INTRODUCTION

Successful antibiotic (AB) treatment depends on:
- Intrinsic sensitivity of bacteria to AB
- Sufficient AB concentration at the site of infection for a sufficient duration.
- But must remain below toxic level

INTRODUCTION

- In vitro activity is only a guide as to whether an AB is likely to be effective for an infection.
- Pharmacokinetics describes the time course of drug concentration in plasma or other body fluid
INTRODUCTION

MIC is the parameter of Intrinsic sensitivity

However:
- In vitro efficacy does not always indicate clinical efficacy
- MIC is very variable from pathogen to pathogen
- Drug concentration is timely variable
- Some infections occur outside blood circulation

INTRODUCTION

To be therapeutically effective, the minimal drug concentration at the infected site should be at least equal to MIC

In most instances it is advisable to achieve multiples of this concentration.

Pharmacokinetic Parameters

- Three most important PK parameters:
  - $C_{\text{max}}$ (peak serum concentration)
  - $C_{\text{min}}$ (trough level)
  - AUC (Area Under the serum concentration time Curve).

- PK parameters quantify the serum level time course, but they do not describe the killing activity of an antibiotic.
Integrating the PK parameters with the MIC gives three PK-PD parameters which quantify the activity of an antibiotic.

PK-PD parameters:
- Peak / MIC
- T > MIC
- AUC$_{24h}$ / MIC.

PK-PD is aimed to design appropriate dosage regimen:
- To obtain a successful therapy
- Avoiding toxicity
- Preventing emergent of resistance
PK-PD Parameters

Patterns of Antimicrobial Activity

Based on the existence of persistent effects, AM pattern can be classified into 3 groups:
1. Concentration dependent with moderate to prolonged persistent effects
2. Time-dependent killing with minimal to moderate persistent effects
3. Time-dependent killing with prolonged persistent effects

Telithromycin: Higher dose $\rightarrow$ higher killing activity
Azithromycin and Clarithromycin: no good correlation between dose and killing activity
1. Concentration Dependent Killing

- **PK parameters**
  - $C_{\text{max}}$/MIC: 8-10
  - $\text{AUC}_{24h}$/MIC: 25-125

- **Goal of treatment:**
  - Maximize concentrations
  - Optimize amount of drug

- Single dose may be better and safer
  - Aminoglycosides, Fluoroquinolones, Ketolides, metronidazole, Ampicillin

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**Time-kill Curves For P. aeruginosa ATCC 27853**

- Tobramycin and Ciprofloxacin: Higher dose → higher killing activity
- Ticarcillin: same response rate with drug level 4, 16, and 64 timesMIC

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$C_{\text{max}}$/MIC ratio need to attain 8-10

- Relationship between $C_{\text{max}}$/MIC ratio and the rate of clinical response
- N = 258 patients, Gram negative bacterial infections
- Aminoglycosides (gentamicin, tobramycin, amikacin)
- Response rate attained submaximal response with $C_{\text{max}}$/MIC ratio ≤ 8.

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Ceftazidim: Time dependent killing

PK/PD Parameters and Efficacy for Fluoroquinolones

- Ciprofloxacin
  - Rate of eradication from sputum significantly lower (only 2-3 days) when the 24-hour AUC/MIC was ≤250
- Levofoxacin
  - Probability of microbiological and clinical cure significantly higher when peak/MIC was 12 (equivalent to 24-hour AUC/MIC of 100)

2. Time-dependent Killing
   (with prolong persistent effects)

- PK parameter: T > MIC (Time above MIC)
- Effective T > MIC: 40-50% (mostly for Gram +)
- Goal of treatment: maximize duration of exposure
- Slow infusion is better
- If using T > MIC, a value of 70% may be needed (mostly Gram -)
  - Beta lactam, macrolides, clindamycin, flucytosine, linezolid
Percentage bacteriologic cure for β-lactam agents against *Streptococcus pneumoniae* (black circle) and *Haemophilus influenzae* (white circle) in children with acute otitis media.


### 3. Time-dependent Killing
(with minimal to moderate persistent effects)

- **PK parameter:** \( \text{AUC}_{24\text{h}} / \text{MIC} \)
- **Goal of treatment:** optimize amount of drug
- **Effective \( \text{AUC}_{24\text{h}} / \text{MIC} \):** 25-125
  - Azithromycin, vancomycin, tetracyclines, fluconazole
**AUC$_{24h}$/MIC of Fluoroquinolones**

**Relationship Between 24-Hour AUC/MIC and Mortality in Animals for Fluoroquinolones Against S pneumoniae**

- **Gram-positive**: AUC/MIC needed: 25-125
- **Gram-negative**: AUC/MIC needed: 100-250

**Correlation of PK/PD Parameters With Efficacy of Temafloxacin Against Streptococcus pneumoniae in Thigs of Neutropenic Mice**

**Summary Of Antimicrobial Pharmacodynamic Parameters**

<table>
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<th>Antimicrobial Class</th>
<th>Pharmacodynamic Characteristics</th>
<th>Goal of Drug Administration</th>
<th>Parameters to Consider with In Vitro Efficacy</th>
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</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Concentrations</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Time</td>
<td>Excess Time</td>
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<tr>
<td>Cephalosporins</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Target Levels</td>
<td>Time Exceeding MIC (mg/L)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Target Levels</td>
<td>Time Exceeding MIC (mg/L)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Target Levels</td>
<td>Time Exceeding MIC (mg/L)</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Target Levels</td>
<td>Time Exceeding MIC (mg/L)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Time-Dependent, Concentration-Dependent Effects</td>
<td>Accumulation of Target Levels</td>
<td>Time Exceeding MIC (mg/L)</td>
</tr>
</tbody>
</table>
How to Perform PK-PD

Unlike the sensitivity test, the data of Cmax and AUC is **not routinely** performed in patient setting.

It needs **serial measures** of drug concentration

Thus, PK-PD is normally performed in animal model

The magnitude of PK/PD parameters required for efficacy is **relatively similar** in different animal species and human being.

Strategies to Increase % Time>MIC
(Example of Doripenem)

- Give a higher dose
- Increase duration of infusion
  - Prolonged infusion
    - Same dose and dosing interval, but prolong the duration of infusion
  - Continuous infusion
    - Loading dose, followed by total daily dose over 24 hours infusion

Strategies to Increase % Time>MIC
(Example of Doripenem)

- Doripenem is the only approved carbapenem for 1-hour and 4-hour extended infusion\(^1\)
- Highest Cummulative Fraction Response (CFR) against *P. aeruginosa* in comparison with imipenem and meropenem\(^2\)
- Superior stability vs. other carbapenems for extended infusion\(^3,5\)

**CFR**: Cumulative Fraction Response

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\(^2\) Doripenem is the only approved carbapenem for 1-hour and 4-hour extended infusion


\(^4\) DORIBAX Prescribing Information (Malaysia) 2008.

**DORIBAX IS THE ONLY APPROVED CARBAPENEM FOR 1-HOUR INFUSION AND 4-HOUR EXTENDED INFUSION**

4-Hour Infusion Allows Targeting of Higher MICs Without Increasing the Dose

![Graph showing concentration over time for 1-hour and 4-hour infusions of DORIBAX.](image)

*Optional infusion time for NP/VAP patients who are at risk for infections with less susceptible pathogens.

**Improved Doripenem Targeting of Higher MICs with 4-hour Infusion**

![Graph showing target attainment percentage against MIC for 4-hour infusions of Doripenem.](image)

**CUMULATIVE FRACTION OF RESPONSE (CFR)**

- CFR is the possibility that the antibiotic regimen will reach its pharmacodynamic index against the entire population of organisms
- The PASSPORT analysis showed that doripenem has the highest CFR against *P. aeruginosa* in comparison with imipenem and meropenem
- Against *P. aeruginosa*, doripenem 1 gm and 2 gm extended infusion achieved > 90% CFR

Doripenem has the highest CFR against P. aeruginosa.


Doripenem achieved 79–93% CFR
Imipenem achieved 60–79% CFR
Meropenem achieved 73–85% CFR

DORIPENEM Provides a Favourable Stability Following Reconstitution

<table>
<thead>
<tr>
<th></th>
<th>Stability time, h</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diluent</td>
</tr>
<tr>
<td>DORIPENEM</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>Doripenem</td>
<td>5% Dextrose</td>
</tr>
<tr>
<td>Imipenem</td>
<td>5% Dextrose</td>
</tr>
<tr>
<td>Meropenem</td>
<td>5% Dextrose</td>
</tr>
</tbody>
</table>

* These exceed the time for refrigeration of infusion/parenteral fluids ipimaipm. Provided the time does not exceed refrigeration stability time.


DORIPENEM Has Superior Stability at Elevated Room Temperatures

<table>
<thead>
<tr>
<th></th>
<th>Temperature</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>30°C</td>
</tr>
<tr>
<td>DORIPENEM</td>
<td>16 h</td>
</tr>
<tr>
<td>Imipenem</td>
<td>6 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>12 h</td>
</tr>
</tbody>
</table>
CONCLUSIONS

PK/PD of antibiotics is aimed to develop a more effective dosage regimen:

- To obtain successful treatment while avoiding toxicity and the emergence of antibiotic resistance.

Optimization of PK/PD can be obtained either by increasing the dose or extending the duration of infusion.

Strategy for improving the PK/PD is determined by the killing pattern of antibiotics.

Thank You