Understanding Pharmacokinetics (PK) and Pharmacodynamics (PD)
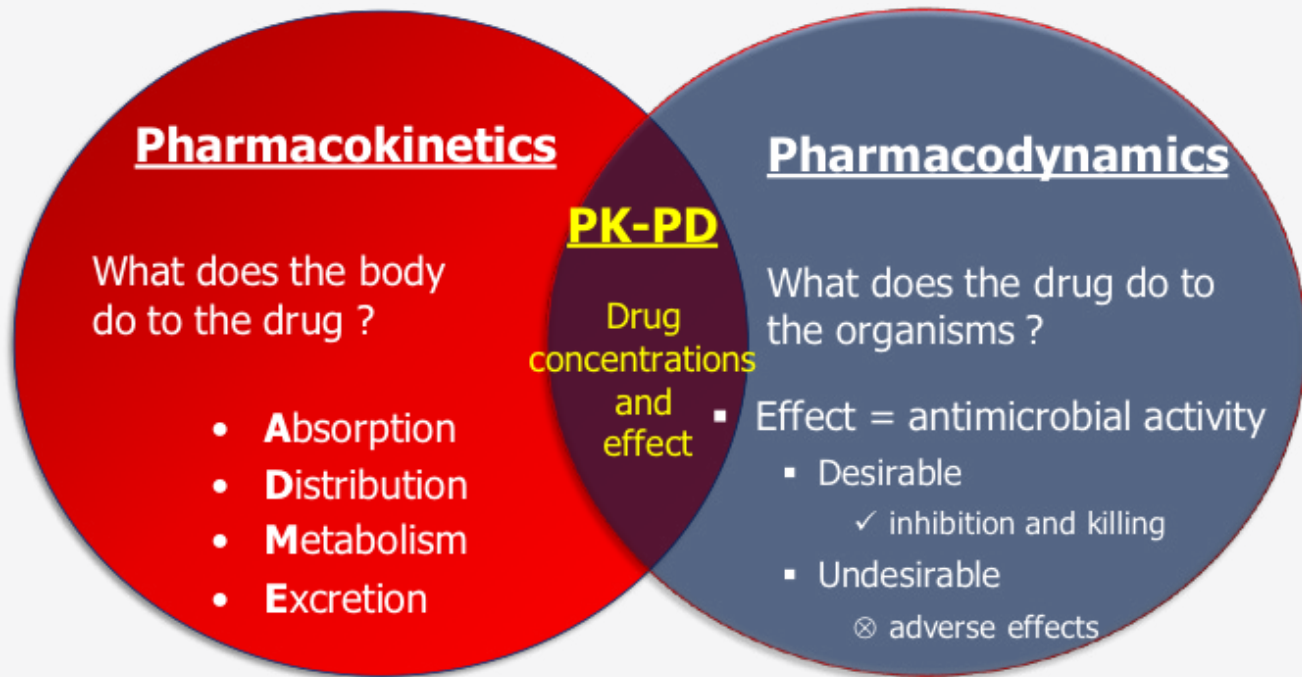
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Figure 1: Interplay between Pharmacokinetics and Pharmacodynamics of Antimicrobial Agents

As microbiologists performing antimicrobial susceptibility testing (AST), we may have heard of the terms pharmacokinetics (PK) and pharmacodynamics (PD). PK and PD parameters of antimicrobials are used to optimize dosing of antimicrobials to maximize their effectiveness while minimizing toxicity to patients **(see Figure 1).** PK/PD is also critical in the process used to determine breakpoints, which are the criteria applied to the Minimum Inhibitory Concentration (MIC) of a patient isolate. Breakpoints are used to categorize the MIC of an isolate as "Susceptible," "Intermediate," "Susceptible-Dose-Dependent", "Non-Susceptible," or "Resistant." When the Clinical and Laboratory Standards Institute (CLSI) sets breakpoints, they use the following different cut-offs:

- MICs of wild-type (WT) isolates (in general, these are isolates lacking resistance mechanisms to the drug) that provide an **epidemiologic cutoff value (ECV)**

- Animal or *in vitro* PK/PD models that provide a **non-clinical PK/PD cutoff**

- PK/PD clinical exposure response (CER) data from patients in clinical trials that provide a **CER cutoff**

- Success/failure data by minimal inhibitory concentration (MIC) from clinical trial data that provide a **clinical cutoff**

These four cutoff values are then used to develop a breakpoint that clinical microbiologists use with MICs to provide susceptibility reports to clinicians. The breakpoint values are those that are published in M100, Performance Standards for Antimicrobial Susceptibility Testing for interpretation of MIC values based on the drug-organism combination. The objective of this article is to provide a basic overview of PK and PD and what they mean to the laboratorian performing AST.

What does the lab need to know about Pharmacokinetics?

PK answers the question *"What does the body do to the drug?"* PK studies evaluate drug absorption, distribution, metabolism and excretion from the body. These parameters are usually measured by studying the achievable drug levels in blood and other body fluids (eg, CSF) in healthy volunteers. Most antimicrobial agents are protein-bound, ranging anywhere from 30% to 95% depending on the agent. While PK can be measured as total drug concentration, it is only the unbound (free) drug that has activity against bacterial pathogens. Therefore, unbound (free) drug concentrations are generally used in assessment of PK for setting breakpoints or determining a dose.

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What about Pharmacodynamics?

PD, on the other hand, studies the relationship between unbound drug concentration over time and the resulting antimicrobial effect on the organism. PD answers the question *"What does the drug do to the organism?"* Ideally, the effect of an antimicrobial agent is to eradicate the infecting organism without adverse effects to the patient.

Antimicrobial agents are generally classified into three classes based on *in vitro* PD drug effect: 1) time-dependent, 2) concentration-dependent, or 3) area under the curve (AUC)/MIC ratio **(see Figure 2):**

1. Time-dependent bactericidal effect:
   - Antimicrobials classified as time-dependent require that the drug concentrations be above the MIC for a certain percentage of the dosing interval to effectively kill the organism.
   - Generally, once the target "time above MIC" is reached for a particular isolate, increasing the free drug concentrations of these drugs above the standard treatment dose has no further effect on bacterial killing of that isolate.
   - Examples of time-dependent antimicrobials are penicillins, cephalosporins, carbapenems, and aztreonam.
2. Concentration-dependent bactericidal effect:
   - Concentration-dependent antimicrobials achieve increasing bactericidal effect with increased serum levels of the drug.
   - These drugs are dosed to achieve maximum safe concentrations at the infection site for optimal bactericidal activity (eg, concentrations that are 10 times the MIC for aminoglycosides).
   - Examples of concentration-dependent antimicrobials are aminoglycosides, daptomycin.

Figure 2: Pharmacodynamic Classification of Antimicrobial Agents.
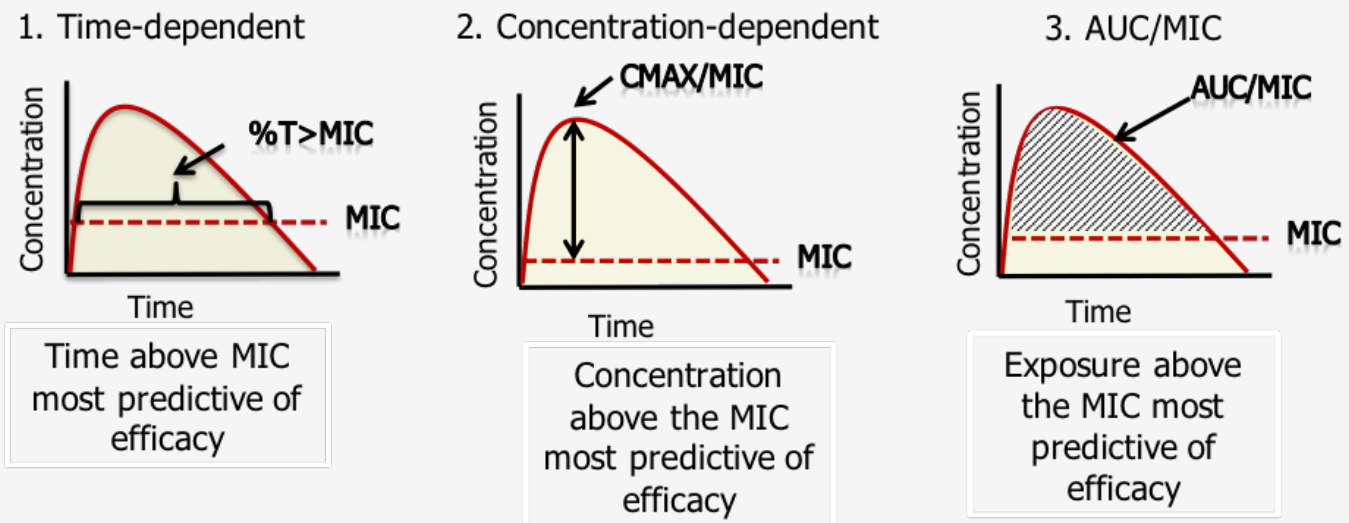
In the three graphs, "time" refers to the dosing interval. "Concentration" refers to the amount of drug attained over time in a patient's blood following administration of the drug. A dose of antimicrobial is initially administered at time 0. The concentration increases, then decreases and at a certain time, a subsequent dose may be given.

Abbreviations: %T > MIC, length of time the concentration of drug in the patient's serum remains above the MIC; CMAX, highest (maximum) concentration of drug attained during the dosing interval; AUC, area under the curve calculated by examining the length of time the drug concentration remains above the MIC together with the overall drug concentration achieved over this time frame. The broken horizontal MIC line refers to the susceptible breakpoint for the antimicrobial drug-organism combination.

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3. Area under the curve (AUC) /MIC ratio:

- Efficacy of antimicrobials in this group is dependent on the total concentration of the drug achieved over 24 hours (eg, area under the curve [AUC]0-24) above the MIC of the organism.

- Examples of AUC/MIC antimicrobials are fluoroquinolones, vancomycin.

So how are PK and PD used in the determination of the breakpoint?

The MIC of a drug for an organism is compared to the achievable unbound drug concentrations at a site of infection, most commonly in blood. Animal or *in vitro* models of infection are used to identify the PK/PD parameter and magnitude of that parameter (ie, % T >MIC, cMAX/MIC, or AUC/MIC [see Figure 2]) that best correlates with efficacy. Generally, the "susceptible" breakpoint is set at the highest MIC where the PK/PD target for efficacy is achieved in approximately 90% of the patient population using standard dosing. As described above, other information, including the epidemiologic cutoff value, the CER cutoff and the clinical cutoff are also used to determine the breakpoint for a drug-organism combination.

Tying It All Together – An Example to Illustrate How CLSI Used PK and PD Data to Establish Ceftazidime Breakpoints for *Enterobacteriaceae*

Now that we understand what PK and PD mean, let's review by looking at an example—the establishment of ceftazidime breakpoints for the *Enterobacteriaceae*. When determining breakpoints, population pharmacokinetics and Monte Carlo simulations are utilized along with the PK/PD targets that have correlated with efficacy in models or in clinical trials. Monte Carlo simulation is a statistical tool that can use a limited data set to predict the likelihood of PK/PD target attainment for a population of patients. In general, the goal is to achieve at least 90% target attainment. The human PK of an antimicrobial varies by individual (ie, absorption, distribution, metabolism, and excretion of the drug in the body over time). Monte Carlo simulations are used to incorporate the potential variability expected in the patient population for an antibiotic and to simulate the likelihood of target attainment for efficacy at different MICs.

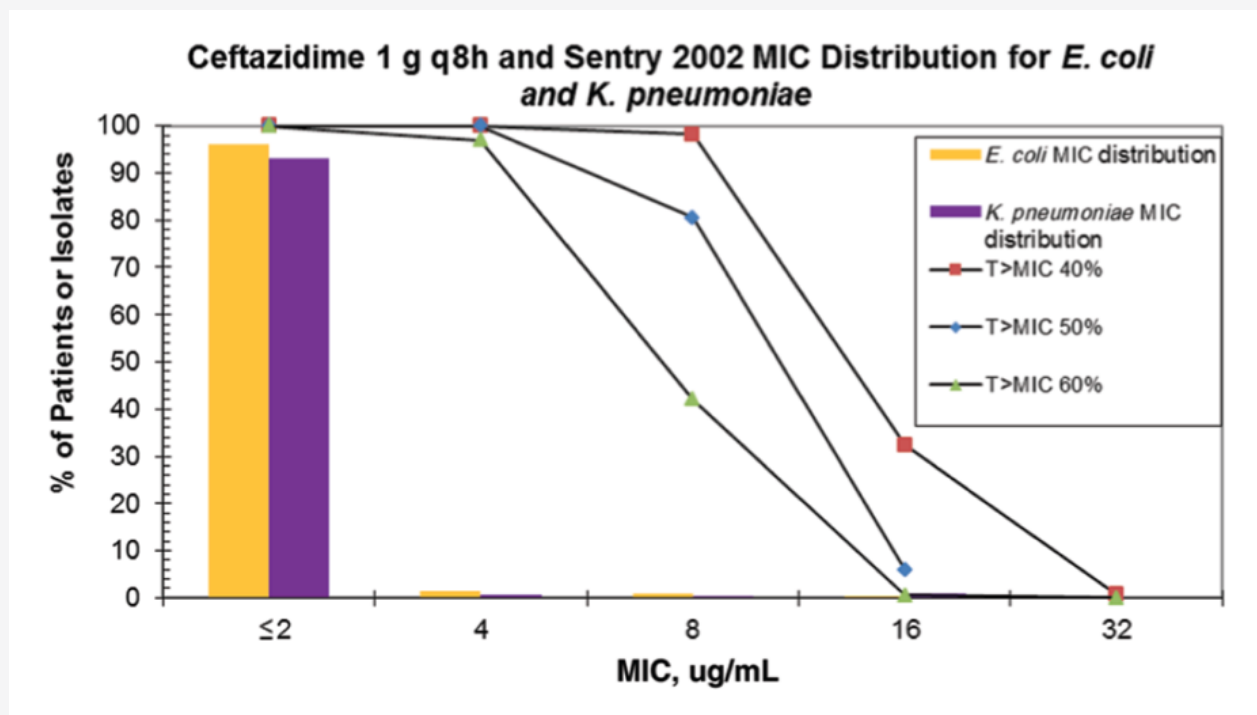**Figure 3: Percent probability of PK/PD target attainment for ceftazidime.**

Figure 3 is derived from Monte Carlo simulation modeling for ceftazidime plotted against the MIC distributions for *Escherichia coli* and *Klebsiella pneumoniae*. These data were used by CLSI to help define the clinical breakpoints for ceftazidime. The figure demonstrates that when ceftazidime is dosed intravenously at 1 g **every 8 hours,** target attainment rates (black lines on figure) of >90% are achieved up to an MIC of 4 µg/mL for T > MIC targets of 40%, 50%, and 60%. At an MIC of 8 µg/mL, only the lower threshold T > MIC target of 40%

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allows a 90% target attainment rate. Animal models indicate that for cephalosporins and *Enterobacteriaceae* a time above MIC of 50% was consistently needed for efficacy. Therefore, for ceftazidime dosed intravenously at 1 g **every 8 hours,** the highest MIC for which at least 90% of patients would be expected to meet the 50% T > MIC target would be an MIC of 4 µg/mL. Thus, the non-clinical PK/PD cut-off is 4 µg/mL. As described earlier in this article, CLSI also evaluates other available data (eg, the epidemiologic cut-off, clinical cut-off, and clinical exposure response cut-off) to set a breakpoint. After evaluation of all the relevant data, CLSI set the susceptible breakpoint for ceftazidime and *Enterobacteriaceae* at ≤ 4 µg/mL.

Recommended Reading:

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