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Celia C. Carlos, MD Research Institute of Tropical Medicine

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Joanna Bisquera-Cacpal, MD, Joseph Dale Gutierrez, MD,
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Post-marketing surveillance of a live-attenuated varicella (oka-strain) vaccine in the philippines
Jose Salazar, MD*, Salvacion Gatchalian, MD**, Hans L Bock MD**
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Determining correct dosing regimens of antibiotics based on the their bactericidal activity*
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MANAGEMENT OF A(H1N1) IN THE HOSPITAL SETTING
DETERMINING CORRECT DOSING REGIMENS OF ANTIBIOTICS BASED ON THE THEIR BACTERICIDAL ACTIVITY*

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*Excerpt from “Rational Antibiotic Use for Pediatrics, A Study Guide and Workbook

KEYWORDS
Antibacterials, antibiotics, rational dosing for antibiotics

OBJECTIVES
Upon completion of this chapter, the learner will be able to:

1. Describe the 2 groups of antibiotics based on their bactericidal activity, namely concentration-dependent antibiotics, and time-dependent antibiotics. Name the pk/pd indices which determine efficacy.
2. Recall and define the following terms: area under the concentration vs. time curve (AUC), minimum inhibitory concentration (MIC), peak level (Cmax).
3. Classify the following antibiotics based on their bactericidal activity: penicillins, cephalosporins, aminoglycosides, vancomycin, fluoroquinolones, and carbapenems. Identify the pharmacologic indices used to determine their efficacy
4. Determine the correct dosing regimen of the above antimicrobials based on their pattern of bactericidal activity.

For appropriate antibiotic dosing and administration, physicians must be familiar with pharmacodynamic concepts that integrate an antibiotic’s microbiologic activity, pharmacokinetic properties, and mode of bacterial killing

Review of Definitions
The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro. It is determined usually in a two-fold dilution system using either broth or agar for growth of the bacteria.

The area under the curve (AUC) is a pharmacokinetic parameter which is a measure of both the extent of the drug absorbed and its persistence in the body. This is the overall amount of drug in the bloodstream after a dose. It is the most reliable reflection of the extent of absorption.

The Cmax (maximum concentration) is the highest concentration of drug in the blood that is measured after a dose. Cmax usually occurs within a few hours after the dose is administered.

Pharmacologic Indices in antibiotics therapy
Peak/MIC (Cmax/MIC) ratio is defined as the peak level divided by the MIC. It is used to predict the efficacy of concentration-dependent antibiotics.

AUC/MIC is defined as the area under the curve over 24 hours divided by the MIC. It
is also used to predict the efficacy of concentration-dependent antibiotics. **T>MIC** is defined as the cumulative percentage of time over a 24 hour period that the drug concentration exceeds the MIC. It is used to predict the efficacy of time-dependent antibiotics. **Postantibiotic effect** defined as persistent suppression of bacterial growth after a brief exposure (1 or 2 h) of bacteria to an antibiotic even in the absence of host defense mechanisms.

**Figure 8.1. Pharmacodynamic/Pharmacokinetic predictors of outcome.**
Example of single dose study of antibiotic X
Concentration Dependent Antibiotics

Antibiotics can be classified based on their pattern of bactericidal activity. The first group of antibiotics is called **concentration-dependent antibiotics**. In this group of antibiotics, if the concentration is increased, the rate and extent of killing of bacteria is also increased. This pattern is observed in aminoglycosides and fluoroquinolones. The indices used to predict or describe this group of antibiotics are **Cmax/MIC ratio** and **AUC/MIC ratio**. Concentration dependent killing for the agents mentioned have been demonstrated in animal models and human trials. Thus increasing drug concentrations but administering it less frequently such as a single daily dose has resulted in greater cidal activity as opposed to giving the same total daily dose given several doses. These agents exhibit a prolonged postantibiotic effect and have been seen in agents which inhibit protein synthesis or nucleic acid synthesis.

For aminoglycosides Cmax: MIC ≥10 translates into improvements in the rate and extent of clinical response. Thus Once-daily dosing (ODD) for aminoglycosides is advocated to maximise efficacy and minimise potential drug accumulation and toxicity-standard of care for adult patients. Table 8.2 shows recommended dose for aminoglycosides based on reaching the Cmax/MIC ratio of more than 10.

### Table 8.1. Classification of antibiotics based on pharmacokinetic/pharmacodynamic parameters of efficacy and bacterial eradication.

<table>
<thead>
<tr>
<th>Pattern of Activity</th>
<th>Antibiotics</th>
<th>Goal of Therapy</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong>&lt;br&gt;Concentration-dependent killing and prolonged persistent effects</td>
<td>Aminoglycosides&lt;br&gt;Daptomycin&lt;br&gt;Fluoroquinolones&lt;br&gt;Ketolides</td>
<td>Maximize concentrations</td>
<td>24h-AUC/MIC ratio&lt;br&gt;Cmax/MIC ratio</td>
</tr>
<tr>
<td><strong>Type II-A</strong>&lt;br&gt;Time-dependent killing and Minimal persistent effects</td>
<td>Carbapenems&lt;br&gt;Cephalosporins&lt;br&gt;Erythromycin&lt;br&gt;Linezolid&lt;br&gt;Penicillins</td>
<td>Maximize duration of exposure</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td><strong>Type II-B</strong>&lt;br&gt;Time-dependent killing and Moderate to prolonged persistent effects.</td>
<td>Azithromycin&lt;br&gt;Clindamycin&lt;br&gt;Oxazolidinones&lt;br&gt;Tetracyclines&lt;br&gt;Vancymycin</td>
<td>Maximize amount of drug</td>
<td>24h-AUC/MIC ratio</td>
</tr>
</tbody>
</table>

### Table 8.2. Dose of aminoglycosides to achieve a Cmax/MIC ratio >10

<table>
<thead>
<tr>
<th>CLCr</th>
<th>Gentamicin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>5 mg/kg/24 hrs</td>
<td>15 mg/kg/24 hrs</td>
</tr>
<tr>
<td>30-49</td>
<td>5 mg/kg/36 hrs</td>
<td>15 mg/kg/36 hrs</td>
</tr>
<tr>
<td>20-29</td>
<td>5 mg/kg/48 hrs</td>
<td>15 mg/kg/48 hrs</td>
</tr>
<tr>
<td>&lt;20</td>
<td>2 mg/kg with monitoring</td>
<td>7.5 mg/kg with monitoring</td>
</tr>
</tbody>
</table>
There are some groups of patients wherein in the once-daily dosing is not applicable since their pharmacokinetics may differ or if gram positive organisms are targeted. These groups include patients with ascites, patients with burns involving >20% body surface area, pregnant patients, patients on dialysis, patients treated for suspected or documented endocarditis, and patients treated for staphylococcal and enterococcal infections when aminoglycoside therapy is used for synergy.

For fluoroquinolones numerous studies (both in animal models and humans) have shown that optimal AUC:MIC ratios result in better outcomes. It has also been noted that the optimal AUC:MIC ratio varied with different organisms. For nosocomial pneumonia treated with ciprofloxacin, AUC:MIC >125 results in clinical cure and bacteriological eradication rates >80%. For community-acquired pneumonia treated with levofloxacin or gatifloxacin, AUC:MIC >34 improve the probability of pneumococcal bacteriological eradication. Quinolones are usually dosed once or twice daily.

**Time Dependent Antibiotics**

The second group of antibiotics is called **time-dependent antibiotics** which kills bacteria at the same rate and to the same extent after reaching a threshold concentration. Thus these drugs kills bacteria only when concentration at the site is higher than the MIC, but once the concentration at the bacterial site is more than 4 times the MIC, the additional killing is only modest. The extent of bacterial killing is dependent on time of exposure because these agents have very short or no postantibiotic effect especially for gram negative organisms. Thus the goal of therapy in this group is to maintain serum concentrations above the MIC for as long as possible during the dosing intervals. For this second group of antibiotics the most important pharmacologic index is T>MIC which has been proven in numerous in vitro and in vivo models as well as observed in human trials. Included in this group are beta lactams, clindamycin, linezolid and vancomycin.

At the moment there is no agreement on the optimal value of the T>MIC, observational studies have shown that values of 40-50% duration T>MIC is the minimum.
goal in dosing for penicillins and cephalosporins. This would lead to at least stasis of most target bacteria. Values of T>MIC of >70% is ideal to maximize killing of the bacteria, while some investigators suggest achieving a T>MIC of 100% to prevent bacterial resistance.

There are several ways by which you can increase the T>MIC. These include: 1) increasing the dose, 2) increasing the dosing frequency, 3) improving the pharmacokinetic profile (such as extended-release formulations), 4) increasing the duration of infusion or by giving parenteral drugs by continuous infusion; and 5) use another drug (e.g. probenecid) that interferes with elimination. Thus, most drugs in this group with short half lives may be given every 4-6 hrs, or as continuous infusion depending on the stability of the drug.

Figure 8.3. Representative Time-kill curves of Time Dependent Antibiotic in In vitro Models

![Time-kill curves of Time Dependent Antibiotic in In vitro Models](image)

Figure 8.4. Pharmacodynamic Goals (T>MIC as percent of Interval) with Beta-Lactams

<table>
<thead>
<tr>
<th>Class</th>
<th>Organism</th>
<th>Stasis (T&gt;MIC)</th>
<th>Maximum killing (T&gt;MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Gram neg bacilli, pneumococcus</td>
<td>40-50</td>
<td>70-80</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Gram neg bacilli, pneumococcus</td>
<td>30-40</td>
<td>60-70</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Gram neg bacilli. Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td></td>
<td>pneumococcus</td>
<td>10-20</td>
<td>25-40</td>
</tr>
</tbody>
</table>
Table 8.3. Preferred Dosing Regimens for Children for Selected Antibiotics based on PK-PD Classification

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Classification</th>
<th>Total dose per day (mg/kg)</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>*CD</td>
<td>1.5</td>
<td>Once daily</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>CD</td>
<td>5</td>
<td>Once daily</td>
</tr>
<tr>
<td>Penicillin</td>
<td>**TD</td>
<td>100,000-200,000</td>
<td>Every 4 hrs</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>TD</td>
<td>50-100</td>
<td>Every 6-8 hrs</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>TD</td>
<td>75-150</td>
<td>Every 6-8 hrs</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>TD</td>
<td>100</td>
<td>Every 12-24 hrs</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>TD</td>
<td>100-150</td>
<td>Every 8 hrs, or continuous infusion</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>TD</td>
<td>240-400</td>
<td>Every 8 hrs or continuous infusion</td>
</tr>
<tr>
<td>Meropenem</td>
<td>TD</td>
<td>60-120</td>
<td>Every 8 hrs as bolus or infused over 3 hrs</td>
</tr>
</tbody>
</table>

*concentration dependent
**time-dependent

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