Determinants of clinical success

- Bacteria
- Antibiotics
- PK/PD profile
- Clinical success
- Host defenses

Bacterial eradication
Determining “potency” of antimicrobial agents

- Minimal inhibitory concentration (MIC) determination
- Minimal bactericidal concentration (MBC) determination
- Subinhibitory and post-antibiotic effects (SME and PAE)
- Interpreting MICs
  - MIC$_{50}$ and MIC$_{90}$ values
  - MIC distributions
  - Interpretative breakpoints
Minimal inhibitory concentration (MIC): measure of “potency”

- MICs are the most common measures used for the evaluation of antimicrobial activity.
- MICs are *in vitro* measurements:
  - the antibiotic concentration required to completely inhibit visible growth in a test tube
  - Bacterial inoculum, medium and incubation time are standardized
  - Antibiotic concentration is constant
Minimal inhibitory concentration

Known quantity of bacteria placed into each tube

Increasing antibiotic concentration

0 µg/mL
0.25 µg/mL
0.5 µg/mL
1.0 µg/mL
2.0 µg/mL
4.0 µg/mL
8.0 µg/mL
16 µg/mL
Minimal inhibitory concentration

Known quantity of bacteria placed into each tube

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

Increasing antibiotic concentration

- 0 µg/mL
- 0.25 µg/mL
- 0.5 µg/mL
- 1.0 µg/mL
- 2.0 µg/mL
- 4.0 µg/mL
- 8.0 µg/mL
- 16 µg/mL

4.0 µg/mL
Minimal inhibitory concentration

The more “potent” the antibiotic, the less is needed to kill the bacteria, and the MIC is LOWER.

Increasing antibiotic concentration

0 µg/mL, 0.25 µg/mL, 0.5 µg/mL, 1.0 µg/mL, 2.0 µg/mL, 4.0 µg/mL, 8.0 µg/mL, 16 µg/mL
**MIC$_{90}$**: the lowest concentration that includes at least 90% of the strains tested

- **MIC$_{50}$** = 0.25 µg/ml
- **MIC$_{90}$** = 4 µg/ml
MIC$_{50}$ and MIC$_{90}$ unimodal population

MIC (µg/ml)

MIC$_{50}$

MIC$_{90}$
**MIC\textsubscript{50} and MIC\textsubscript{90} bimodal population**

- **MIC** (ug/ml):
  - 50% at 0.25
  - 90% at 16

- **MIC** (ug/ml):
  - 0.015 to 0.32
Streptococcus pneumoniae

Penicillin MIC variation by method

Streptococcus pneumoniae
Erythromycin MIC variation by method

**S. pneumoniae Pen-R:** The Alexander Project 2000

Penicillin-resistant isolates (%)

Penicillin-resistant defined as penicillin MIC ≥2 µg/mL

Subinhibitory effects of antibiotics
Postantibiotic effect;
PAE in vitro

Definition:
• Suppression of bacterial growth after short exposure of organisms to antibiotics
  $\text{PAE} = T - C$
  
  $T =$ The time required for the exposed culture to increase one $\log_{10}$ above the count observed immediately after drug removal
  
  $C =$ The corresponding time for the unexposed control

Odenhalt 2001
Postantibiotic effect in vivo

Definition
\[ \text{PAE} = T - C - M \]

- \( T \) = the time required for the counts of cfu in thighs of treated mice to increase one \( \log_{10} \) above the count closest to but not less than the time \( M \)
- \( C \) = the time required for the counts of cfu in thighs of untreated mice to increase one \( \log_{10} \) above the count at time zero
- \( M \) = the time serum concentration exceeds the MIC

Odenhalt 2001
The postantibiotic effect of gentamicin against K. pneumoniae in vivo

Prolonged *in vivo* PAE present

Fantin et al. JAC, 1990
PA SME of telithromycin against H. influenzae

PAE of ≈7 h present
PA SME increases PAE by a further 4-7 h at different subinhibitory drug concentrations

Odenhalt 2001
Subinhibitory effects of antibiotics

Subinhibitory effects such as PAE and PAE-SME can often be demonstrated and may account in part for concentration-dependent PK/PD interactions in vivo.
Bactericidal activity
Bactericidal activity: Time-kill determination

- MICs do not provide data on whether the isolate has only been inhibited or has been "killed"

- MBCs provide data on bacterial killing (defined as a $3 \log_{10}$ kill in 24 h)

- Time-kill curves provide more detailed data on extent and time course of killing
Gemifloxacin time kill of a penicillin resistant strain of *S. pneumoniae* (gemifloxacin MIC 0.016 ug/ml)
Time Kill of S. pneumoniae for telithromycin (MIC 0.125 mg/L)

- **MIC** 0.125 ug/ml
- **MBC** 0.125 ug/ml

**Log10 cfu/mL**
- 8 x MIC
- 4 x MIC
- 2 x MIC
- MIC
- 0.5 x MIC
- 0.25 x MIC

**Threshold**
- Growth control

**Time (hours)**
- 0
- 6
- 12
- 18
- 24
### Time Kill of S. pneumoniae for pristinomycin (MIC 0.5 mg/L)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log10 cfu/mL</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

- **MIC 0.5 ug/ml**
- **MBC 1 ug/ml**

- **8 x MIC**
- **4 x MIC**
- **2 x MIC**
- **MIC**
- **0.5 x MIC**
- **0.25 x MIC**
- **Growth control**
- **Threshold**
Time kill of *S.* pneumoniae

3 log$_{10}$ kill in 24 hours

- Bactericidal activity against most strains at MICs for quinolones compared to at 2X MICs for beta-lactams

![Graph showing the number of strains killed by different antibiotics at 1X MIC and 2X MIC levels.](graph)

Legend:
- Levofloxacin
- Gatifloxacin
- Sparfloxacin
- Trovafloxacin
- Ciprofloxacin
- Amoxicillin
- Cefuroxime
- Ceftriaxone
- Clarithromycin

- Levofloxacin exhibits the highest kill rate at both 1X and 2X MIC levels, followed by Gatifloxacin, Sparfloxacin, Trovafloxacin, Ciprofloxacin, and Amoxicillin.
- Beta-lactams (Cefuroxime, Ceftriaxone) show lower kill rates compared to quinolones.

**Note:** The graph illustrates the comparative bactericidal activity of various antibiotics against *S.* pneumoniae, highlighting the superior activity of quinolones at both MIC levels compared to beta-lactams.
Time kill of *S. pneumoniae*

Little bactericidal activity at MIC at 3 h
Bactericidal activity against up to half of the strains at 6 h
Bactericidal activity against most strains at 12 h, with faster killing by quinolones that by beta-lactams
Little change between 12 and 24 h
MIC distributions of RTI pathogens
MIC distributions of RTI pathogens

- Can MIC distributions provide a basis for comparing susceptibilities of different bacterial species causing infections at the same sites?

- Can MIC distributions show if discrimination between isolates with different MICs is likely to be possible in clinical studies?

- Can MIC distributions be applied to clinically determined breakpoints to determine susceptibility of isolates?
MIC distributions
Streptococcus pneumoniae
MIC distributions of penicillin and selected cephalosporins

Source: The Alexander Project 1996
Haemophilus influenzae
MIC distributions of cephalosporins

Source: The Alexander Project 1996
**Haemophilus Influenzae**

MIC distributions of macrolides

Source: The Alexander Project 1996
Amoxicillin

MIC in ug/mL

% of strains

Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Amoxicillin-clavulanate

Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), AugSR M. catarrhalis (n=972)
Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Adapted from Alexander Project 2000; GlaxoSmithKline, data on file.
Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Cefprozil

Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Alexander Project USA 2000:  *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)
Adapted from Jacobs ICAAC 1997 abstr E103, Kelly ICAAC 1999 abstr 2323, and Spectracef Prescribing Information 2002
Ceftibuten

Adapted from Jacobs ICAAC 1997 abstr E103, and Cedax Prescribing Information 2002
Azithromycin

Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), AugSR M. catarrhalis (n=969)
Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), AugSR M. catarrhalis (n=969)
Alexander Project USA 2000:  S. pneumoniae (n=1362)
AugSR H. influenzae (n=3793)  M. catarrhalis 2000 (n=970)
Alexander Project USA 2000:  S. pneumoniae (n=1362),  H. influenzae (n=634),  M. catarrhalis 2000 (n=206)
Trimethoprim-sulfamethoxazole

Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis AugSR (n=972)
Ciprofloxacin

Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis AugSR (n=972)
Alexander Project USA 2000:  S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis AugSR (n=972)
MIC distributions can provide a basis for comparing susceptibilities of different bacterial species causing infections at the same sites.

MIC distributions can show if discrimination between isolates with different MICs is likely to be possible in clinical studies.

MIC distributions can be applied to clinically determined breakpoints to determine susceptibility of isolates.