# Antibiotic Pharmacokinetics and Pharmacodynamics

## Basic concepts

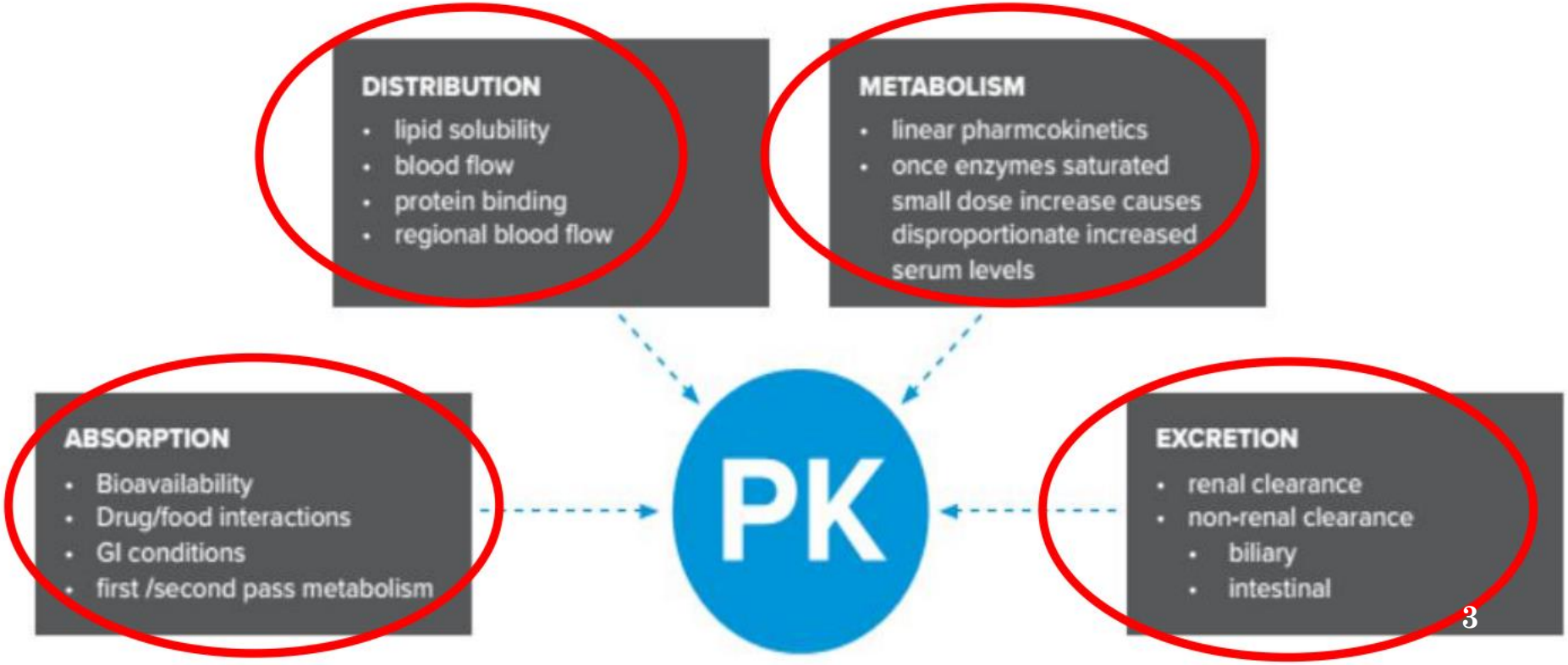
# WHAT IS PHARMACOKINETICS?

**Refers to how antibiotics enter the body, where they go once they are "inside," and how they get out.**

**Can be described as absorption, distribution, and metabolism/excretion ("ADME").**

**So, Pharmacokinetics means what the body does with the drug.**

# KINETIC = MOVING



# IMPORTANCE OF PHARMACOKINETICS

The pharmacokinetics of antibiotics are **key to the effectiveness** of the drugs in clinical practice

There is no benefit if an antibiotic that is **great at killing bugs** if it never gets to the site of the infection at a high enough concentration to work.

# How PK parameters are studied?

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.

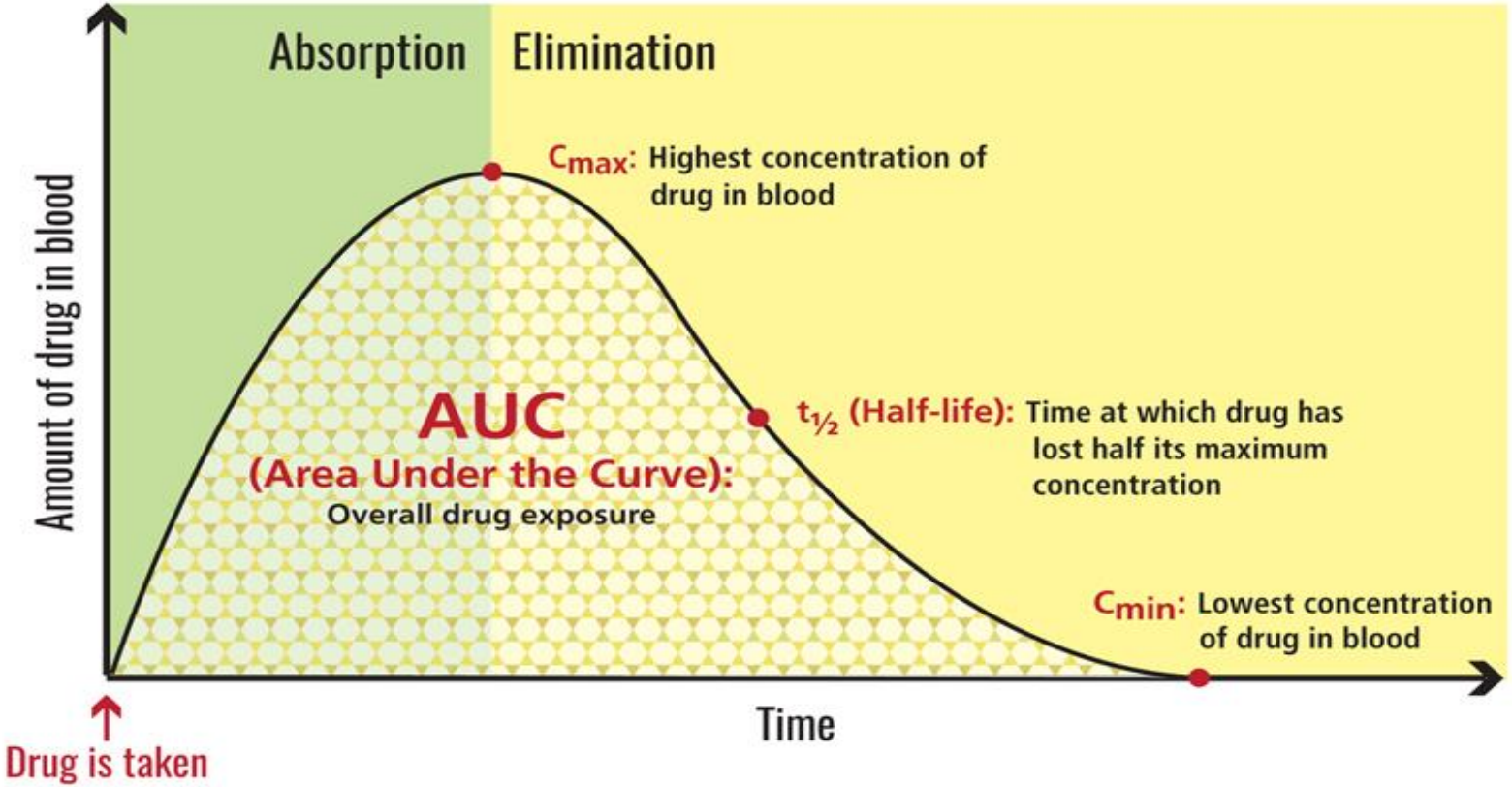
# THREE PHARMACOKINETIC PARAMETERS

That are most important for evaluating antibiotic efficacy are the

- Peak serum level (Cmax)
- The trough level (Cmin)
- The Area Under Curve (AUC).

While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic. Which are described by Pharmacodynamics

# Pharmacokinetics



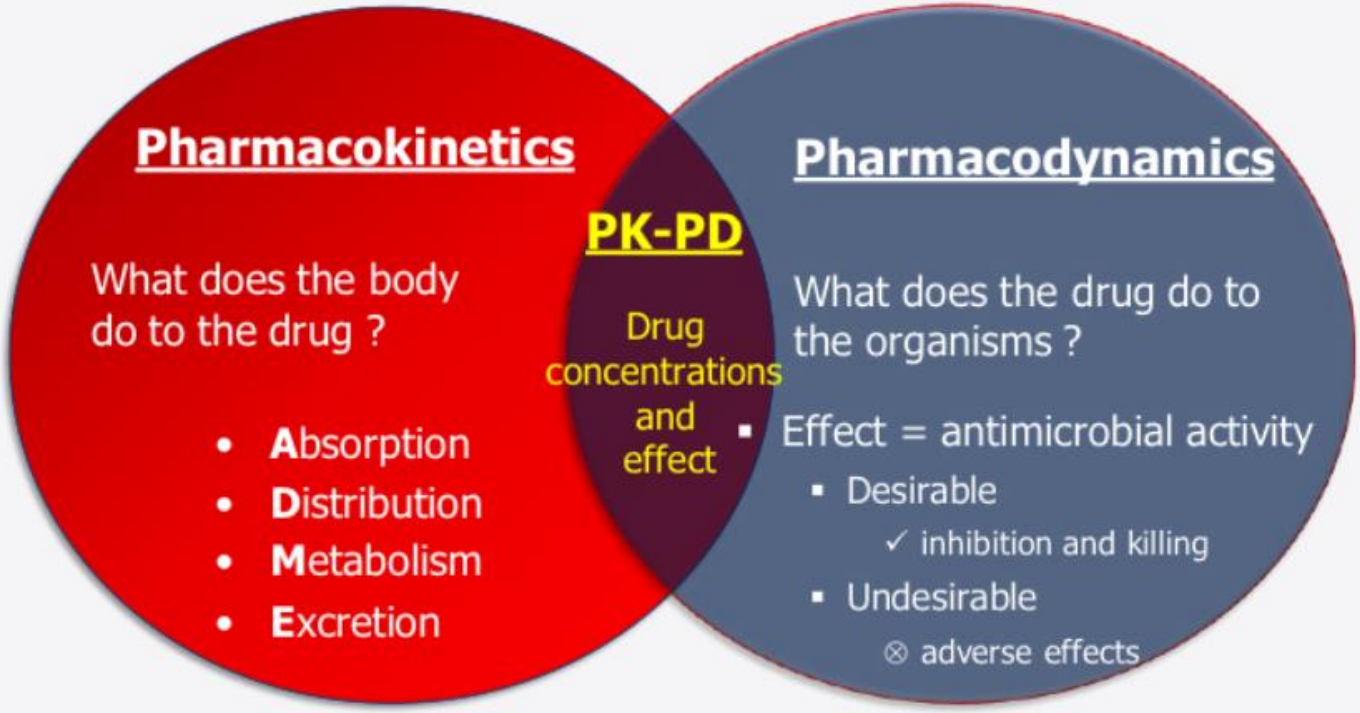
# WHAT IS PHARMACODYNAMICS?

PD, 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(and host)?"

Ideally, the effect of an antimicrobial agent is to eradicate the infecting organism without adverse effects to the patient.

Figure 1: Interplay between Pharmacokinetics and Pharmacodynamics of Antimicrobial Agents



# MINIMUM INHIBITORY CONCENTRATION (MIC)

The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.

Developed in the 1950's to forecast response to therapy

While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity.

# MIC…

Therefore, the unfortunate truth is that an MIC on its own is a relatively blunt instrument tasked with addressing an extremely complex problem.

MIC values are limited in that they measure antibacterial activity over fixed concentrations of drug. Such a metric does not account for the time course of antibacterial activity as a function of fluctuating concentrations of drug in patients.

# PK-PD INTEGRATION

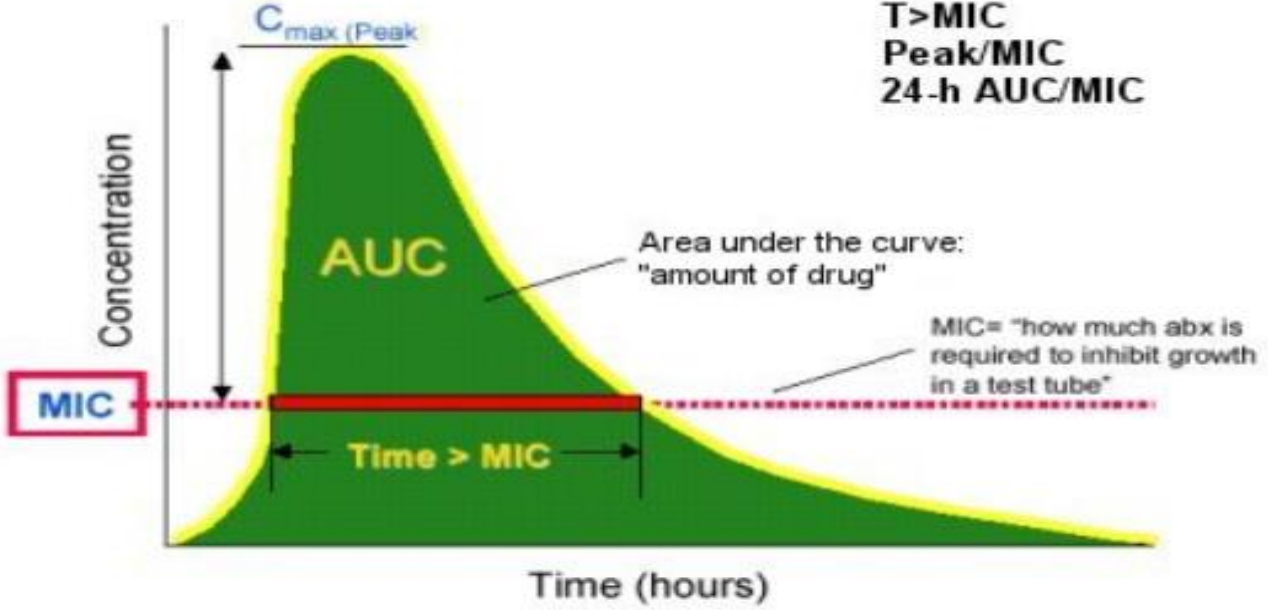
- Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic:

  - the Peak/MIC ratio
  - the %T>MIC
  - the 24h-AUC/MIC ratio

# Pharmacokinetic/Pharmacodynamic Predictors of Efficacy

**PK/PD parameters**

**T>MIC**
**Peak/MIC**
**24-h AUC/MIC**



# UNDERSTANDING TERMS OF PK/PD

- The Peak/MIC ratio is simply the Cmax divided by the MIC.
- The %T>MIC (time above MIC) is the percentage of a dosage interval in which the serum level exceeds the MIC.
- The 24h-AUC/MIC ratio is determined by dividing the 24-hour-AUC by the MIC.

# 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-organism combination.

# Area Under the Curve (AUC)

- The AUC is a measure of total systemic exposure to the drug, which expresses how much drug reaches a person's bloodstream in a given period of time after a dose is given.
- The information is useful for determining dosing and for identifying potential drug interactions.
- Units : µg/ml x hrs
- It helps to evaluate and compare bioavailability profiles between medicines.

# AREA UNDER THE CURVE (AUC)…

- Typically, the area is calculated starting from the time the medicine is administered until the time when the concentration in plasma is insignificant.

$C_{max}$: The maximum concentration or maximum systemic exposure

$T_{max}$: The time of maximum concentration or maximum systemic exposure

$t_{1/2}$ or half-life: The time required to reduce the plasma concentration to one-half of its initial value

# IMPORTANCE OF PK/PD

PK-PD target threshold helps to …

- **Select a dose** with clinical response rates consistent with regulatory approval
- Select appropriate **susceptibility breakpoint**
- Prevent **resistance amplification**
- Optimize **speed of response**

# Further Use of PK/PD

PK/PD is also critical in determining breakpoints that are used to categorize the MIC of an isolate as

"Susceptible,"

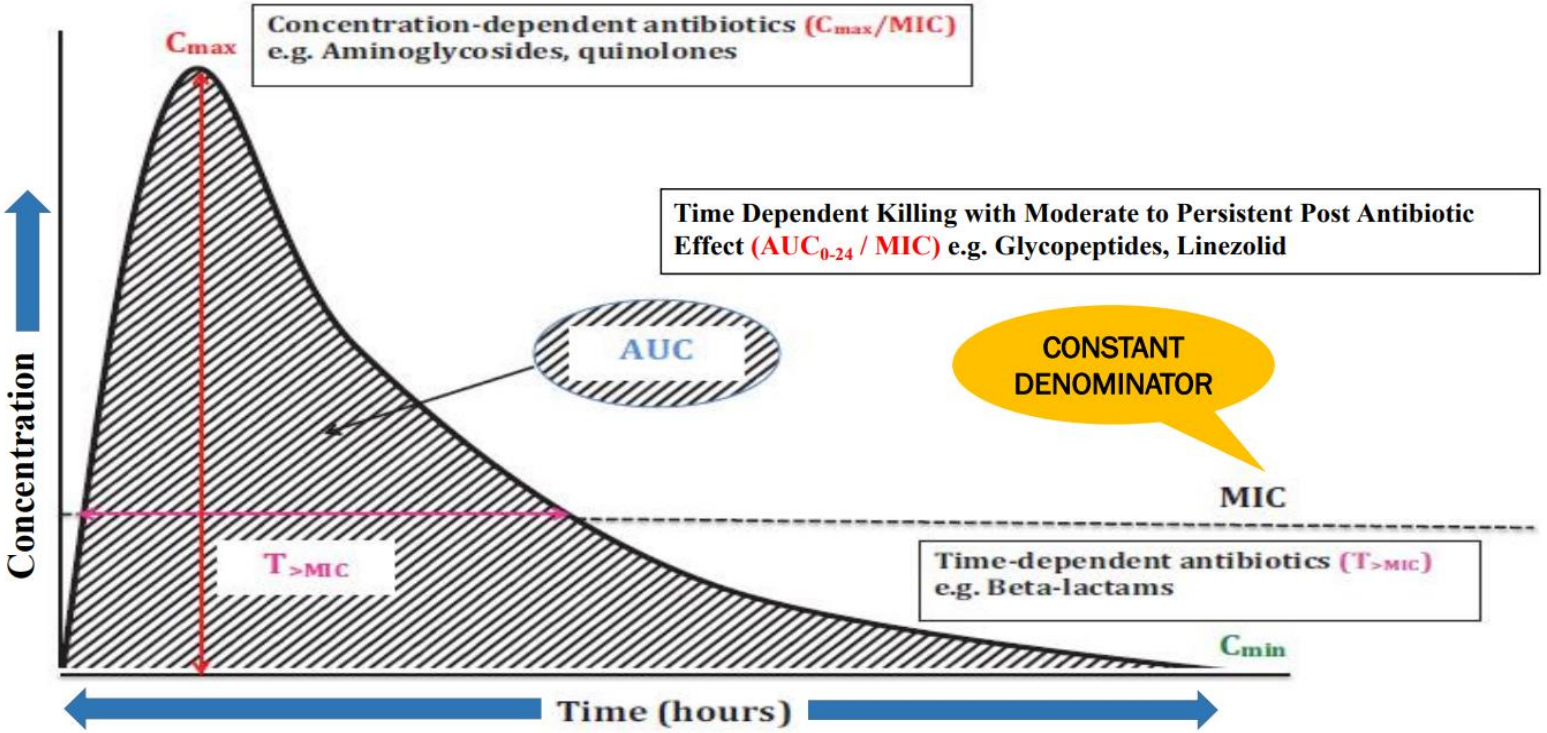
"Intermediate,"

"Susceptible-Dose-Dependent",

"Non-Susceptible," or "Resistant."

Done by Clinical and Laboratory Standards Institute (CLSI)

# Combine PK with PD
# Typical Concentration-Time Curve



# ANTIMICROBIAL PATTERNS

The three Pharmacodynamics properties of antibiotics that best describe killing activity are -

1. Time-dependent- The rate of killing is determined by the length of time necessary to kill .
2. Concentration-dependent- the effect of increasing concentrations .
3. Persistent effects- Post-Antibiotic Effect -PAE is the persistent suppression of bacterial growth following antibiotic exposure.

# TYPE I ANTIBIOTICS - TIME-DEPENDENT

## Aminoglycosides, fluoroquinolones

The ideal dosing regimen would maximize **concentration**, because the higher the concentration, the more extensive and the faster is the degree of killing.

- Therefore, the **Peak/MIC ratio is the important predictors** of antibiotic efficacy.
- For aminoglycosides, it is best to have a Peak/MIC ratio of **at least 8-10** to prevent resistance.

# GENTAMICIN IS PROTOTYPE OF TYPE -1

- Exhibit maximum activity with high concentrations and long PAE.
- Substantial PAE
- Immunomodulatory action (leucocyte enhancement)
- Adaptive resistance (ability to revert to susceptible)
- Nephrotoxicity: reversible; drug binding to brush border of renal cells.
- Ototoxicity: Irreversible; free radicals damage vestibular and cochlear cells.
- PK/PD parameter :Cmax /MIC ratio should be 8-10 for MIC ≤1ug/ml
- Goal trough levels 0.5-1ug/ml before redosing

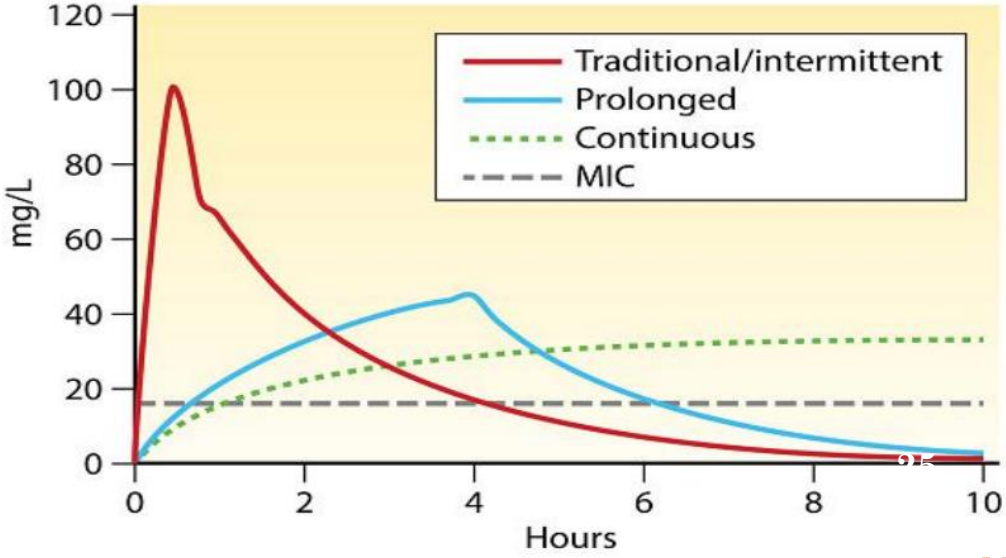
# TYPE II ANTIBIOTICS- CONCENTRATION-DEPENDENT

**Beta-lactams, Clindamycin, Erythromycin, and Linezolid**

- The ideal dosing regimen for these antibiotics maximizes the **duration** of exposure.
- The T>MIC is the parameter that best correlates with efficacy.
- For beta-lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval.

# II – Time Dependent with No PAE

- Beta Lactams / Monobactam (Aztreonam) / Erythromycin
- PK/PD parameter for Best Clinical Efficacy: percentage of Time when concentration stays above the MIC (T%>MIC). **Assuming MIC in "S"**
  - Cepahlosporins (Slow killing): at least 60 – 70%
  - Penicillin: at least 50%
  - Carbapenems: at least 40%




AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Continuous and Prolonged Intravenous β-Lactam Dosing: Implications for the Clinical Laboratory

**Mordechai Grupper, Joseph L. Kuti, David P. Nicolau**
Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA

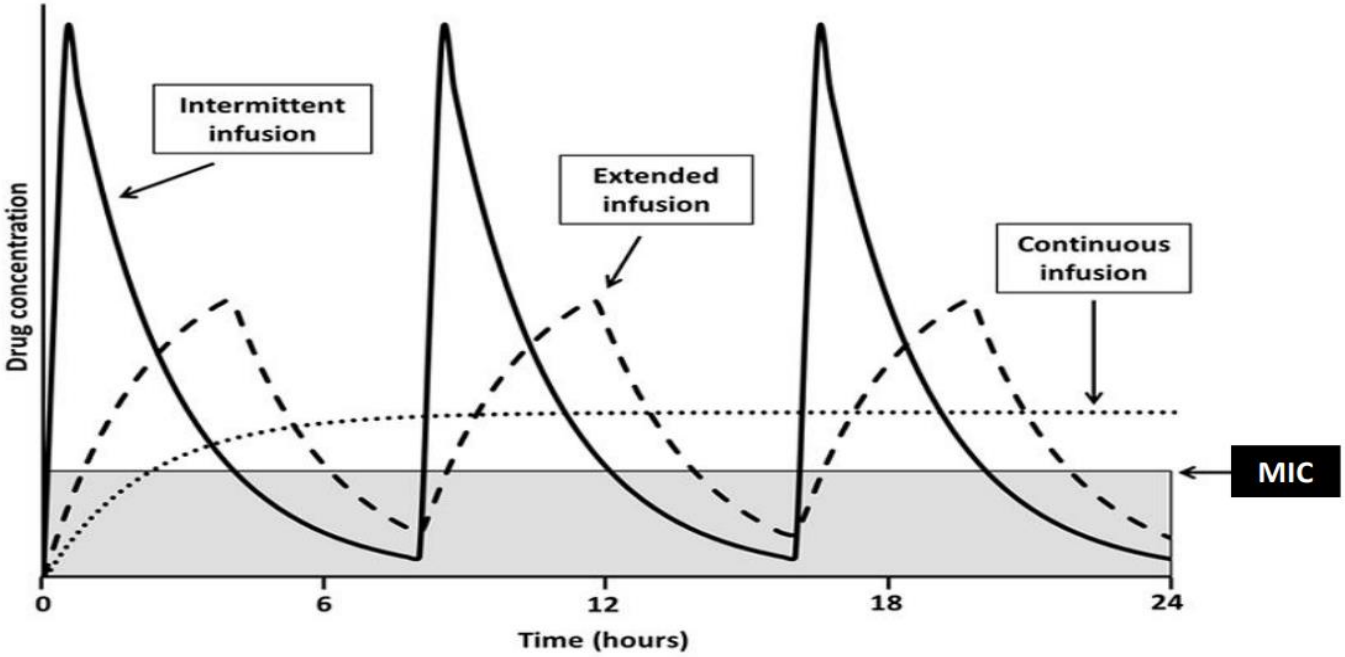



**Fig. 2.**
Time above the minimum inhibitory concentration (MIC) for intermittent, extended and continuous infusion of time-dependent drugs. Extended or continuous infusion of time-dependent drugs can improve the percentage of the dosing interval above the MIC ($T_{>MIC}$), particularly when treating infections with elevated MICs. Intermittent infusion (solid line), extended infusion (dashed line) and continuous infusion (dotted line) are compared with the time that each dosing regimen is below the MIC, highlighted by the grey area. Curves were generated using the same total daily dose and consistent pharmacokinetic parameters for each regimen.

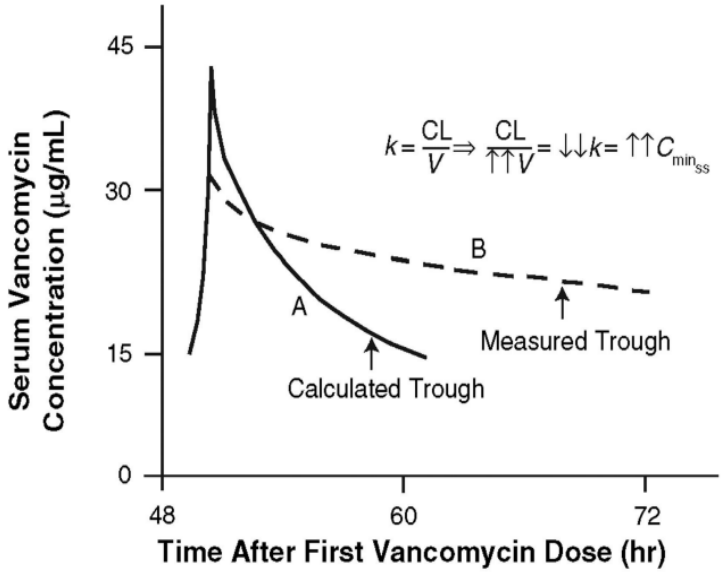
# TYPE III ANTIBIOTICS

## Vancomycin, Tetracyclines, Azithromycin

- Have mixed properties, they have time-dependent killing and moderate persistent effects.
- The ideal dosing regimen for these antibiotics maximizes the **amount** of drug received.
- Therefore, **the 24h-AUC/MIC ratio is the parameter that correlates with efficacy.**
- For vancomycin, a 24h-AUC/MIC ratio of at least **400** is necessary for MRSA.

# III – Time Dependent with Significant PAE

- Total Drug administered matters: PK Parameter is the AUC
- The Defined PK/PD parameter in such drugs is $AUC_{0\text{-}24}$/MIC ratio
- Total amount of drug exposed in 24 hours / MIC. **Assuming MIC in "S"**
  - ✓Macrolides
  - ✓Clindamycin
  - ✓Tetracyclines
  - ✓Linezolid
  - ✓Vancomycin



# VANCOMYCIN: Classical Example

- Maintain $AUC_{0-24}$/MIC > 400 successful clinical outcome
- HOW?
- Loading Dose in Children for serious MRSA Infections: 25 mg/kg stat
- Maintenance dose: 15 – 20 mg/kg/dose q6hrly
- **Total Daily Dose NOT LESS THAN 60mg/kg/day**
- WHEN VANCOMYCIN M.I.C. IS ≤1 µg/mL
- Maintain trough levels @ 15-20 µg/mL both for adults and children

# Vancomycin Dosing and Frequency Depends Upon Creatinine Clearance

**D. VANCOMYCIN[a]**

**Empiric Dosage[b,c] (mg/kg/dose) by Gestational Age and Serum Creatinine**

| ≤28 wk | | | >28 wk | | |
|---|---|---|---|---|---|
| **Serum Creatinine** | **Dose** | **Frequency** | **Serum Creatinine** | **Dose** | **Frequency** |
| <0.5 | 15 | q12h | <0.7 | 15 | q12h |
| 0.5–0.7 | 20 | q24h | 0.7–0.9 | 20 | q24h |
| 0.8–1 | 15 | q24h | 1–1.2 | 15 | q24h |
| 1.1–1.4 | 10 | q24h | 1.3–1.6 | 10 | q24h |
| >1.4 | 15 | q48h | >1.6 | 15 | q48h |

[a] Serum creatinine concentrations normally fluctuate and are partly influenced by transplacental maternal creatinine in the first week of age. Cautious use of creatinine-based dosing strategy with frequent reassessment of renal function and vancomycin serum concentrations are recommended in neonates ≤7 days old.

[b] Up through 60 days of age. If >60 days of age, 45–60 mg/kg/day div q8h (see Chapter 11).

[c] Desired serum concentrations vary by pathogen, site of infection, degree of illness; for MRSA and MSSA, aim for a target based on the ratio of the area under the curve–minimum inhibitory concentration of ~400 mg/L × hr, which will require peak and trough measurement. For coagulase-negative staphylococci and *Enterococcus*, troughs of 5–10 mg/L are likely to be effective.

Pattern of activity of different antibacterial drugs and their associated pharmacokinetic/pharmacodynamic (PK/PD) targets [a]

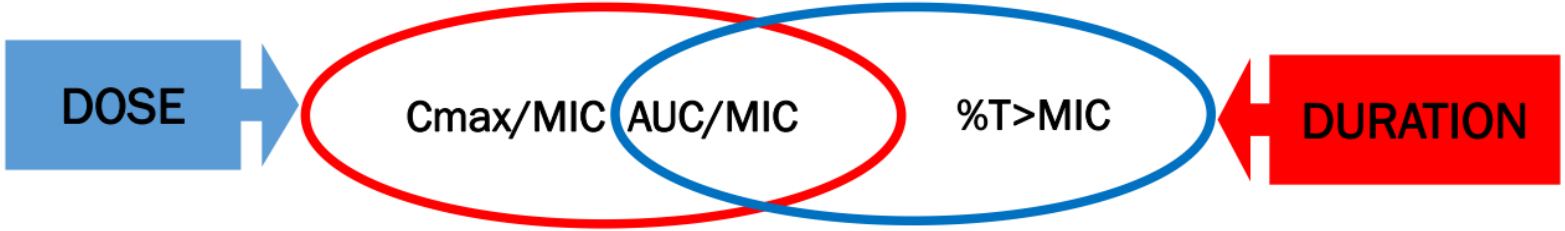
| Mechanism of bactericidal effects based on in vitro data | Antibiotic class | PK/PD parameter(s) associated with efficacy | Goal of dosing regimen |
|---|---|---|---|
| Concentration- dependent killing with moderate-to-persistent bactericidal effects<br>**CONC DEP / GOOD PAE** | Aminoglycosides<br>Fluoroquinolones<br>Metronidazole<br>Daptomycin<br>Ketolides | $C_{max}$/MIC<br>$AUC_{0-24}$/MIC | **Maximise concentration**: increase dose |
| Time-dependent killing with minimal-to-no persistent bactericidal effects<br>**TIME DEP / POOR PAE** | β-Lactams:<br>Penicillins<br>Cephalosporins<br>Carbapenems<br>Aztreonam<br>Erythromycin | $T_{>MIC}$ | **Maximise the duration of exposure**: increase duration of infusion or frequency of administration |
| Time-dependent killing with moderate-to-prolonged persistent bactericidal effects<br>**TIME DEP / GOOD PAE** | Macrolides<br>Tetracyclines<br>Glycopeptides<br>Clindamycin<br>Linezolid [b] | $AUC_{0-24}$/MIC | **Maximise drug exposure**: increase dose, frequency of administration or duration of infusion |

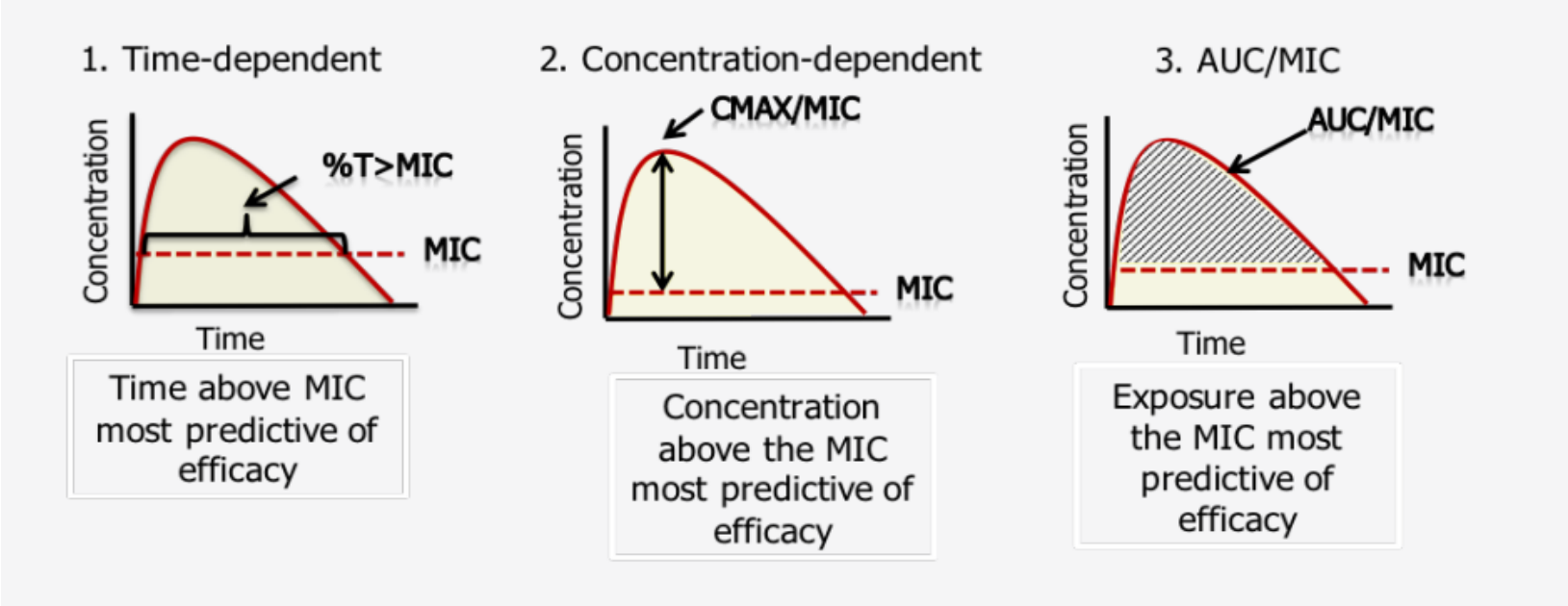
## POST ANTIBIOTIC EFFECT

- Protein Bound Drug Getting released slowly
- Damage caused to genetic machinery

# Some Basic Fundamentals to Remember

- Altering the **DOSE** primarily affects **Cmax: MIC** and **AUC: MIC**
- Altering the **DOSING INTERVAL / DURATION** affects **AUC: MIC** and **%T>MIC**
- For **time dependent agents**, the rate of bacterial killing is maximised at a low multiple of the MIC and achieving **higher concentrations does not result in greater killing.**
- For concentration dependent agents an increase in Vd will reduce the ability for a standard dose to achieve a high Cmax.






"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.

# Aminoglycoside Pharmacodynamics in Vivo

| Initial serum peak level | Died | Survived |
|---|---|---|
| < 5mcg/ml | **21%** | **79%** |
| >= 5mcg/ml | **2%** | **98%** |

Moore et al, J Infect Dis 149: 443, 1984

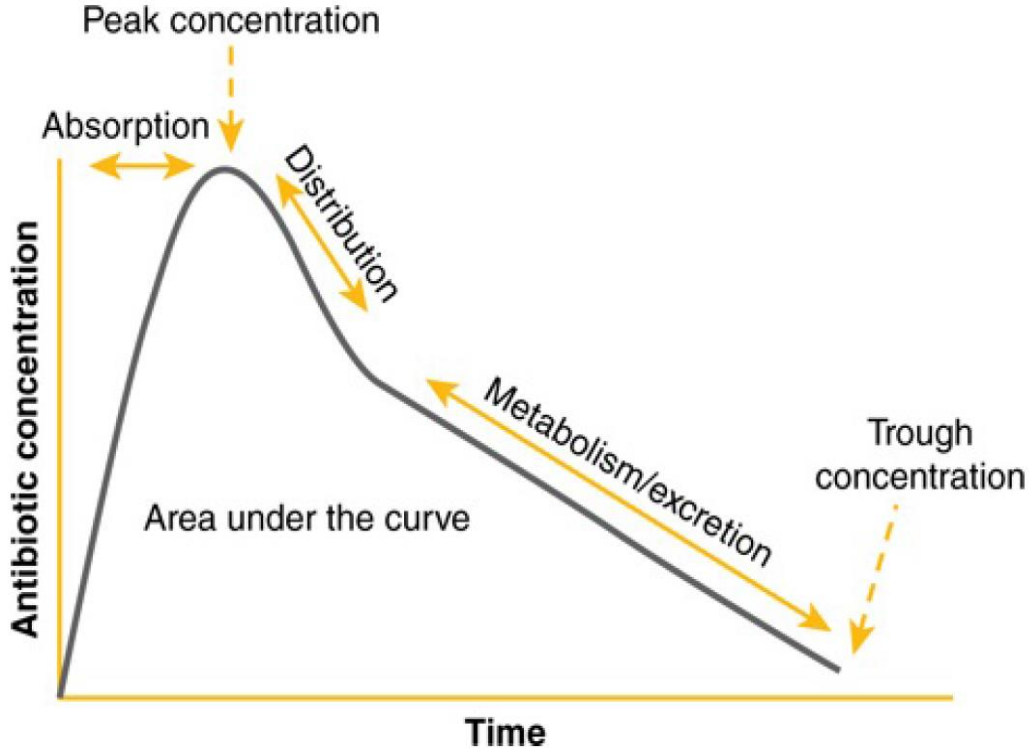



**Figure 3–1** Pharmacokinetic Phases and Parameters

# How can we alter Dose / Duration / Frequency of Antibiotic?

## FIRST UNDERSTAND THE BASIC P.K. & P.D.

**PHARMACOKINETICS**

- Absorption
- Distribution
- Metabolism
- Elimination
- Protein Binding

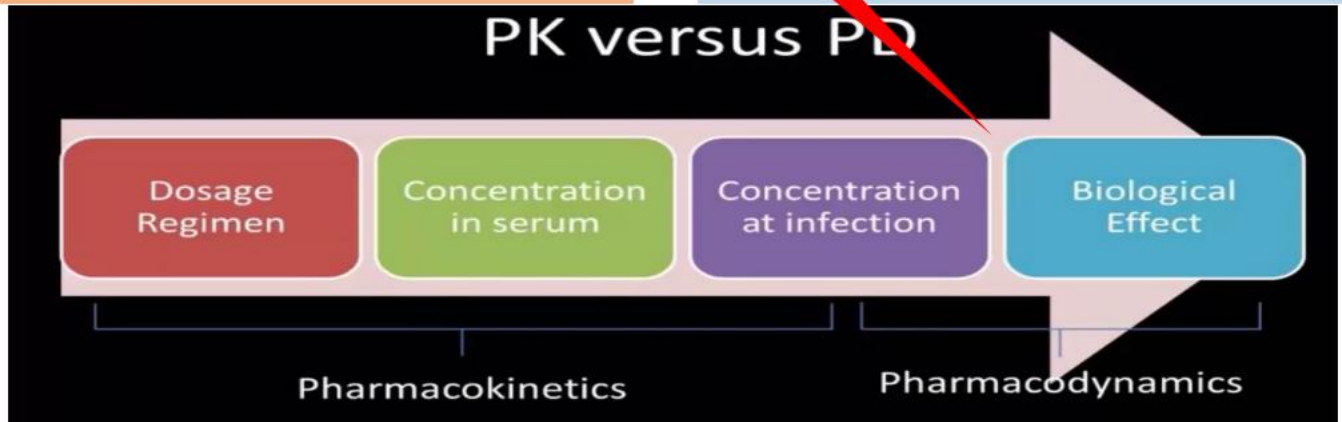
**WHAT THE BODY DOES TO THE DRUG?**

**PHARMACODYNAMICS**

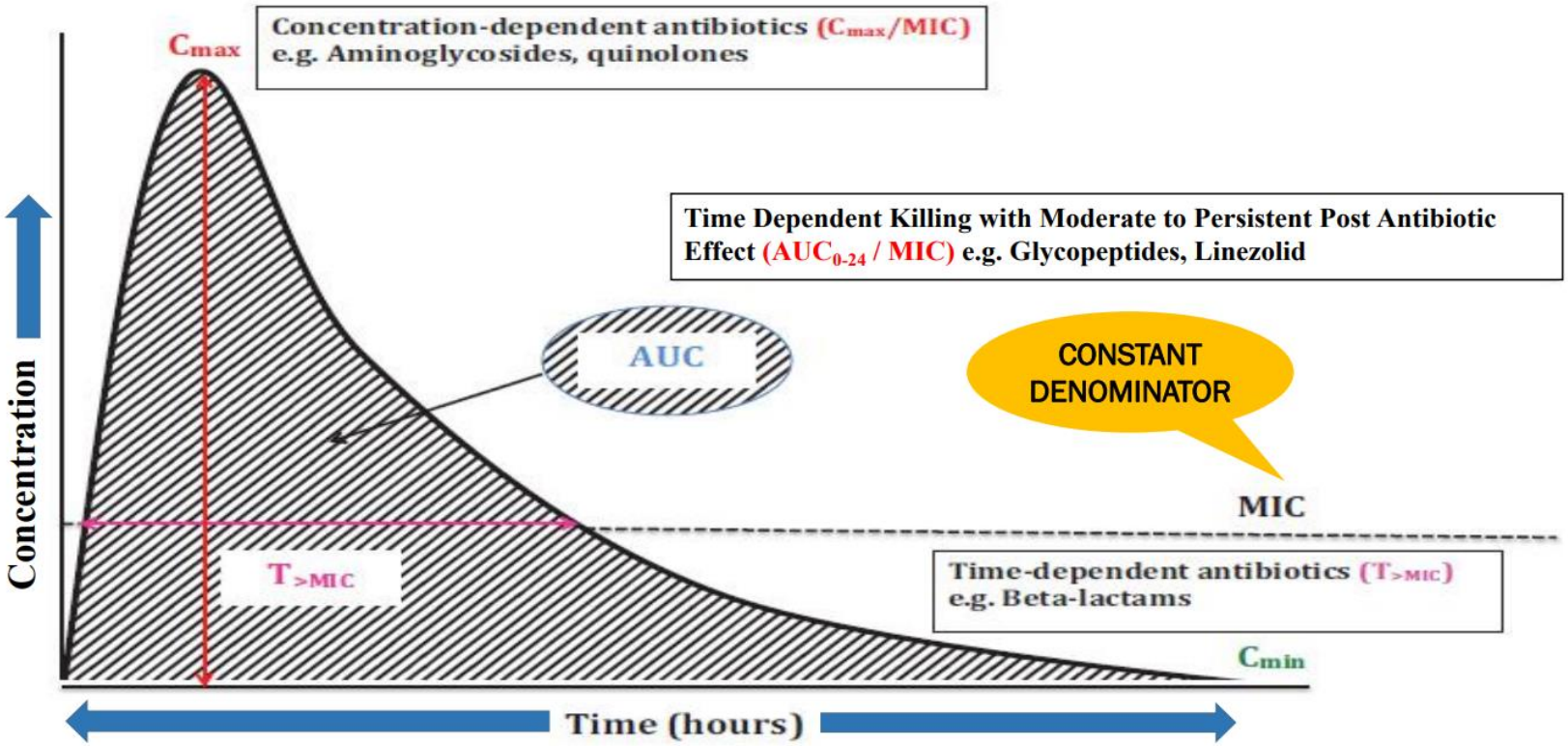
- Drug Effects on Target pathogens
- Drug Toxicity / Side Effects

**WHAT THE DRUG DOES TO THE BACTERIA / BODY**

**MIC**



# Combine PK with PD
# Typical Concentration-Time Curve



Pattern of activity of different antibacterial drugs and their associated pharmacokinetic/pharmacodynamic (PK/PD) targets [a]

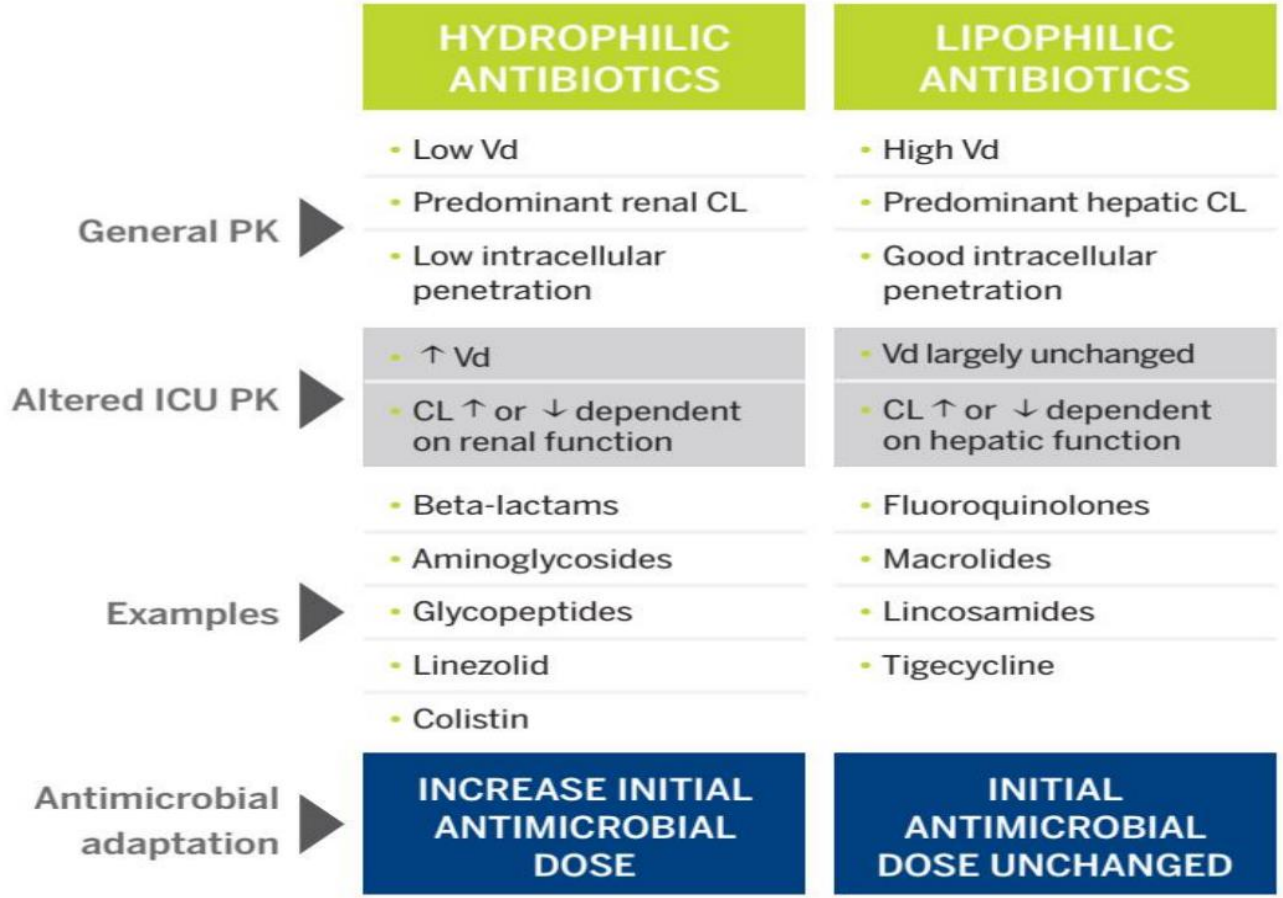
| Mechanism of bactericidal effects based on in vitro data | Antibiotic class | PK/PD parameter(s) associated with efficacy | Goal of dosing regimen |
|---|---|---|---|
| Concentration- dependent killing with moderate-to-persistent bactericidal effects<br>**CONC DEP / GOOD PAE** | Aminoglycosides<br>Fluoroquinolones<br>Metronidazole<br>Daptomycin<br>Ketolides | $C_{max}$/MIC<br>$AUC_{0-24}$/MIC | **Maximise concentration**: increase dose |
| Time-dependent killing with minimal-to-no persistent bactericidal effects<br>**TIME DEP / POOR PAE** | β-Lactams:<br>Penicillins<br>Cephalosporins<br>Carbapenems<br>Aztreonam<br>Erythromycin | $T_{>MIC}$ | **Maximise the duration of exposure**: increase duration of infusion or frequency of administration |
| Time-dependent killing with moderate-to-prolonged persistent bactericidal effects<br>**TIME DEP / GOOD PAE** | Macrolides<br>Tetracyclines<br>Glycopeptides<br>Clindamycin<br>Linezolid [b] | $AUC_{0-24}$/MIC | **Maximise drug exposure**: increase dose, frequency of administration or duration of infusion |

## POST ANTIBIOTIC EFFECT

- Protein Bound Drug Getting released slowly
- Damage caused to genetic machinery

# Some Basic Fundamentals to Remember

- **Hydrophilic agents** (beta-lactams, glycopeptides, aminoglycosides)
  - Cannot passively diffuse through the cytoplasmic membrane
  - Inactive against intracellular organisms
  - They have a limited extracellular distribution
  - Excreted renally.
- **Lipophilic agents** (macrolides, tetracyclines, fluoroquinolones)
  - Freely cross membranes
  - Have activity against intracellular organisms
  - Wide distribution and intracellular accumulation
  - Hepatic metabolism




*Vd - Volume of distribution; CL - clearance*

| CLASS | EXAMPLE | EFFECT | DISTRIBUTION | EXCRETION | PRIMARY PD PARAMETER | PAE | TDM |
|---|---|---|---|---|---|---|---|
| Beta Lactams | Amoxicillin | Bactericidal | Low protein binding and hydrophilic | Renal | T>MIC | Short or no PAE | Not routine |
| Glycopeptides | Vancomycin | Bactericidal | Hydrophilic | Renal | AUC:MIC | Short PAE | Recommended for all patients |
| Aminoglycosides | Gentamicin | Bactericidal | Hydrophilic | Renal | $C_{MAX}$:MIC & AUC:MIC | Significant | Recommended for all patients |
| Fluoroquinolones | Ciprofloxacin | Bactericidal | Lipophilic wide distribution | Renal & hepatobiliary | $C_{MAX}$:MIC & AUC:MIC | Significant | Not recommended |
| Macrolides | Azithromycin | Bacteriostatic | Lipophilic wide distribution | Hepatobiliary | T>MIC & AUC:MIC | Significant | Not recommended |
| Tetracyclines | Doxycyline | Bacteriostatic | Lipophilic wide distribution | Hepatobiliary | AUC:MIC | Significant | Not recommended |
| Lincosamide | Clindamycin | Bacteriostatic | Lipophilic wide distribution | Hepatobiliary | AUC:MIC | Demonstrated in *S.aureus* | Not recommended |
| Oxazolidinone | Linezolid | Bacteriostatic | Lipophilic wide distribution | Renal | AUC:MIC | Short | CF, ESRF, neonates, burns, MIC >2mg/l interacting meds |
| Lipopeptide | Daptomycin | Bactericidal | Highly protein bound hydrophilic | Renal | $C_{MAX}$:MIC & AUC:MIC | Significant | dosing >6mg/kg, renal impairment |
| Polymyxin | Colistin (colistimethate sodium) | Bactericidal | Hydrophilic and lipophilic properties | Renal | AUC:MIC | Significant | Recommended for all patients |

# WHEN IS PK / PD CLINICALLY RELEVANT?

| | Potential altered PK/PD | Example |
|---|---|---|
| Obesity | Reduced tissue penetration | Quinolones |
| | Shorter mean $T_{1/2}$ * | Vancomycin |
| | Increased Vd** | Aminoglycosides |
| | Increased clearance | Aminoglycosides |
| Renal insufficiency | Decreased clearance | Aminoglycosides |
| Neonates | Decreased clearance | Aminoglycosides |
| | | Glycopeptides |
| Children | Increased clearance | Aminoglycosides |
| Critical illness | Increased Vd | Aminoglycosides |
| | | Beta lactams |
| | | Glycopeptides |
| | | Colistin |
| | Increased clearance | Beta lactams |
| Pregnancy | Increased clearance | Aminoglycosides |
| | | Cefuroxime |
| | Increased Vd | Hydrophilic agents |
| Cystic fibrosis | Increased clearance | Aminoglycosides |

*$T_{1/2}$ half life, **Vd volume of distribution)

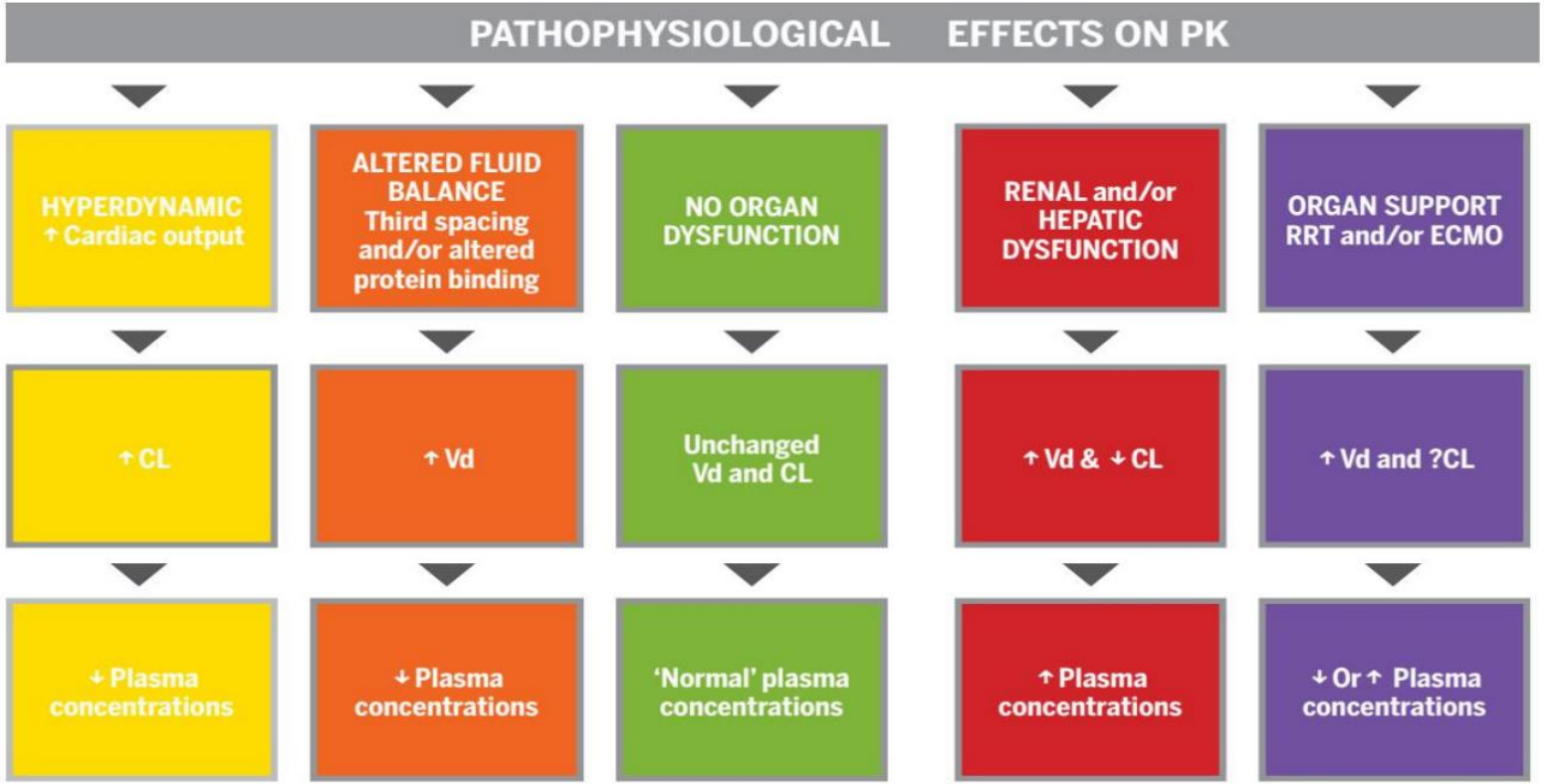
# Should You Know the Elimination Route?

| HEPATOBILIARY | | RENAL | |
|---|---|---|---|
| Chloramphenicol | Isoniazid | Most Fluoroquinolones | Amantadine |
| Moxifloxacin | Rifampin | Aminoglycosides | Rimantadine |
| Tigecycline | Pyrazinamide | Carbapenems | Acyclovir |
| Doxycycline | Ethambutol | Nitrofurantoin | Valacyclovir |
| Minocycline | | Tetracycline | Famciclovir |
| Cefoperazone | Ketoconazole | Aztreonam | Valganiciclovir |
| Ceftriaxone | Voriconazole | Poly B, Colistin | Oseltamivir |
| Macrolides | Posaconazole | Most Beta Lactams | Zanamivir |
| Nafcillin | Itraconazole | Vancomycin | Peramavir |
| Clindamycin | Caspofungin | Oxacillin | |
| Quinu/Dalfo | Micafungin | Daptomycin | |
| Linezolid | Anidulafungin | Telavancin | Fluconazole |
| Metronidazole | | Ceftaroline | Amphotericin B |

# Should You Know About the Bioavailability?

| Bioavailability | Antimicrobials | | |
|---|---|---|---|
| Excellent (>90%) | Amoxicillin | Tmp-Smx | Linezolid |
| | Cepahlexin | Doxycycline | Fluconazole |
| | Cefprozil | Minocycline | Voriconazole |
| | Cefadroxil | Chloramphenicol | Rifampin |
| | Clindamycin | Metronidazole | Isoniazid |
| | Quinolones | Cycloserine | Pyrazinamide |
| Good (60-90%) | Cefixime | Valacyclovir | Ethambutol |
| | Cefpodoxime | Famciclovir | 5-Flucytosine |
| | Ceftibuten | Valganiciclovir | Posaconazole |
| | Cefuroxime | Macrolides | Itraconazole |
| | Cefaclor | Nitrofurantoin | Nitazoxanide (w food) |
| Poor (<60%) | Vancomycin | Cefdinir | Nitazoxanide (w/o food) |
| | Acyclovir | Cefditoren | Fosfomycin |

Roberts JA et al. Lancet Inf Dis April 2014, Review




CL – creatinine clearance
Vd – volume of distribution
RRT – renal replacement therapy
ECMO – extracorporeal membrane oxygenation
?CL – possible increased clearance

# FACTORS IN ANTIBIOTIC DOSING

**Renal Insufficiency:**

- Most antibiotics cleared by kidneys have wide toxic – therapeutic ratio
- Dosing regimens frequently based on formula derived estimates of CrCl

**CrCL: 40-60 mL/min:**

- **↓dose by 50%**
- **USUAL dosing interval**

**CrCL: 10-40 mL/min:**

- **↓dose by 50%**
- **DOUBLE dosing interval**

**Alternative: Use Hepatically eliminated Abx in Usual Dose**

**Hepatic Insufficiency: ↓dose by 50%** in clinically severe liver dis.

**Alternative: Use Renal eliminated Abx in Usual Dose**

# BECOME AN ANTIBIOTIC GUARDIAN

Keep Antibiotics Working