PHAR 538 Special Topics: Advanced Pharmacology

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Principles of Antimicrobial Therapy

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- Antimicrobial therapy takes advantage of the biochemical differences between microorganisms and human beings.

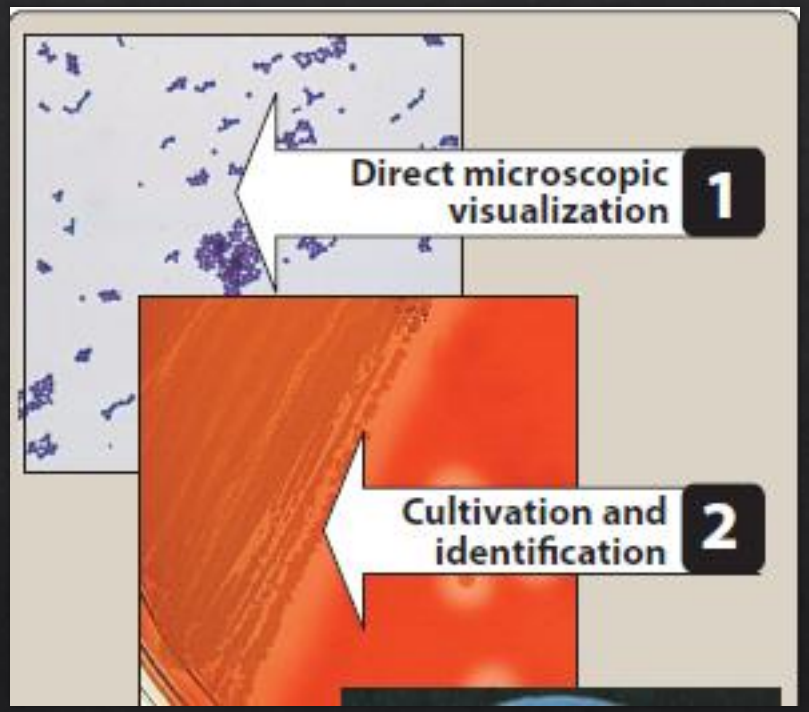
- Antimicrobial drugs are effective in the treatment of infections because of their **selective toxicity**; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host.

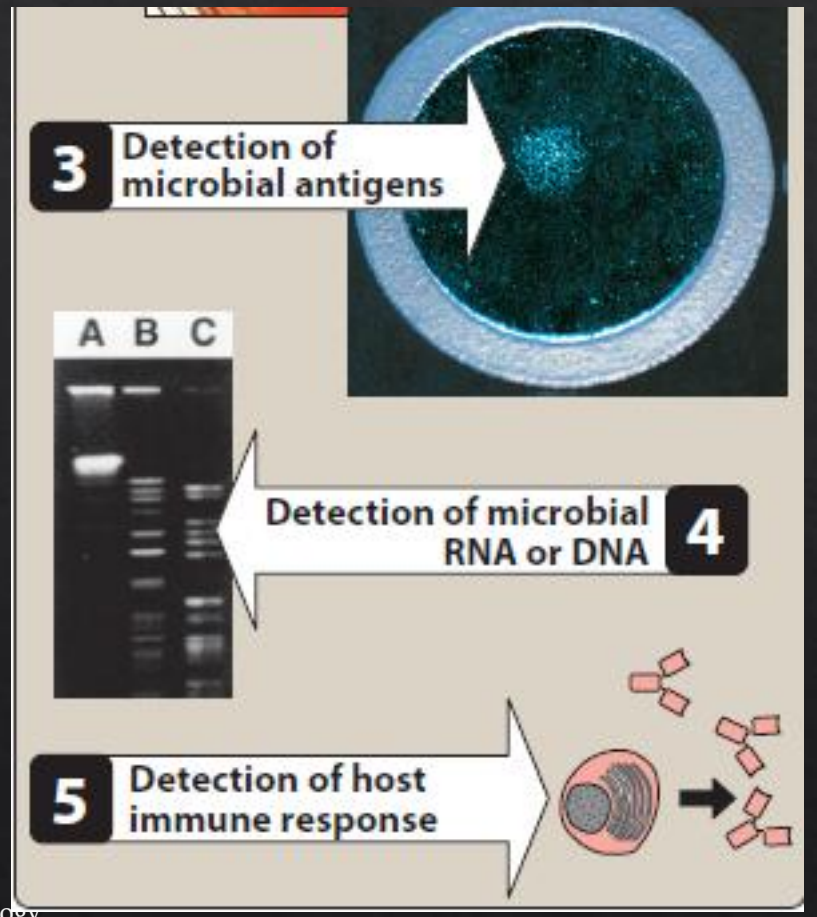
SELECTION OF ANTIMICROBIAL AGENTS

- Selection of the most appropriate antimicrobial agent requires knowing
  - 1) the organism's identity,
  - 2) the organism's susceptibility to a particular agent,
  - 3) the site of the infection,
  - 4) patient factors,
  - 5) the safety of the agent, and
  - 6) the cost of therapy.

- some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

Identification of the infecting organism





Empiric therapy

- Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established.

- However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.
- Acutely ill patients with infections of unknown origin—for example,
  - a neutropenic patient or
  - a patient with meningitis.
- If possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.

Selecting a drug for empiric regimen

- Drug choice in the absence of susceptibility data is influenced by
  - the site of infection and
  - the patient's history (for example,
    - previous infections,
    - age,
    - recent travel history,
    - recent antimicrobial therapy,
    - immune status, and
    - whether the infection was hospital- or community-acquired).

- Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely.

- The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting.

- For example, gram-positive cocci in the spinal fluid of a newborn infant is unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a group B streptococci), which is sensitive to penicillin G.

- By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This organism is frequently resistant to penicillin G and often requires treatment with a high-dose third generation cephalosporin (such as ceftriaxone) or vancomycin

Determining antimicrobial susceptibility of infective organisms

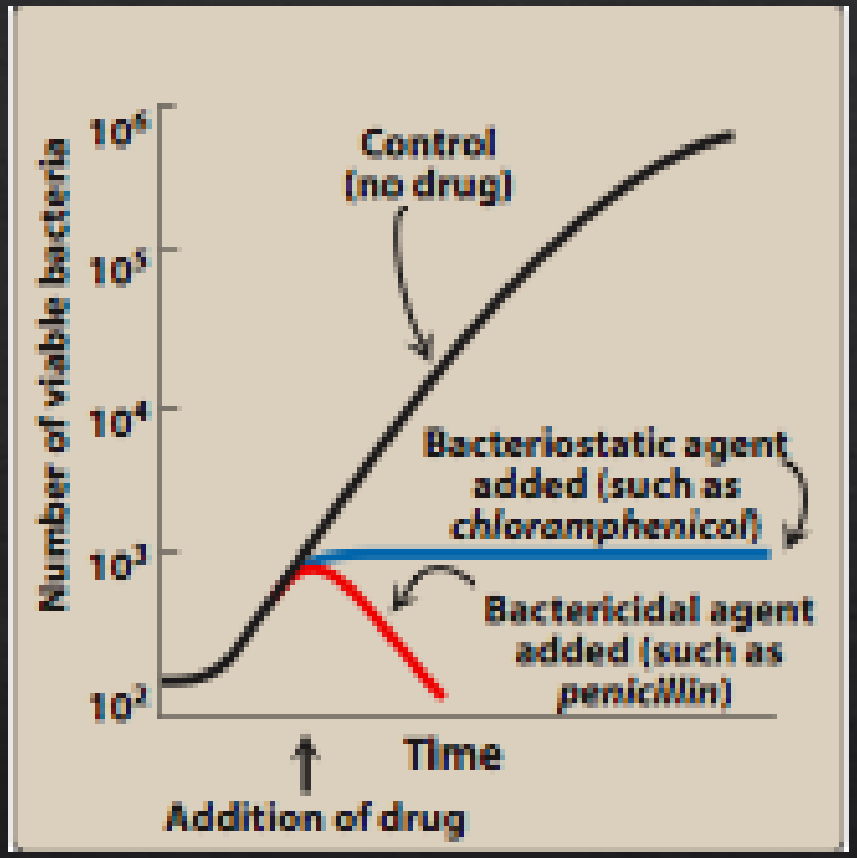
- After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy.
- Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics.
- In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy.
- The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined

Bacteriostatic VS bactericidal

- Bacteriostatic drugs arrest the growth and replication of bacteria at serum(or urine) levels achievable in the patient, thus limiting the spread of infection until the immune system attacks

- If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection.

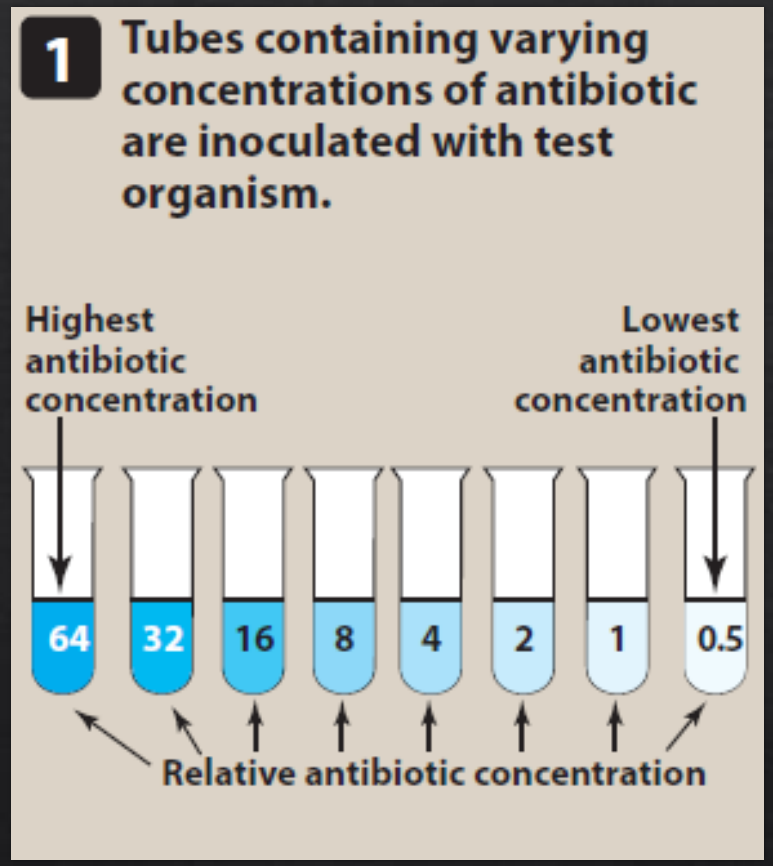
- Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.

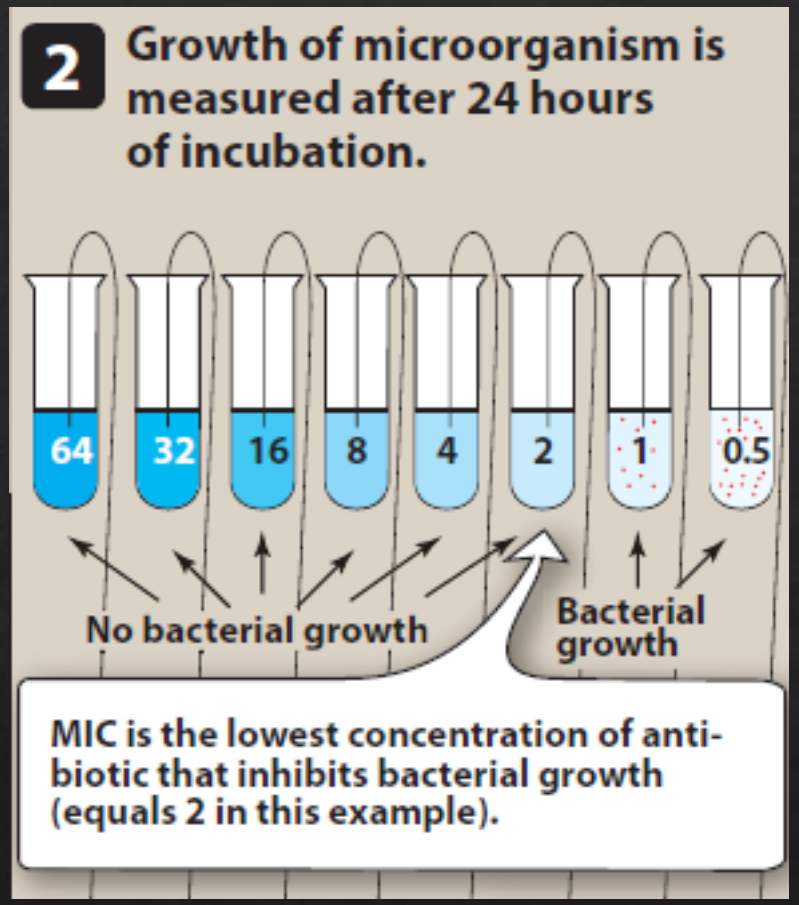


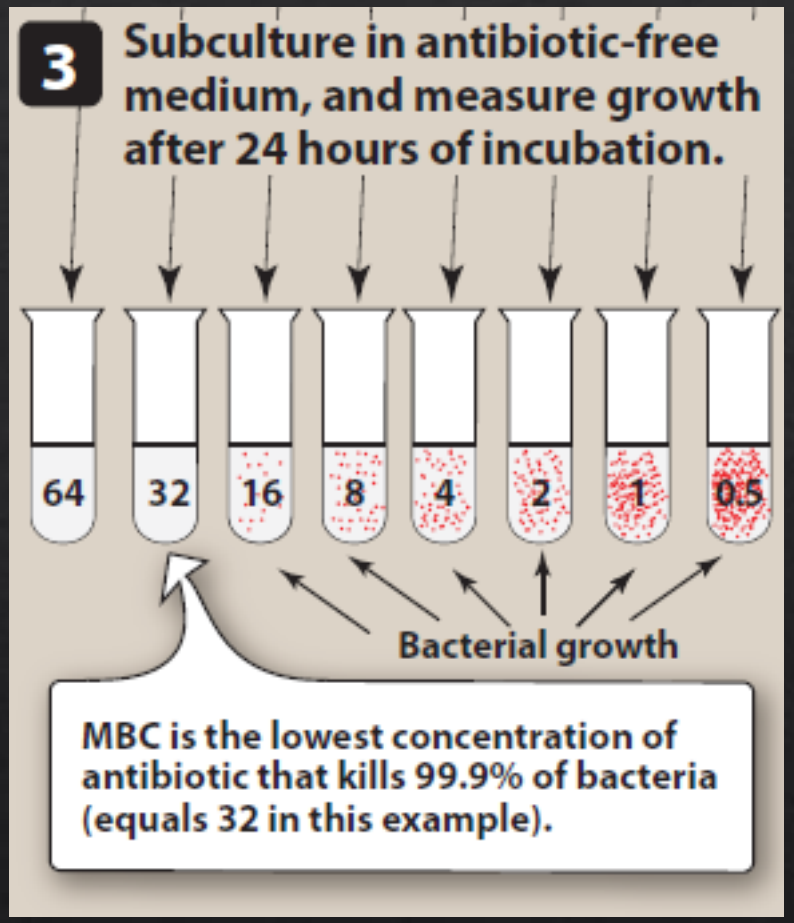
- it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another.

- For example, linezolid is bacteriostatic against *Staphylococcus aureus* and *enterococci* but is bactericidal against most strains of *S. pneumoniae*.

MIC and MBC







Effect of the site of infection on therapy: the blood–brain barrier

- Capillaries with varying degrees of permeability carry drugs to the body tissues.

- Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as
  - the prostate,
  - testes,
  - placenta,
  - the vitreous body of the eye, and
  - the central nervous system (CNS).

- Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier.

- This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic.

- The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

1. Lipid solubility of the drug:

- Lipid- soluble drugs, such as *chloramphenicol* and *metronidazole*, have signicant penetration into the CNS, whereas

- β-lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood–brain barrier under normal circumstances.

- In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.

2: Molecular weight of the drug:

- A compound with a low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas
- compounds with a high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

3:Protein binding of the drug:

- A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

Patient factors

- **1. Immune system:** Factors that can affect immune functions:
  - Alcoholism,
  - diabetes,
  - HIV infection,
  - malnutrition,
  - autoimmune diseases,
  - pregnancy, or a
  - advanced age
  - immunosuppressive drugs.
- High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

2. Renal dysfunction:

- Poor kidney function may cause accumulation of certain antibiotics.
- Dosage adjustment prevents drug accumulation and therefore adverse effects.
- Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.
- However, direct monitoring of serum levels of some antibiotics (for example, vancomycin, aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities.
- [Note: The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys.]

3. Hepatic dysfunction:

- Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.

4. Poor perfusion:

- Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that area, making these infections diffcult to treat.

5. Age:

- Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of chloramphenicol and sulfonamides.
- Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively.
- Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

6. Pregnancy and lactation:

- Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk.

CATE-GORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfa-methoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *genta-micin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

Figure 37.4
FDA categories of antimicrobials and fetal risk.

7. Risk factors for multidrug-resistant organisms:

- prior antimicrobial therapy in the preceding 90 days,
- hospitalization for greater than 2 days within the preceding 90 days,
- current hospitalization exceeding 5 days,
- high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms),
- immunosuppressive diseases and/or therapies.

- Infections with multidrug-resistant pathogens need broader antibiotic coverage when initiating empiric therapy.

Safety of the agent

- Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms.

- Other antimicrobial agents (for example, chloramphenicol) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient.

- [Note: Safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity.]

Cost of therapy

- Often several drugs may show similar efficacy in treating an infection but vary widely in cost.

- For example, treatment of *methicillin-resistant* Staphylococcus aureus (MRSA) generally includes one of the following: *vancomycin, clindamycin, daptomycin, or linezolid.*
- *Although* choice of therapy usually centers on the
  - site of infection,
  - severity of the illness, and
  - ability to take oral medications,
- it is also important to consider the cost of the medication.

Figure 37.5
Relative cost of some drugs used for the treatment of Staphylococcus aureus.

ROUTE OF ADMINISTRATION

- The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases.

- In hospitalized patients requiring intravenous therapy initially, the switch to oral agents should occur as soon as possible.

- However, some antibiotics, such as *vancomycin*, *the aminoglycosides*, and *amphotericin B* *are so poorly absorbed from the gastrointestinal (GI)* tract that adequate serum levels cannot be obtained by oral administration.

- Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents.

DETERMINANTS OF RATIONAL DOSING

- Rational dosing of antimicrobial agents is based on their pharmacodynamics and pharmacokinetic properties

- Three important properties that have a significant influence on the frequency of dosing are
  - Concentration dependent killing,
  - time-dependent killing, and
  - postantibiotic effect (PAE).

- Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

A. Concentration-dependent killing

- Certain antimicrobial agents, including aminoglycosides and *daptomycin*, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism.

- Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

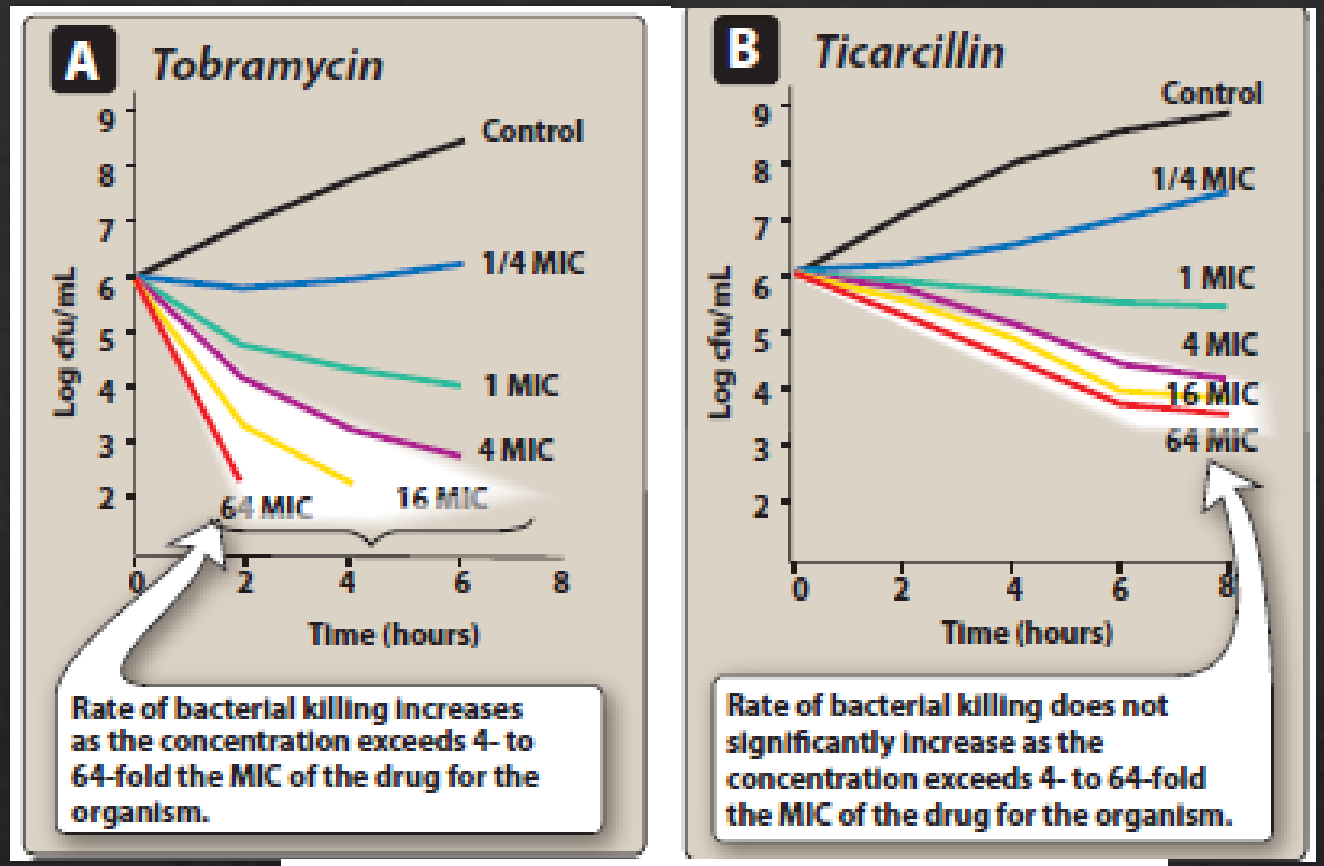


Figure 37.6
A. Significant dose-dependent killing effect shown by *tobramycin*.
B. Nonsignificant dose-dependent killing effect shown by *ticarcillin*.
(cfu = colony-forming units; MIC = minimum inhibitory concentration.)

B. Time-dependent (concentration-independent) killing

- In contrast, β-lactams, glycopeptides, macrolides, *clindamycin, and linezolid do not exhibit concentration-dependent killing.*
- The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC.
- For example, dosing schedules for the penicillins and cephalosporins that ensure blood levels greater than the MIC for 50% and 60% of the time, respectively, provide the most clinical efficacy.
- Therefore, extended (generally 3 to 4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria.

C. Postantibiotic effect

- The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

- Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram negative bacteria.

V. CHEMOTHERAPEUTIC SPECTRA

- **Narrow-spectrum antibiotics:** acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid*

- **Extended-spectrum antibiotics:** antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin*

- **Broad-spectrum antibiotics:** affect a wide variety of microbial species such as *tetracycline, fluoroquinolones and carbapenems*

- Administration of broadspectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

VI. COMBINATIONS OF ANTIMICROBIAL DRUGS

- It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism.
  - reduces the possibility of superinfections,
  - decreases the emergence of resistant organisms, and
  - minimizes toxicity.

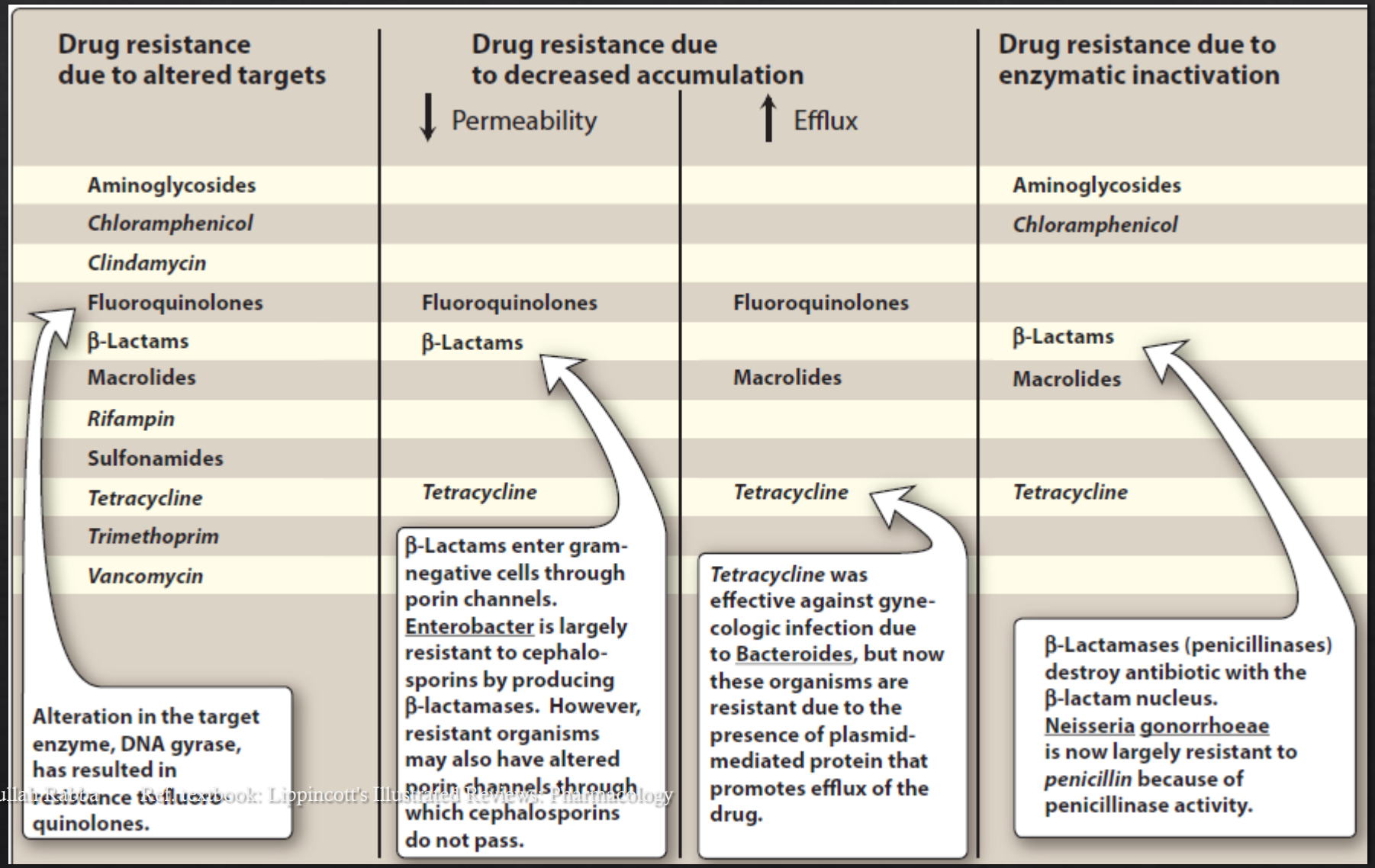
- However, some situations require combinations of antimicrobial drugs. For example, the treatment of tuberculosis benefits from drug combinations.

- Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately

- A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.

- For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins.

VII. DRUG RESISTANCE



COMPLICATIONS OF ANTIBIOTIC THERAPY

- **A. Hypersensitivity**
  - **E.g. penicilins**
- **B. Direct toxicity**
  - **E.g. aminiglycocides**
- **C. Superinfections**
  - Especially, broad spectrum antibiotics eradicating the normal flora and permitting the overgrowth of opportunistic organisms

SITES OF ANTIMICROBIAL ACTIONS