Demystifying MIC
Making MIC work for you

Prof. Ashok Rattan,
MD, MAMS, INSA DFG, WHO Lab Director
Academics, Industry: Research, Diagnosis, Public Health, Academics
Discovery & Development of Anti-bacterial is one of the most important discovery of the 20th Century.
Introductions of New Antibiotic Classes

- Sulfas 1936
- Penicillin 1940
- Tetracycline 1949
- Aminoglycosides 1950
- Macrolides 1952
- Glycopeptides 1958
- Quinolones 1962
- Streptogramin 1962
- Oxazolidinone 2000
- Quinolones 1962
- Streptogramin 1962
- Glycopeptides 1958
- Macrolides 1952
- Aminoglycosides 1950
- Tetracycline 1949
- Penicillin 1940
- Sulfas 1936
- Me too drugs
- Different Generations
- Ertapenem 2001
- Daptomycin 2003
- Telithromycin 2004
- Tigecycline 2006
- Doripenem 2007
- Ceftaroline 2010
- Oxazolidinone 2000
# Power of antibiotics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre Antibiotic era deaths</th>
<th>Deaths with antibiotics</th>
<th>Change in deaths due to antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP (1)</td>
<td>35%</td>
<td>10%</td>
<td>- 25%</td>
</tr>
<tr>
<td>HAP (2)</td>
<td>60%</td>
<td>30%</td>
<td>- 30%</td>
</tr>
<tr>
<td>Heart Infection (3)</td>
<td>100%</td>
<td>25%</td>
<td>- 75%</td>
</tr>
<tr>
<td>Brain Infections (4)</td>
<td>&gt; 80%</td>
<td>&lt; 20%</td>
<td>- 60%</td>
</tr>
<tr>
<td>Skin Infection (5)</td>
<td>11%</td>
<td>&lt; 0.5%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

By comparison…. Treatment of heart attacks with aspirin or clot busting drugs (6) - 3%

---

(2) IDSA/ACCP/ATS/SCCM position paper. CID 2010; 51 (S1): 51 – 3  
(3) Kerr AJ. SABE Lancet 1935; 226: 383 – 4  
Mankind has always had the benefit of “good” advice

“By the year 2000, nearly all experts agree that bacterial and viral diseases will have been virtually wiped out…”

The futurists: looking toward year 2000
(Time magazine, February 25, 1966)

US surgeon general William Stewart:

“The time has come to close the book on infectious diseases” (1969)
Increasing Incidence of Resistance in the US
MRSE, MRSA, VRE, PRSP, GISA
1980-2006

Percentage of Pathogens Resistant to Antibiotics


MRSE, MRSA, VRE, PRSP, GISA
We must make the best use of what we have

New and novel antibiotics

Resistance in important pathogens
Consequences of antibiotic use

- Clinical cure
- Inhibition of non-pathogenic bacteria
- Selection of resistant mutants
- Toxicity / side effects

• Clinical cure

[Diagram showing balance with consequences of antibiotic use on either side]
Problem of MDR

- **Act of GOD**
  - Resistance is already present & giving antibiotics selects for resistance

- **Act of MAN**
  - Inadequate Infection control practices also transfer of MDR from one to another
Microbiological evaluation was (classically) static

identification

sensitivity

MIC

Breakpoints

by static techniques
Definition: Lowest concentration of an antimicrobial agent that prevents visible growth of a micro organism in an agar or broth dilution susceptibility test

True MIC: somewhere between lowest test concentration (MIC reading) and next lower concentration

50%; 80% decrease in measured (OD) growth; tailing effect

Dilution used: base as 2
- 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 μg/ml

Acceptable reproducibility: within one twofold dilution

Report must provide interpretive category: S, I, R

Breakpoint MIC

$\text{MIC}_{50}, \text{MIC}_{90}$
Drug potency is measured by determining lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism after overnight exposure.

Known bacterial inoculum placed into each tube.

- 0.25 µg/mL
- 0.5 µg/mL
- 1.0 µg/mL
- 2.0 µg/mL
- 4.0 µg/mL (MIC)
- 8.0 µg/mL
- 16 µg/mL

Increasing Antibiotic Concentration

MIC = 4.0 µg/mL
MICROTITER MIC PHOTO (Post-Incubation)

Courtesy of Antimicrobial Test Laboratories
- highly diluted quaternary ammonium
- same antimicrobial agent in all rows

Range of product dilutions are analyzed

---

C- 0.8 0.4 0.2 0.1 0.05 0.025 0.012 0.005 0.003 0.001 C+

AMB

ITZ

C- 1 0.5 0.25 0.12 0.06 0.03 0.015 0.008 0.004 0.002 C+

ITZ - AMB
Different concentrations of Lincomycin in Mueller-Hinton II agar:

Increase the concentration of Lincomycin
**Breakpoint MIC**

<table>
<thead>
<tr>
<th></th>
<th>MIC (µg/mL)</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>≤ 4</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8-16</td>
<td>15-19</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥32</td>
<td>≤14</td>
</tr>
</tbody>
</table>

“Susceptible breakpoint” is 4 µg/mL or 20 mm
“Resistant breakpoint” is 32 µg/mL or 14 mm
Disk Diffusion

Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized Single Disk method

National Committee for Clinical Laboratory Standards (NCCLS)
Now Clinical Laboratory Standard Institute (CLSI)
  Nonprofit, autonomous, educational organization
  Formed by professionals, academics, government and industry
  Consensus documents based on the principle that voluntary consensus standards are essential for high quality assured work essential for quality patient care
M 2 : Disk Diffusion
M 6 : Evaluating dehydrated Mueller Hinton Agar
M 7 : MIC for aerobic bacteria
M 11 : AST for anaerobes
M 23 : Development of susceptibility testing criteria
M 24 : For mycobacteria
M 27 : For yeast
M 38 : Filamentous fungi
M 39 : Analysis and presentation of cumulative AST data
M 100: Performance standards for AST

M denotes a microbiology document
2 is a number assigned by CLSI for disk diffusion
A means it is an approved document (P, T)
12 indicated the seventh edition of M 2

M 2 and M 7 are revised every three years
M 100 is updated every year
Comparison of Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing guidelines for the interpretation of antibiotic susceptibility at a University teaching hospital in:

Concodance between CLSI and EUCAST results

5165 E.coli had 78.2 to 100%
1103 S aureus had 94.6 to 100%
532 Ps aeruginosa had 89.1 to 95.5%
Table 3A. Zone Diameter Interpretive Standards and equivalent Minimal Inhibitory Concentration (MIC) breakpoints for Entamoeba histolytica

<table>
<thead>
<tr>
<th>Testing Condition</th>
<th>GC Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium: Mueller-Hinton agar</td>
<td>Enteric agar, 1% NaCl, 10% sheep blood, 1% yeast extract, 0.5% glucose</td>
</tr>
<tr>
<td>Incubation: 37°C, anaerobic, 10 to 14 days</td>
<td>Aerobic, incubation for a total of 14 days</td>
</tr>
<tr>
<td>Resistance Evaluation:</td>
<td></td>
</tr>
</tbody>
</table>

**General Comments:**

1. For isolates of *G. lamblia* and *G. hominis*, only aspirin, a phenol, amoxicillin/clavulanic acid, and levofloxacin should be tested and reported routinely. In addition, chlorhexidine and a trisodium citrate/NaOH solution should be tested and reported for enteric isolation of *Entamoeba* sp.

**Note:** Information for these species is considered tentative for use in research.

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
<th>Zone Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>E. coli</td>
<td>E. coli</td>
<td>P. aeruginosa</td>
<td>P. aeruginosa</td>
<td>S. aureus</td>
<td>S. aureus</td>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCTC</td>
<td>ATCC</td>
<td>NCTC</td>
<td>ATCC</td>
<td>NCTC</td>
<td>ATCC</td>
<td>ATCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>10418</td>
<td>25922</td>
<td>10662</td>
<td>27853</td>
<td>6571</td>
<td>25923</td>
<td>29213</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT 492</td>
<td>0.015</td>
<td>0.03</td>
<td>0.25</td>
<td>0.25</td>
<td>0.001</td>
<td>0.004</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT 773</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.015</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>2</td>
<td>4</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>0.12</td>
<td>0.25</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2</td>
<td>4</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.12</td>
<td>0.12</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azlocillin</td>
<td>4</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>0.03</td>
<td>0.25</td>
<td>4</td>
<td>4</td>
<td>&gt;128</td>
<td>-</td>
<td>&gt;128</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>2</td>
<td>-</td>
<td>32</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>1</td>
<td>2</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0.25</td>
<td>-</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.06</td>
<td>0.25</td>
<td>16</td>
<td>-</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.03</td>
<td>0.06</td>
<td>8</td>
<td>8</td>
<td>0.5</td>
<td>-</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotetan</td>
<td>0.06</td>
<td>-</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>4</td>
<td>-</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cepirime</td>
<td>0.03</td>
<td>0.03</td>
<td>4</td>
<td>1</td>
<td>0.25</td>
<td>-</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>0.25</td>
<td>0.25</td>
<td>128</td>
<td>&gt;128</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazidime</td>
<td>0.06</td>
<td>0.25</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>-</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefizoxime</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.03</td>
<td>0.06</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2</td>
<td>4</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalorodil</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>4</td>
<td>8</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>0.5</td>
<td>-</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephradine</td>
<td>-</td>
<td>-</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2</td>
<td>4</td>
<td>128</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.015</td>
<td>0.015</td>
<td>0.25</td>
<td>0.25</td>
<td>0.12</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.06</td>
<td>0.12</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MIC of Reference Stains
Parameters of Antimicrobial Activity

• **Potency:**
  - MIC
  - MBC

• **Time course of activity**
  - Rate of killing & effect of increasing concentration
  - Persistant effects
    • PAE, SMPAE, PALE
PK / PD consideration & application

Clinical cure

- Inhibition of non-pathogenic bacteria
- Selection of resistant mutants
- Toxicity / side effects
Pharmacology of Antimicrobial Therapy

Dosage Regimen
- Time course of serum levels
- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacokinetics
What the body does to the drug

Time course of levels in tissues
- Time course of pharma & tox effect

Pharmacodynamics
What the drug does to the body & bacteria

Time course of levels at site
- Time course of antimicrobial activity
What body does to the drug

What drug does to the body & the bacteria
PK/PD terminology &
central role of MIC

<table>
<thead>
<tr>
<th>Serum Conc. (ug/ml)</th>
<th>C max/ MIC</th>
<th>AUC / MIC</th>
<th>t &gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C max

AUC / MIC

t > MIC

Time > MIC

MIC
PK/PD parameters predictive of success

- Cmax / MIC > 10
- AUC / MIC > 100
- T > MIC > 40% of dosing interval

Variables affecting concentration:

- Volume of distribution (Vd)
  - Clearance (Cl)

  \[ T \frac{1}{2} = 0.693 \times Vd \]
  - Cl
SEPSIS
Patterns of antimicrobial activity

- Concentration dependent killing and prolonged persistent effect
- Seen with Aminoglycosides, Quinolones, daptomycin, ketolides, amphotericin B
- Goal of dosing: maximize concentration
- AUC/MIC and Cmax/MIC major parameters of efficacy

![Kill Kinetics of Synercid IV against MRSA 562](chart.png)
Patterns of antimicrobial activity

- Concentration independent killing
- Minimal to moderate persistent effects
- Seen with all β-lactams, clindamycin, macrolides, oxazolidinones, Flucytosine
- Goal of dosing: Optimize duration
- $t > \text{MIC}$ major parameter of efficacy

**Kill Kinetics Of Linezolid Against E. faecalis Sp346**

![Graph showing kill kinetics of Linezolid against E. faecalis Sp346.](image-url)
Experimental models to investigate PK/PD relationships: Overview

• Use neutropenic animals
• Evaluate 20 - 30 different dosing regimens (5 dose levels, 4-6 different intervals)
• Measure efficacy by change in $\log_{10}$ cfu per thigh or lung at end of 24 hours therapy
• Correlate efficacy with various PK/PD parameters
  • $(t > \text{MIC},$
  • $\text{Cmax/MIC},$
  • $24$ hours $\text{AUC/MIC}$)
1. Microbial eradication
2. Selection of resistance

-2 hr
Infect

0 hr
Begin therapy

24 hr
Sacrifice, harvest, homogenize muscle
Dissociating PK covariables

- C_{max} / MIC
- T > MIC
- Peak/MIC
- T > MIC
- AUC / MIC

Concentration, ng/mL

Time, hours

qd dosing
bid dosing
tid dosing
MIC 90
Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model

$R^2 = 94\%$

- **Graphic 1:**
  - **Y-axis:** Log$_{10}$ CFU per Lung at 24 Hours
  - **X-axis:** Time Above MIC (Percent)

- **Graphic 2:**
  - **X-axis:** 24-Hour AUC/MIC Ratio
  - **Y-axis:** Log$_{10}$ CFU per Lung at 24 Hours

- **Graphic 3:**
  - **X-axis:** Peak/MIC Ratio
  - **Y-axis:** Log$_{10}$ CFU per Lung at 24 Hours
S. pneumoniae & Levofloxacin
PK/PD relationship is class dependent
PK/PD correlation with efficacy

• T > MIC
  – Penicillin
  – Cephalosporins
  – Carbapenems
  – Monobactam
  – Macrolides
  – Clindamycin
  – Oxazolidinones
  – Glycylcyclines
  – Flucytosine

• AUC or Cmax/MIC
  – Aminoglycosides
  – Fluoroquinolones
  – Metronidazole
  – Daptomycin
  – Ketolides
  – Azithromycin
  – Streptogramin
  – Glycopeptides
  – Amphotericin
  – Fluconazole
Relationship between time > MIC and efficacy in animal infection models infected with *S. pneumoniae*.
Relationship Between T>MIC and Bacterial Eradication with Beta-Lactams in Otitis Media (Circles) and Maxillary Sinusitis (Squares)
Relationship between AUC/MIC and Survival for Fluoroquinolones

Relationship Between AUC/MIC and Outcomes for Ciprofloxacin

Levofloxacin PK/PD correlation

Clinical outcome

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td>100</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUC:MIC</th>
<th>Peak:MIC</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>&lt;3</td>
<td>4</td>
</tr>
<tr>
<td>25-100</td>
<td>3-12</td>
<td>23</td>
</tr>
<tr>
<td>&gt;100</td>
<td>&gt;12</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical failure rate

- AUC:MIC <25: 43%
- AUC:MIC 25-100: 11.5%
- AUC:MIC >100: 1%
Ciprofloxacin  500 mg or 750 mg BID

Adapted from Drusano G et al. J Chemother 1997 (suppl n.3);9:38-44 and Craig CID 1999

24-h AUC=23 - 40 mg-l/hr

Protein binding 30%

Peak conc. = 2.4 - 4.3 ug/ml

S. pneumoniae: MIC\textsubscript{90} = 2 ug/ml; AUC:MIC ratio= 12 - 24

PK/PD bkpt. 1 ug/ml

Haemophilus/Moraxella: MIC\textsubscript{90} <0.06 ug/ml; AUC:MIC ratio >1000
Levofloxacin 500 mg qd

Adapted from Drusano G et al. J Chemother 1997 (suppl n.3);9:38-44 and Craig CID 1999

24-h AUC=47.5 mg-l/hr
Protein binding 31%
Peak conc. = 5.1 ug/ml

S. pneumoniae: MIC$_{90}$ = 1 ug/ml; AUC:MIC ratio= 47

Haemophilus/Moraxella: MIC$_{90}$ <0.06 ug/ml; AUC:MIC ratio >1000
Moxifloxacin 400 mg qd


24-h AUC=48 mg-l/hr
Protein binding 50%
Peak conc. = 4.5 ug/ml

S. pneumoniae: MIC$_{90}$ = 0.25 ug/ml; AUC:MIC ratio=192
Haemophilus/Moraxella: MIC$_{90}$ <0.06 ug/ml; AUC:MIC ratio >1000

It has excellent activity against *M. tuberculosis* & its use may become restricted
Monte Carlo Simulation

PK Variation In Normal Volunteers or Patients → Simulate → PK Variation in 10,000 Patients

Determine Percentage of Patients that would meet the PK/PD Target required for efficacy

Drusano et al
Concentration-time profile of a beta-lactam in patients ... simulation with a coeff.var. of 20%
PK of Imipenem

Dosage: 500 mg x 4, 1G x 4

Cmax (mg/L): 30 – 40, 60 – 70
Cmin: 0.25 – 0.5, 0.5 – 1
Total body Clearance (L): 11 – 15, 11 – 15
T ½ (hr): 1, 1
Fraction Unbound: 80, 80
Volume of Distribution (L/kg): 14 – 15, 14 – 15

PD of Imipenem

GNB GPC
% f T>MIC: 25 – 40, 15 – 20

Probable Target Attainments

% f T>MIC (experimental): 25 – 40, 15 – 20
% f T>MIC (clinical): 54

3. Breakpoints prior to harmonisation (mg/L) S< R>

<table>
<thead>
<tr>
<th>BSAC</th>
<th>CA-SFM</th>
<th>CRG</th>
<th>DIN</th>
<th>NWGA</th>
<th>SRGA</th>
<th>CLSI</th>
</tr>
</thead>
</table>
Impact of Longer Infusion Times on Probability of Target Attainment (T>MIC_{40%})
Doripenem 500 mg q8h

- MIC=1
- MIC=2
- MIC=4

Probability of Target Attainment (%)

Infusion time:
- 1 hr
- 3 hr
- 5 hr

The concept of Mutant Selective Window

- Serum or tissue drug concentration vs. Time post-administration
- $C_{\text{max}}$
The Mutant Selection Window
- MPC
- MIC
"Window" where selection of mutants takes place ...

- Eradication of the first mutants
- Selection of the first mutants
- No therapeutic effect

Time after administration

concentration

MPC
MSW
MIC

## Potency of anti-TB drugs against *M. tuberculosis*

<table>
<thead>
<tr>
<th>Antibiotic $^b$</th>
<th>MIC$_{99}$ (µg/ml)$^c$</th>
<th>MPC (µg/ml)$^d$</th>
<th>Dose (mg)$^e$</th>
<th>$C_{max}^f$</th>
<th>MPC/$C_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>0.02</td>
<td>$&gt;80$</td>
<td>600</td>
<td>9.5</td>
<td>$&gt;8$</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.2</td>
<td>$&gt;320$</td>
<td>1000</td>
<td>34</td>
<td>$&gt;9$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>0.06</td>
<td>20</td>
<td>250</td>
<td>7.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>2.0</td>
<td>160</td>
<td>1,000</td>
<td>33</td>
<td>4.8</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1.5</td>
<td>$&gt;800$</td>
<td>500</td>
<td>21</td>
<td>$&gt;38$</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>14</td>
<td>70</td>
<td>750</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.15</td>
<td>8.0</td>
<td>750</td>
<td>4.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.037</td>
<td>2.5</td>
<td>400</td>
<td>4.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.03</td>
<td>1.5</td>
<td>300</td>
<td>3.7</td>
<td>0.41</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.075</td>
<td>2.5</td>
<td>200</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Countries with XDR-TB confirmed cases as of February 2008

50 countries

Based on information provided to WHO Stop TB Department - February 2008
What are the PK/PD parameters predictive of antimicrobial’s success?

In case of concentration dependent antibiotics like FQ, Aminoglycosides

In case of concentration independent of time dependent antibiotics like β lactams and cephalosporins
PK/PD correlation with efficacy

- \( T > \text{MIC (>40\%)} \)
  - Penicillin
  - Cephalosporins
  - Carbapenems
  - Monobactam
  - Macrolides
  - Clindamycin
  - Oxazolidinones
  - Glycylcyclines
  - Flucytosine

- AUC or Cmax/MIC
  - \( >100 \)
  - \( >10 \)
  - Aminoglycosides
  - Fluoroquinolones
  - Metronidazole
  - Daptomycin
  - Ketolides
  - Azithromycin
  - Streptogramin
  - Glycopeptides