q6
- 25 q12
- 50 q24

Total length of bars corresponds to Time > MIC

Concentration mg/L

MIC 2 mg/L

Time (h)
Exposure-response Emax model
microbiological eradication

- Individual exposures to CAZ
- Categorised (%/T>MIC per 10%)
- Eradication rate per group
- 154 patients

Ceftazidime in patients with nosocomial pneumonia

CART analysis
- to differentiate between lower and higher response rate

<table>
<thead>
<tr>
<th>%/T&gt;MIC</th>
<th>Success</th>
<th>Failure</th>
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<tbody>
<tr>
<td>≥44.9</td>
<td>83 (90.2%)</td>
<td>9 (8.1%)</td>
</tr>
<tr>
<td>&lt;44.9</td>
<td>31 (50%)</td>
<td>9 (50%)</td>
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</table>

P<0.0001

Probability plot of the logistic regression analysis for ceftazidime showing the relationship between %/T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC

P=0.002
Probability plot of the logistic regression analysis for ceftobiprole showing the relationship between %fT>MIC and probability of cure at TOC – nosocomial pneumonia

Muller et al. AAC 2014

Any idea where we are today?
No idea…
May be a mouse?
Might be a human, though…

An elephant…
Today it is an elephant!
Neutropenic Mouse Thigh-Infection Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1
2. Bacteria injected into thighs on day 0 (10⁶ - 7)
3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days
4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

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Fig 2. 24-Hr AUC/MIC

24-Hr AUC/MIC

-10 -100 -1000

Log10 CFU/Thigh at 24 Hrs

2

4

6

8

10

Peak/MIC

1 10 100 1000

Time Above MIC

0 25 50 75 100

-1

3

5

7

9

10

Peak/MIC

1 10 100 1000

Time Above MIC

0 25 50 75 100

levofloxacin
ceftazidim
pk/pd Index (NOT dose!!!) matches
-qualitatively
-quantitatively

**PK/PD Index**

- Animal Correlation
- Treatment - Effect
- Outcome parameter

- Human Correlation
- Treatment - Effect
- Outcome parameter

**T>MIC**
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
- Triactams

**AUC**
- Aminoglycosides
- Fluoroquinolones
- Ketolides
- Macrolides
- Oxazolidinones
- Azoles

**NOTE:** MICs by EUCAST method

**Relationship PK/PD and Effect**

**Probability of cure after treatment with fluconazole**

*Oropharyngeal Candidiasis n=132*

**Pharmacodynamic Target**

**Uncertainty**

**Rodriguez-Tudela et al, AAC 2007**

**EC50:** 43.69

**R²:** 0.9938

**AUC/MIC prob cure**
### LAB REPORT

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Organism 1</th>
<th>Escherichia coli</th>
<th>≥10001 cm/μl</th>
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<tbody>
<tr>
<td></td>
<td>Name</td>
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**BASED ON EXPOSURES OF COMMON DOSES**

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

**LAB REPORT**

**BASED ON EXPOSURES OF COMMON DOSES**

IN ADULTS - < 50 Y (mostly)

EXPOSURES IN Elderly?

Consequences for dosing?

Overdosing?

Underdosing?
Ceftazidime AUCs, 6 gr total daily dose

Mouton & Muller Unpublished data

Ceftazidime Cmins, 3x2 gr

• Increased exposure
• Increased variation

DOSE ADJUSTMENTS Necessary

Mouton & Muller Unpublished data
So what can we conclude from all this?

- Pharmacodynamic targets have been described for many antimicrobials
- Clinical breakpoints are based on exposures in adults – but not the elderly!
- Exposures in the elderly show more variation
- Exposures in special populations need to be determined and dosing adjusted where applicable – if at all possible