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DETERMINING CORRECT DOSING REGIMENS OF ANTIBIOTICS BASED ON THE THEIR BACTERICIDAL ACTIVITY*

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KEYWORDS
Äntibacterials, 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.

TOPIC SUMMARY

In the past, the dosing of antibiotics was largely based on habit rather than on science. In the previous decades, investigators have been able to identify pharmacological indices which facilitate comparisons of the activity of these antibiotics as well as help determine the optimal dosing regimen.

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.[1] This is the overall amount of drug in the bloodstream after a dose. It is the most reliable reflection of the extent of absorption.

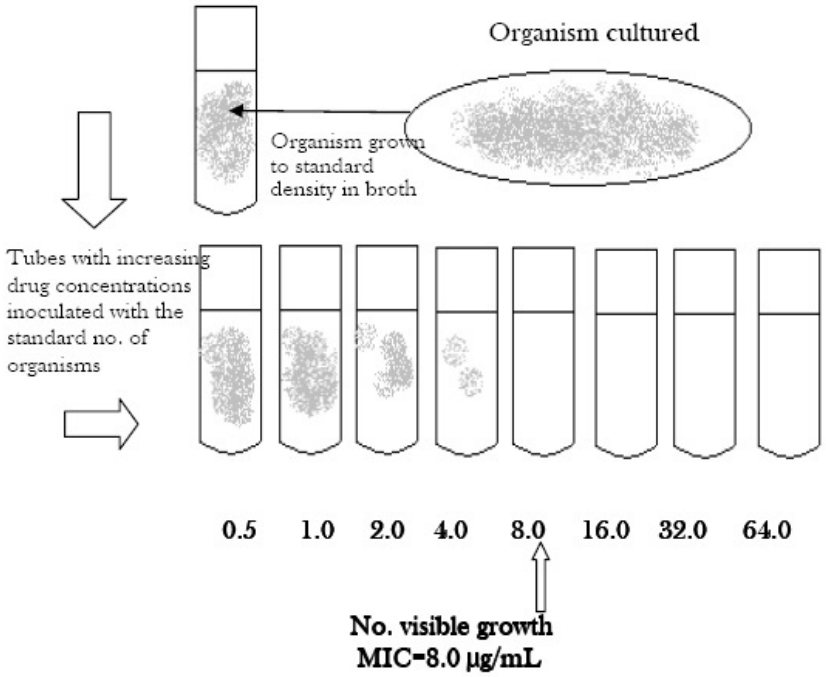
The **C_{max} (maximum concentration)** is the highest concentration of drug in the blood that is measured after a dose. C_{max} usually occurs within a few hours after the dose is administered.

Pharmacologic Indices in antibiotics therapy

Peak/MIC (C_{max}/MIC) ratio is defined as the peak level divided by the MIC[2]. 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[2]. It

Figure 8.1. Determination of MIC using the broth dilution test

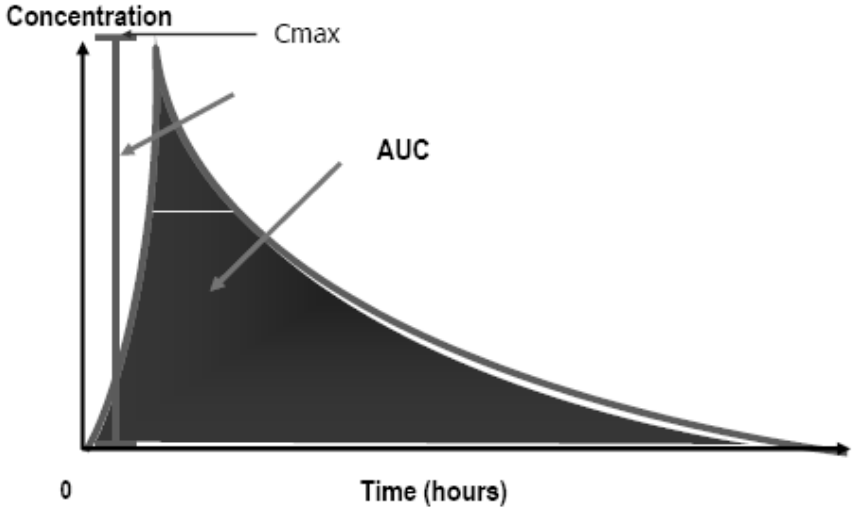


is also used to predict the efficacy of concentration-dependent antibiotics.

T>MIC is defined as the cumulative percentage of time over a 24 hour period that the drug concentration exceeds the MIC[2]. 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



AUC = Area under the concentration–time curve

C_{max} = Maximum plasma concentration

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.

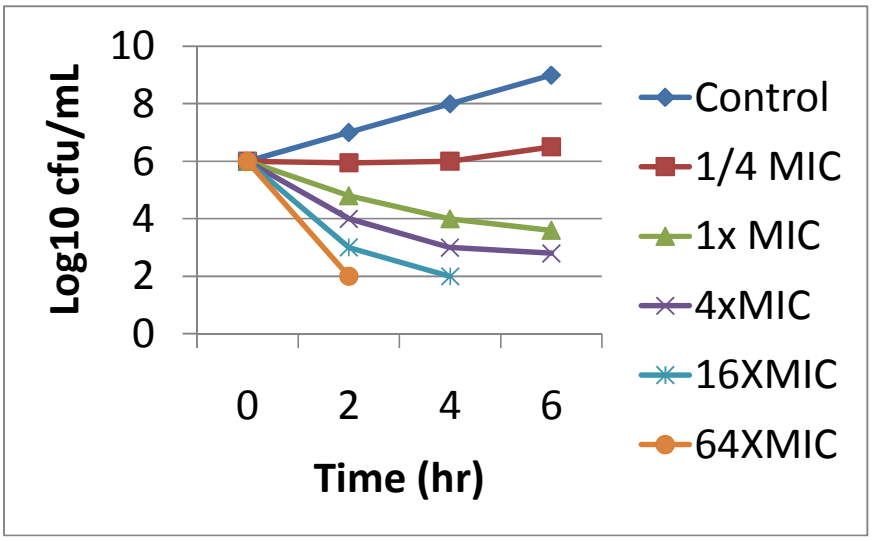
Table 8.1. Classification of antibiotics based on pharmacokinetic/pharmacodynamic parameters of efficacy and bacterial eradication.

Pattern of Activity	Antibiotics	Goal of Therapy	PK/PD Parameter
Type I Concentration-dependent killing and prolonged persistent effects	Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Maximize concentrations	24h-AUC/MIC ratio Cmax/MIC ratio
Type II-A Time-dependent killing and Minimal persistent effects	Carbapenems Cephalosporins Erythromycin Linezolid Penicillins	Maximize duration of exposure	T>MIC
Type II-B Time-dependent killing and Moderate to prolonged persistent effects.	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin	Maximize amount of drug	24h-AUC/MIC ratio

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

ClCr	Gentamicin	Amikacin
>50	5 mg/kg/24 hrs	15 mg/kg/24 hrs
30-49	5 mg/kg/36 hrs	15 mg/kg/36 hrs
20-29	5 mg/kg/48 hrs	15 mg/kg/48 hrs
<20	2 mg/kg with monitoring	7.5 mg/kg with monitoring

Figure 8.2. Representative Time-kill curves of Concentration Dependent Antibiotic in In vitro Models



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 wells 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

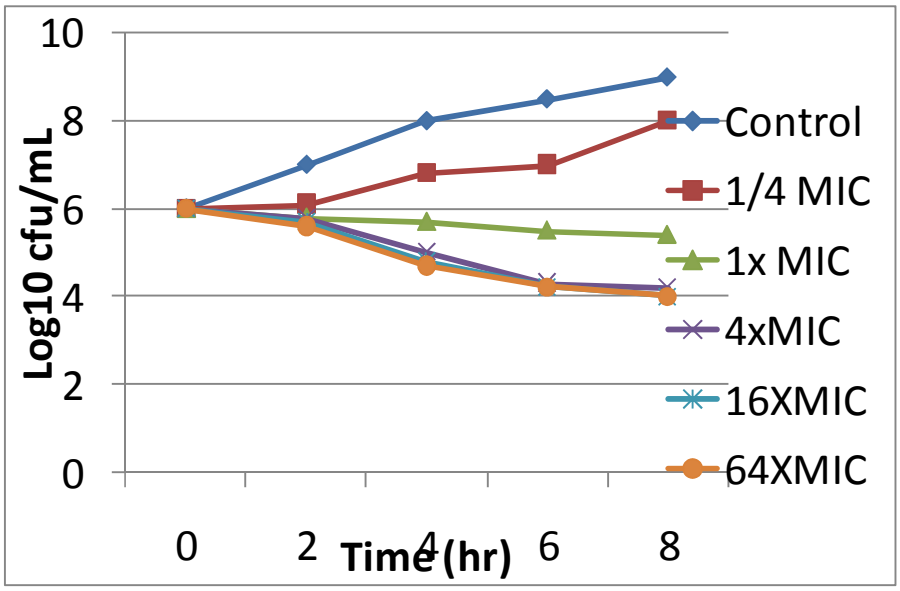


Figure 8.4. Pharmacodynamic Goals (T>MIC as percent of Interval) with Beta-Lactams

Class	Organism	Stasis (T>MIC)	Maximum killing (T>MIC)
Cephalosporins	Gram neg bacilli, pneumococcus Staphylococcus	40-50 20-30	70-80 40-50
Penicillins	Gram neg bacilli, pneumococcus Staphylococcus	30-40 20-30	60-70 40-50
Carbapenems	Gram neg bacilli. Staphylococcus pneumococcus	20-30 10-20	40-50 25-40

Table 8.3. Preferred Dosing Regimens for Children for Selected Antibiotics based on PK-PD Classification

Antibiotic	Classification	Total dose per day (mg/kg)	Dosing Frequency
Amikacin	*CD	15	Once daily
Gentamicin	CD	5	Once daily
Penicillin	**TD	100,000-200,000	Every 4 hrs
Cefazolin	TD	50-100	Every 6-8 hrs
Cefuroxime	TD	75-150	Every 6-8 hrs
Ceftriaxone	TD	100	Every 12-24 hrs
Ceftazidime	TD	100-150	Every 8 hrs, or continuous infusion
Piperacillin-tazobactam	TD	240-400	Every 8 hrs or continuous infusion
Meropenem	TD	60-120	Every 8 hrs as bolus or infused over 3 hrs

*concentration dependent
**time-dependent

BIBLIOGRAPHY:

Textbook of pediatric infectious diseases, edited by Feigin, R. et al. 5th Edition. Saunders, Pennsylvania 2004; Chapter 234

Moore RD, Lietman PS, Smith CR. **Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration.** J Infect Dis 1987; 155:93-99

DP Nicolau, CD Freeman, PP Belliveau, CH Nightingale, JW Ross, R Quintiliani. **Experience with a once-daily aminoglycoside program administered to 2,184 adult patients.** Antimicrob. Agents Chemother Mar 01, 1995; 39: 650-655

A Forrest, D E Nix, C H Ballow, T F Goss, M C Birmingham, and J J Schentag **Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients.** Antimicrob Agents Chemother. May 1993, 37: 1073-1081

Paul G. Ambrose, Dennis M. Grasela, Thaddeus H. Grasela, Julie Passarell, Howard B. Mayer, and Phillip F. Pierce. **Pharmacodynamics of Fluoroquinolones against *Streptococcus pneumoniae* in Patients with Community-Acquired Respiratory Tract Infections.** Antimicrob Agents Chemother. October 2001 45: 2793-2797

Quintiliani R Sr, Quintiliani R Jr, **Pharmacokinetics/Pharmacodynamics for Critical Care Clinicians.** Critical Care Clinicians 2008, 24: 335-348.

Amsden GW, Ballow CH, et al. "Pharmacokinetics and Pharmacodynamics of Anti-infective agents," *Principles and Practice of Infectious Diseases,* 7th Edition. Vol. 1, Churchill Livingstone, Philadelphia, 2010, Chapter 20.

INTERNET RESOURCES

Rxkinetics. <wwww.rxkinetics.com/antibiotic_pk_pd.html>

Gunderson BW et al. **What do we really know about Antibiotic Pharmacodynamics** Pharmacotherapy 21(11s)2001;302s-318s.

<http://www.medscape.com/viewarticle/415068_print>

Jo Carol J. McNabb, Charles H. Nightingale., Richard Quintiliani, and David P. Nicolau. **Cost-Effectiveness of Ceftazidime by Continuous Infusion versus Intermittent Infusion for Nosocomial Pneumonia.** Pharmacotherapy 21(5):549-555, 2001.

<http://www.medscape.com/viewarticle/409720>