New Ways to Use Old and Coming Antibiotics
a PK/PD perspective

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Jansen
J&J
Pfizer
Merck
GSK
Schering-Plough
Astra-Zeneca
Gilead
Astellas
Durata
Cerexa
Cubist
Angelini
Biomerieux
Beckton-Dickinson
Basic questions in dosing regimens

which dose?

frequency of dosing? Duration?

⇒ to optimise antibacterial effect but minimise risk of emergence of resistance
Efficacy of the drug

Potency of a drug (MIC)

Exposure to the bug

*In vivo*

(PK)
Potency of a drug in vitro (MIC)

Exposure to the bug in vivo (PK)

Dosing Regimen

Antimicrobial Efficacy of the Drug (Microbiological Cure)

Effect on Host (Clinical Cure)
Any idea where we are today?

No idea…
may be a mouse?

Might be a human,
though…
An elephant....
Today it is an elephant!
The pharmacodynamic index

Three main ones used -
- Cmax/MIC; T>MIC; AUC/MIC

[c] (mg/L)

AUC (mg/L.h)

Cmax (mg/L)

pathogen MIC (mg/L)

T>MIC

time (h)
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

• Prob cure correlates with AUC/MIC
• POSITIVE correlation with EXPOSURE
• INVERSE correlation with MIC

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

Rodriguez- Tudela et al, AAC 2007
Preclinical Models
Dose response curve moxifloxacin against E coli using human pharmacokinetics

Adapted from MacGowan et al.
It is not only for Mice
- effects in mice and men are comparable

<table>
<thead>
<tr>
<th>Disease state, drug</th>
<th>Clinically-derived PK-PD target [reference(s)]</th>
<th>Animal infection model; organism studied</th>
<th>Animal-derived PK-PD target [reference(s)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital-acquired pneumonia</strong></td>
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<tr>
<td>Quinolones</td>
<td>fAUC_{0-24}:MIC ratio, 62–75 [11, 12]</td>
<td>Neutropenic mouse thigh; gram-negative bacilli</td>
<td>fAUC_{0-24}:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]</td>
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<td><strong>Community-acquired respiratory tract infections</strong></td>
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<tr>
<td>Quinolones</td>
<td>fAUC_{0-24}:MIC ratio, 34 [22]</td>
<td>Immunocompetent mouse thigh; <em>Streptococcus pneumoniae</em></td>
<td>fAUC_{0-24}:MIC ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>T&gt;MIC, 40% of the dosing interval [14]</td>
<td>Immunocompetent mouse thigh; <em>S. pneumoniae</em></td>
<td>T&gt;MIC, 30–40% of the dosing interval for 90% animal survival [14]</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>AUC_{0-24}:MIC ratio, 3,875 [20]</td>
<td>Neutropenic mouse thigh; <em>S. pneumoniae</em></td>
<td>AUC_{0-24}:MIC ratio, 1,000 for stasis [24]</td>
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<td><strong>Bacteremia</strong></td>
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<tr>
<td>Oritavancin</td>
<td>T&gt;MIC, 22% of the dosing interval for <em>Staphylococcus aureus</em> [25]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>fT&gt;MIC, 20% of the dosing interval for a 0.5 log-unit kill [26]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>AUC_{0-24}:MIC ratio, 55 for <em>S. aureus or Enterococcus faecium</em> [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>AUC_{0-24}:MIC ratio, 83 for stasis [33]</td>
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<td><strong>Complicated skin and soft-tissue infections</strong></td>
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<tr>
<td>Tetracycline</td>
<td>AUC_{0-24}:MIC ratio, 17.9 [28]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>AUC_{0-24}:MIC ratio, 15–20 for stasis [29]</td>
</tr>
<tr>
<td>Linezolid</td>
<td>AUC_{0-24}:MIC ratio, 110 [27]</td>
<td>Neutropenic mouse thigh; <em>S. aureus</em></td>
<td>AUC_{0-24}:MIC ratio, 83 for stasis [33]</td>
</tr>
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</table>

**NOTE.** AUC_{0-24}:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{\text{max}}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.
Preclinical Models

Dose response curve moxifloxacin against E coli using human pharmacokinetics

AUC/MIC stasis = 46

AUC/MIC 99.9% kill = 84

AUC/MIC 95% max effect = 118

AUC/MIC max effect = 390

Adapted from MacGowan et al.

JWM Milan10-05-2011
Preclinical Models

What we need for efficacy? And to suppress resistance? the recommended (approved) doses fits the desired PK/PD magnitude?

Eno gh for efficacy?

Enough to delay or suppress resistance?

AUC/MIC 99.9% kill = 84
AUC/MIC 95% max effect = 118
AUC/MIC max effect = 390

The recommended (approved) doses fits the desired PK/PD magnitude?
Saving drugs – Reduce Resistance
Dose and Schedule Choices to Suppress Emergence of Resistance

Cell Kill –

Monotonic Function

Dose and Schedule Choices to Suppress Emergence of Resistance

Cell Kill –

Monotonic Function

Resistance Suppression –

Non-Monotonic Function


Tam et al, modified
Effect of Dosing and Dosing Frequency on the Efficacy of Ceftizoxime and the Emergence of Ceftizoxime Resistance during the Early Development of Murine Abscesses Caused by *Bacteroides fragilis* and *Enterobacter cloacae* Mixed Infection.

Lorna E. T. Stearne, Wil H. F. Goessens, Johan W. Mouton, and Inge C. Gyssens

**Static effect is optimal**

For selecting resistance....

Stearne et al, AAC 2007
Relationship between $fAUC/MIC$ and Effect

121 patients with *S. pneumoniae* respiratory infection

- $fAUC/MIC$ cut-off $\sim 34$

- 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.

A good clinical effect does NOT mean that the regimen is optimal!!!!

Zinner et al, JAC 2003
P. aeruginosa

Levofloxacin Effect: Mouse Thigh Infection Model
Preventing Emergence of the Resistant Mutant Population

AUC/MIC ratio of 157 Shuts Off Growth of Resistant Mutants

Log_{10}(CFU/ml) vs Dose (mg/Kg)

Jumbe et al, JCI 2003
• Higher exposure is needed to prevent emergence resistance compared to optimizing efficacy

• Relatively low doses promote emergence of resistance
DURATION OF THERAPY
Impact on Resistance Amplification

Flight of Time’s Arrow

The longer therapy goes, the higher the drug exposure that is required to suppress resistance.

Lessons learned:
* Go in with high intensity therapy to suppress resistance
* Stop quickly

Increase in MIC of pseudomonas is dependent on total number of days treated (total dose)

- 34 CF patients followed for > 3 years prior to 1992
- Number of days IV therapy
- Mean 2log increase of MICs for 15 antimicrobials

\[ R_s = 0.57 \]
\[ p = 0.004 \]

Adapted from Mouton JW et al, JAC 1993 31:919-926
Evidence: Duration of surgical prophylaxis and selection of resistance

<table>
<thead>
<tr>
<th>Cardiovascular surgery</th>
<th>n= 2'641, multivariate analysis</th>
<th>&lt; 48 h prophylaxis</th>
<th>&gt; 48 h prophylaxis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 48 h prophylaxis</td>
<td></td>
</tr>
<tr>
<td>SSI</td>
<td>1.0 (0.8-1.3)</td>
<td>ns</td>
<td></td>
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<tr>
<td>Resistant</td>
<td>1.7 (1.1-2.7)</td>
<td>0.027</td>
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<tr>
<td>Enterobacteriaceae/enterococci</td>
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</tbody>
</table>

Some solutions

- efficacy
- resistance
“If one is good, two must be better”
<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference: JWM Milan 10-05-2011</td>
<td></td>
<td></td>
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<tr>
<td>Kumar et al CCM 2010</td>
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</table>

**Diagram:**

- The diagram illustrates the odds ratio of death against various criteria.
- The x-axis represents the odds ratio, while the y-axis shows the criteria.
- The shaded area indicates the confidence interval for the odds ratio.

**Note:**

The image contains graphs and data tables that are not fully legible due to the resolution or quality of the image. The text and data are presented in a structured format to ensure clarity and readability.
Synergy In Vivo of Combination

Single drug

Predict effect combination

Line of no interaction

Mouton ea., aac 1999
PK model in vitro

single tobra/cefta

combination

Examples where combinations do work

HIV
TBC
Malaria

In other type of infections difficult to demonstrate

low power
poorly designed studies

Effect has been shown in:

Pseudomonas, acinetobacter (hypermutators!!)
Severely ill patients

Extensive non-clinical evidence
Cycling

- In most situations, cycling does not prevent resistance
- Cycling may promote resistance
- Discourage use
Reducing Length of Exposure
Reduce duration Therapy
Scenario in CAP

1. 3 to 5 days
2. At least 5 days & afebrile for 48 h
3. At least 7 days
4. At least 10 days
5. 14 days
Meta-analysis of 15 randomised trials
No differences in clinical success for short courses (≤7 days) vs extended courses (>7 days)
Agents: β-lactams, fluoro-quinolones, ketolides, azithromycin
3 – 5 days: Evidence?

- 100,000 IU Penicillin per day for 2 to 3 d
  
  Keefer et al, JAMA 1943

- 60,000 IU Penicillin per day for 1 to 2 d
  
  Dawson et al, JAMA 1944

- Most patients treated for 3 to 4 d
  
  Tillett et al, Bull NY Acad Med 1944
Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E E van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer and Jan M Prins

*BMJ* 2006;332:1355-
doi:10.1136/bmj.332.7554.1355

Research question:
Antibiotic treatment duration for hospitalized adult ...

1) ... with CAP
2) ... mild to moderate (PSI score ≤ 110)
3) ... good response after 3d of IV amoxicilline
Proportion of patients considered clinical successes in intention to treat population

Cumulative event free outcome

Days since start of treatment

Three days’ amoxicillin
Eight days’ amoxicillin

el Moussaoui, R. et al. BMJ 2006;332:1355
Scenario in CAP

1. 3 to 5 days
2. At least 5 days & afebrile for 48 h
3. At least 7 days
4. At least 10 days
5. 14 days
Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD
Mirjam Christ-Crain, MD
Robert Thomann, MD
Claudine Falconnier, MD
Marcel Wolbers, PhD
Isabelle Widmer, MD
Stefanie Neidert, MD

Context In previous smaller trials, a procalcitonin (PCT) algorithm reduced antibiotic use in patients with lower respiratory tract infections (LRTIs).

Objective To examine whether a PCT algorithm can reduce antibiotic exposure, increasing the risk for serious adverse outcomes.


JAMA 2009; 302: 1059-66
-- 09.09.09 --
Main results

• Rate of adverse outcomes similar in PCT and control group (15.4% vs. 18.9%)
• In the PCT group, antibiotic exposure significantly lower as compared to controls (35% reduction, p<0.001)
• Antibiotic-associated side effects less frequent in the PCT group (19.8% vs. 28.1%; p<0.001)

Reduce Duration Exposure / Therapy

• Prophylaxis: tons of evidence: 1 dose only unless

• CAP: 3 or 5 or 7 days? – may depend on country but not longer!! – High dose, short duration

• Biomarkers highly needed and shown to reduce duration of therapy
Minimizing bacterial resistance

Frapper fort et frapper vite

(Ehrlich, 1913)

(hit hard and hit early)
Summary

• Higher doses, shorter duration
• Implement prophylaxis knowledge
• Knowledge database, involve available technology
• Diagnostics, biomarkers
• Revise indications and dosing generics
• New drugs: revise regulatory aspects
• Rational and uniform clinical breakpoints
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