Antimicrobial Therapy

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Principles of Antimicrobial Therapy

Antimicrobial therapy takes advantage of the biochemical differences that exist 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*.

In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by 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.

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

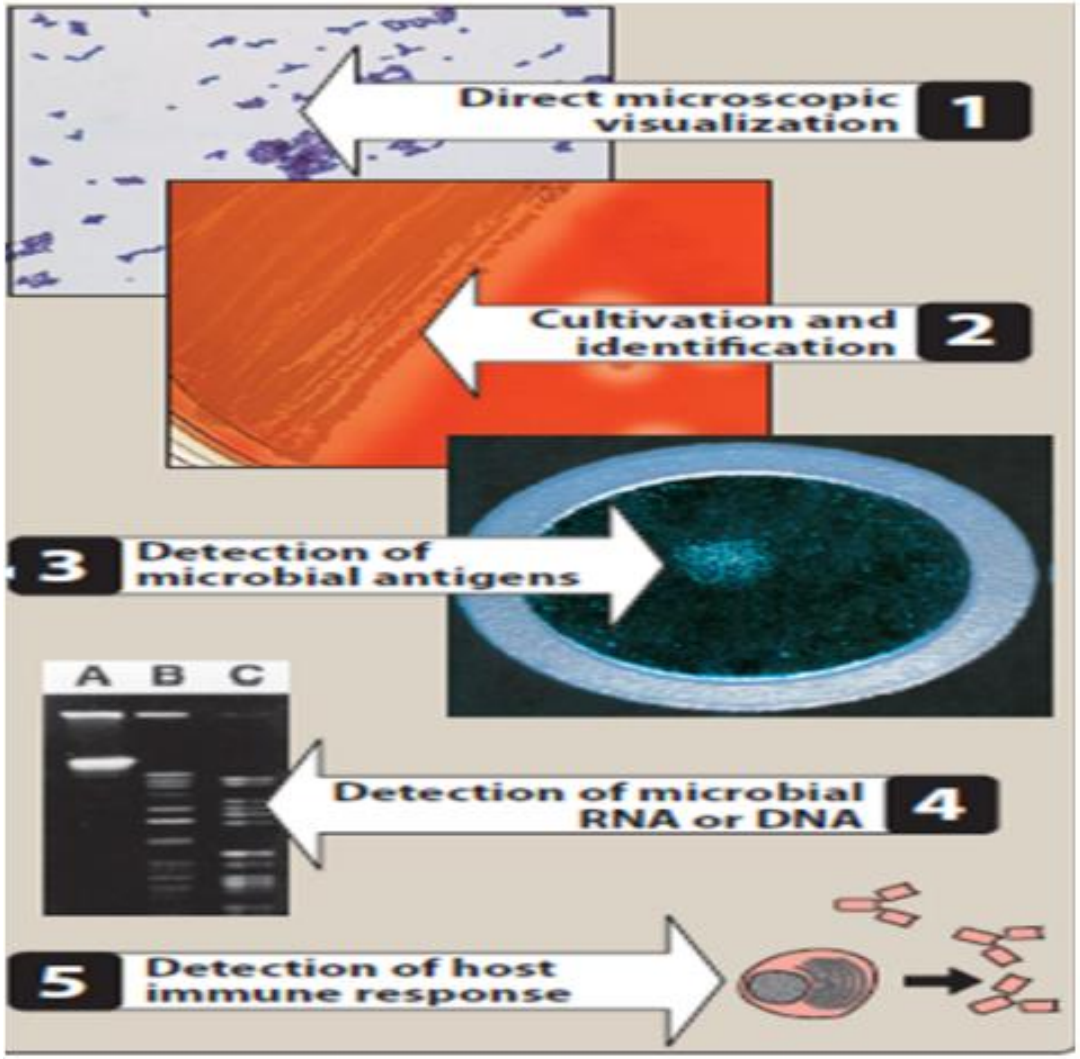


Figure 37.1
Some laboratory techniques that are useful in the diagnosis of microbial diseases.

A. Identification of the infecting organism

A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine).

B. Empiric therapy prior to identification of the organism

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

1- Timing:

Acutely ill patients with infections of unknown origin For example, a neutropenic patient (a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord) require immediate treatment. 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.

2. Selecting a drug:

Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely. For example, gram-positive cocci in the spinal fluid of a newborn infant is most likely to be Streptococcus agalactiae 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

C. Determining antimicrobial susceptibility of infective organisms:

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.

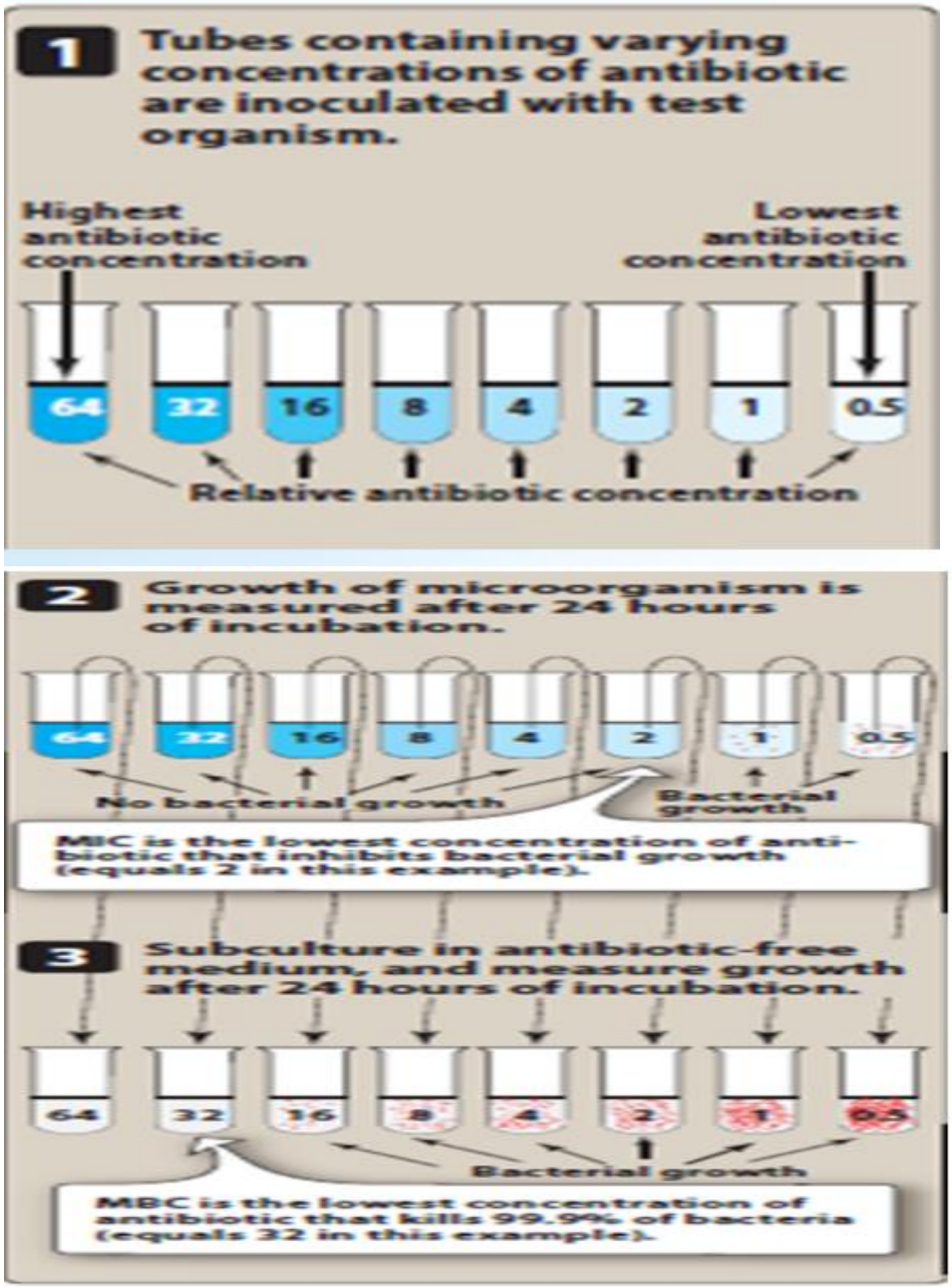


Figure 37.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

1. Bacteriostatic versus bactericidal drugs:

Antimicrobial drugs are classified as either bacteriostatic or bactericidal.

-Bacteriostatic drugs arrest the growth and replication of bacteria at serum(or urine) levels

-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.

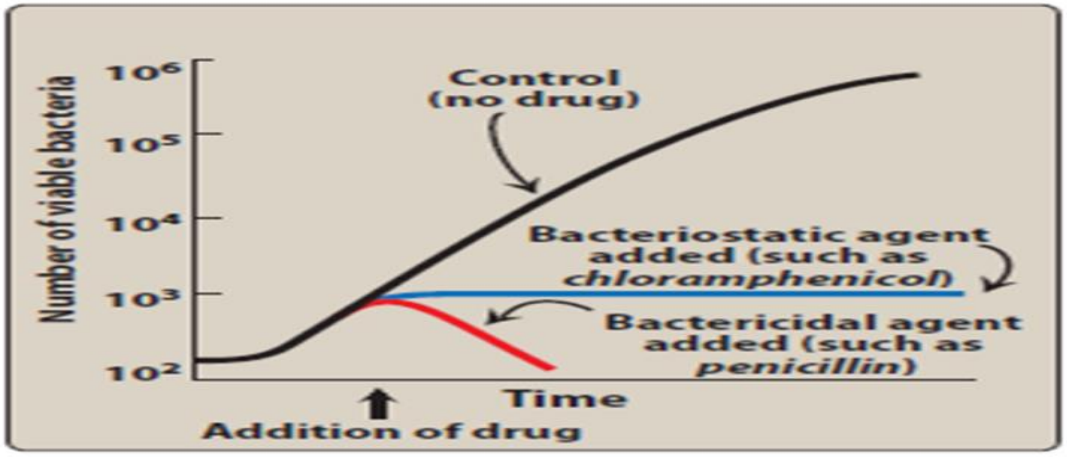


Figure 37.3
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

2. Minimum inhibitory concentration: The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation.

3. Minimum bactericidal concentration: The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations.

D. Effect of the site of infection on therapy:

The blood–brain barrier BBB: 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 significant penetration into the CNS, whereas β-lactam antibiotics, such as penicillin, are ionized at physiologic pH and have low solubility in lipids.

In infections such as meningitis, 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 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.

E. Patient factors

the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

1. Immune system: Alcoholism,diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect a patient's immunocompetence

High doses of bactericidal agents or longer courses of treatment may be required

2. Renal dysfunction: Poor kidney function may cause accumulation of certain antibiotics. (for eg, vancomycin, aminoglycosides)

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 difficult 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. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

CATEGORY	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-sulfamethoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

Figure 37.4
FDA categories of antimicrobials and fetal risk.

F. 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.

G. 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

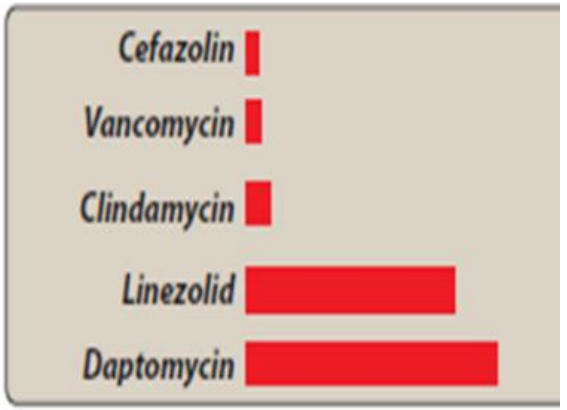


Figure 37.5
Relative cost of some drugs used for the treatment of Staphylococcus aureus.

Staphylococcus aureus (MRSA) generally includes one of the following: vancomycin, clindamycin, daptomycin, or linezolid.

❑ ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis.

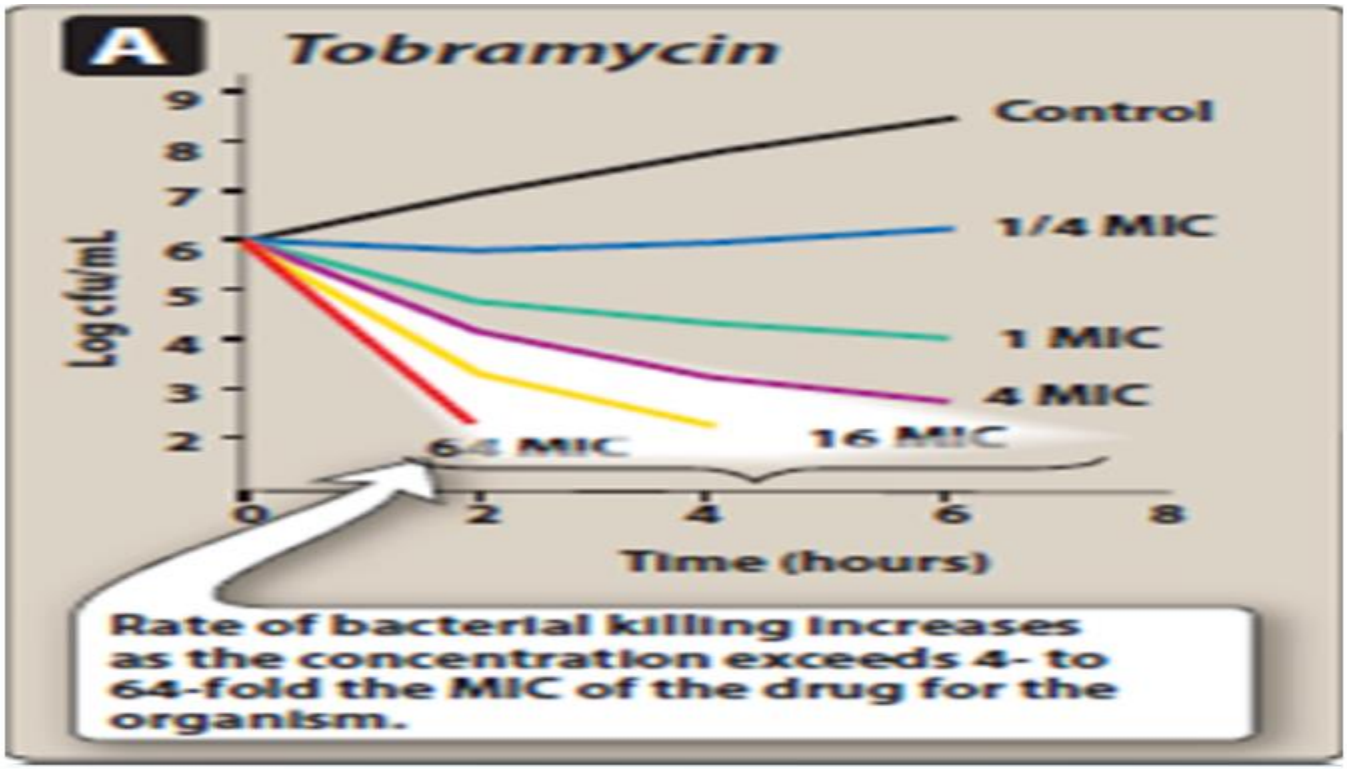
In hospitalized patients requiring intravenous therapy initially, the switch to oral agents should occur as soon as possible.

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.

❑ DETERMINANTS OF RATIONAL DOSING

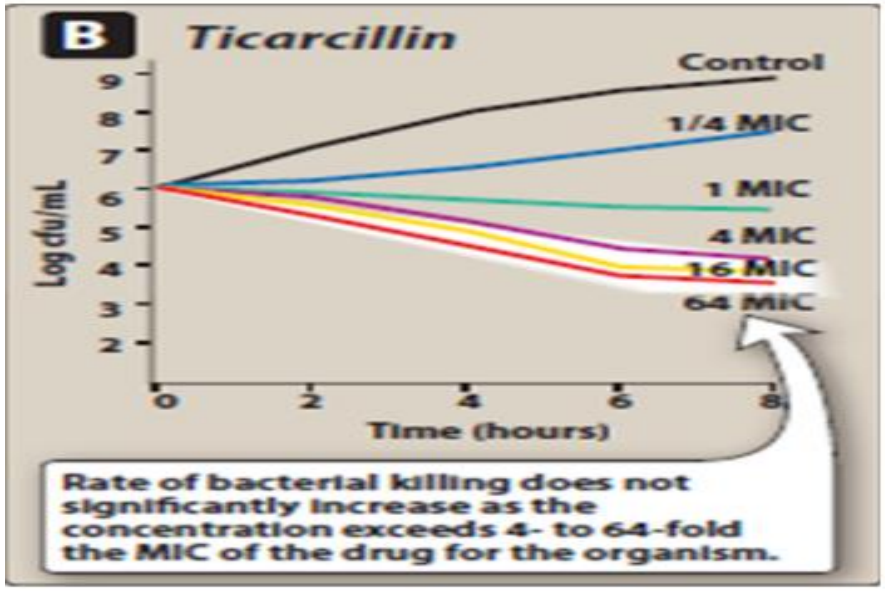
A. Concentration-dependent killing Certain antimicrobial agents, including aminoglycosides and daptomycin, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism. Giving drugs once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.



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. This effect is sometimes called concentration-independent or time-dependent killing.



C. Postantibiotic effect: PAE

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

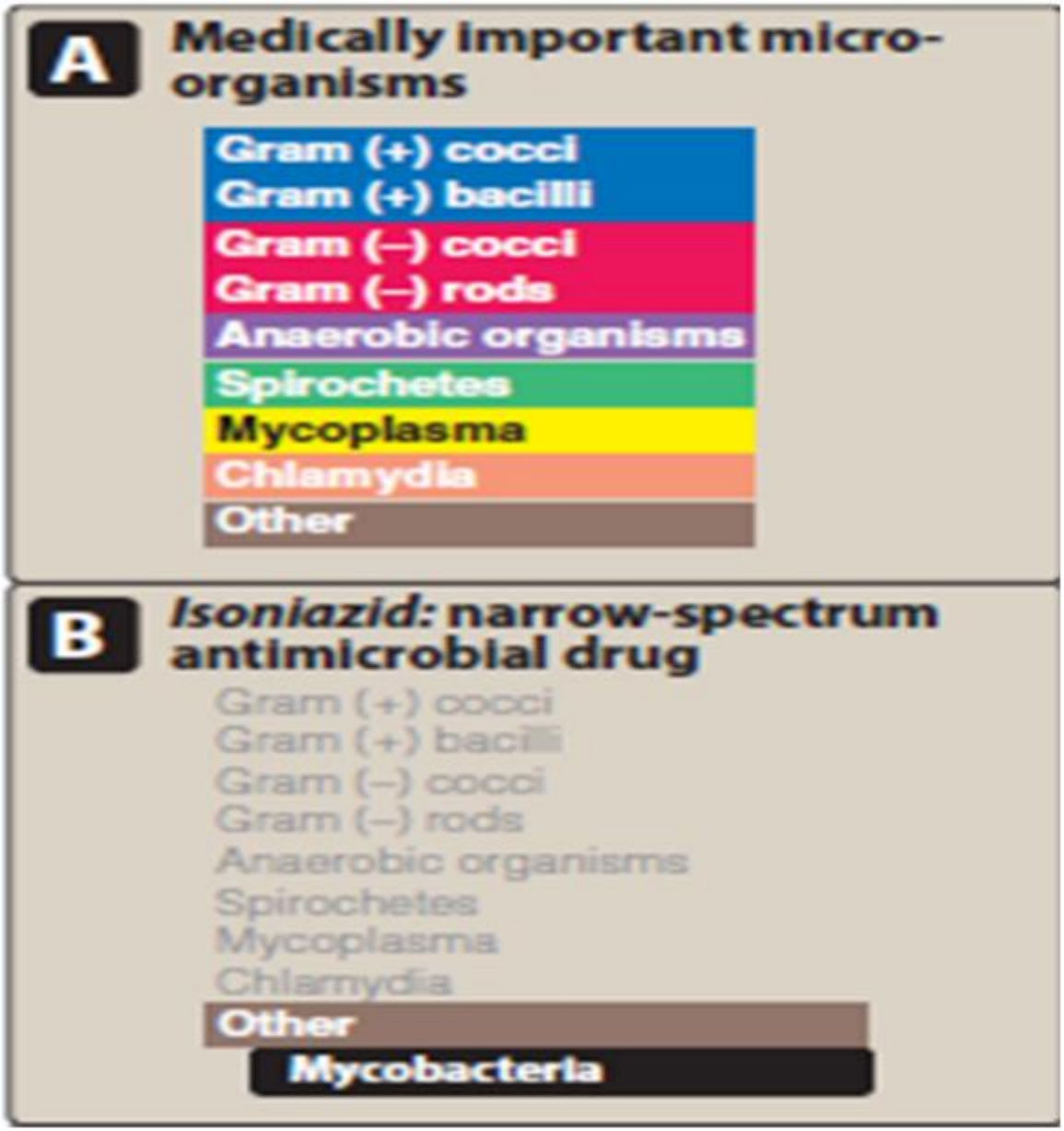
Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram negative bacteria.

❑ CHEMOTHERAPEUTIC SPECTRA

The clinically important bacteria have been organized into eight groups *based on Gram stain, morphology, and biochemical or other characteristics*. They are represented as a color-coded list (Figure 37.7A).

A. Narrow-spectrum antibiotics

Agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, isoniazid is active only against Mycobacterium tuberculosis.


A
Medically important micro-organisms
Gram (+) cocci
Gram (+) bacilli
Gram (–) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
B
Isoniazid: narrow-spectrum antimicrobial drug
Gram (+) cocci
Gram (+) bacilli
Gram (–) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
Mycobacteria

B. Extended-spectrum antibiotics

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

C. Broad-spectrum antibiotics

Drugs such as tetracycline, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics

COMBINATIONS OF ANTIMICROBIAL DRUGS:

A. Advantages of 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.

Multiple drugs used in combination are only indicated in special situations (for example, *when an infection is of unknown origin or in the treatment of enterococcal endocarditis*).

B. Disadvantages of drug combinations

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.*

Another concern is the development of antibiotic resistance by giving unnecessary combination therapy.

DRUG RESISTANCE:

Drug resistance is mediated by:

1. Modification of target sites: For example, *S.pneumoniae* resistance to β-lactam antimicrobials involves alterations in one or more of the major bacterial penicillin-binding proteins.

2. Decreased accumulation: Decreased uptake or increased efflux of an antibiotic. For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

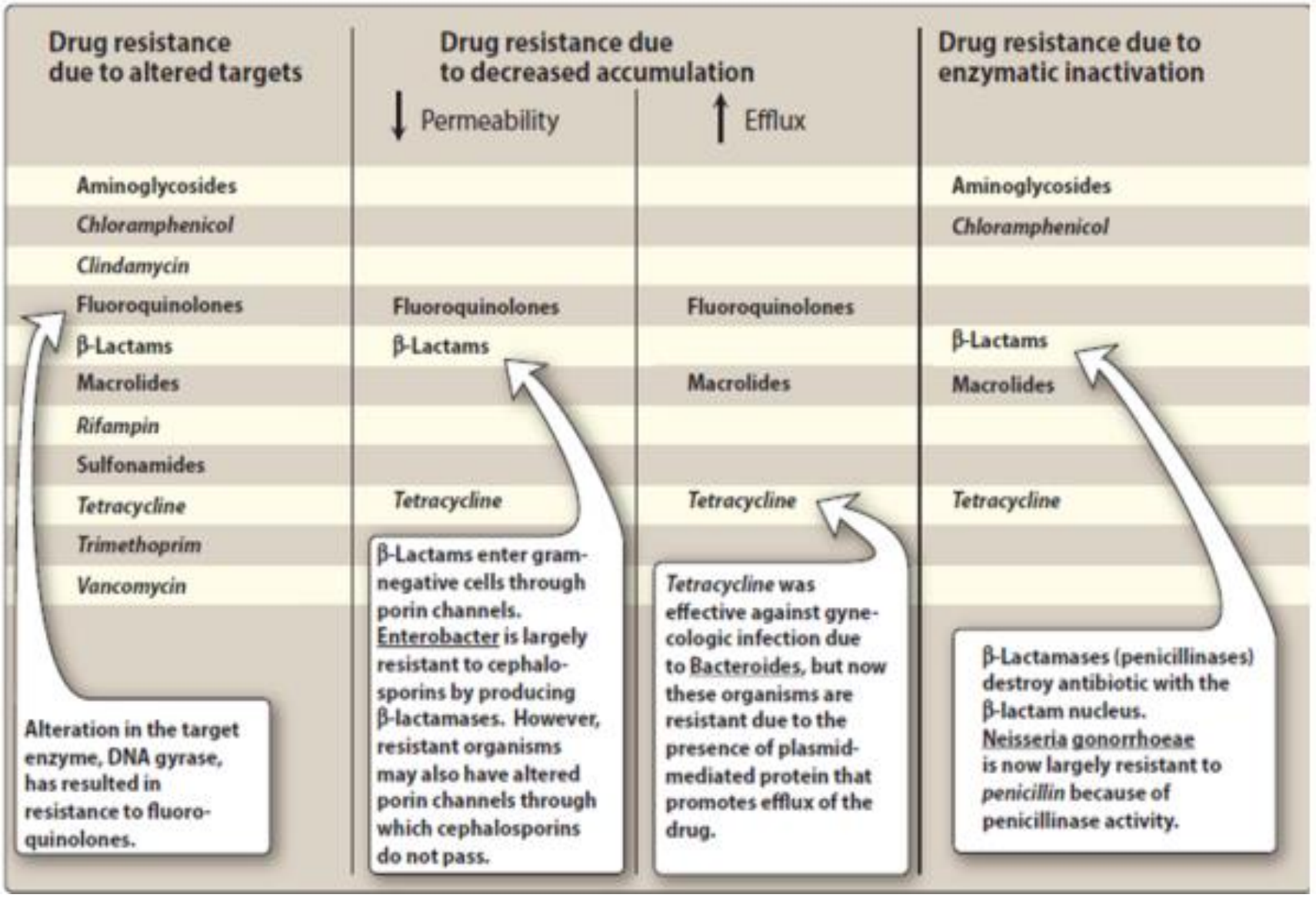
3. Enzymatic inactivation: The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms.

Examples of antibiotic-inactivating enzymes include

1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs.

2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides; and

3) esterases that hydrolyze the lactone ring of macrolides.



Some mechanisms of resistance to antibiotics.

PROPHYLACTIC USE OF ANTIBIOTICS

Clinical situations, such as dental procedures and surgeries, require the use of antibiotics for the prevention rather than for the treatment of infections.

Because the unselective use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.

The duration of prophylaxis should be closely observed to prevent the unnecessary development of antibiotic resistance.

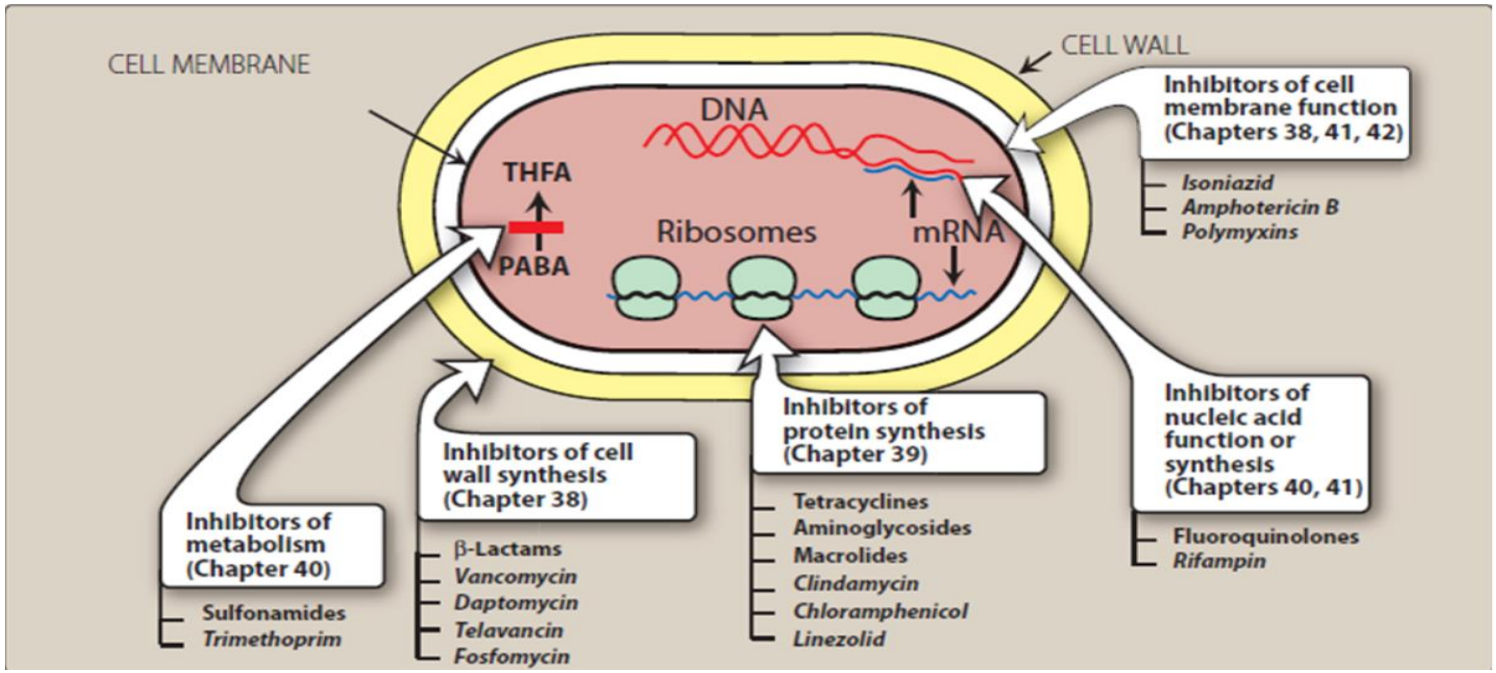
COMPLICATIONS OF ANTIBIOTIC THERAPY

A. Hypersensitivity: the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity: For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells.

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.



Cell Wall Inhibitors

Penicillins and cephalosporins are the major antibiotics that inhibit bacterial cell wall synthesis. They are called beta-lactams because of the unusual 4-member ring that is common to all their members .The beta-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections.

- Synthetic Production of Penicillin Professor Alexander Fleming, holder of the Chair of Bacteriology at London University, **who first discovered the mould *Penicillium notatum***.
- Here in his laboratory at St Mary's, Paddington, London.

PENICILLINS

- *Amoxicillin* AMOXIL
- *Ampicillin* PRINCIPEN
- *Dicloxacillin* DYNAPEN
- *Nafcillin*
- *Oxacillin*
- *Penicillin G* PFIZERPEN
- *Penicillin V*
- *Piperacillin*
- *Ticarcillin*

CEPHALOSPORINS

- *Cefaclor* CECLOR
- *Cefadroxil* DURACEF
- *Cefazolin* KEFZOL
- *Cefdinir* OMNICEF
- *Cefepime* MAXIPIME
- *Cefixime* SUPRAX
- *Cefotaxime* CLAFORAN
- *Cefotetan* CEFOTAN
- *Cefoxitin* MEFOXIN
- *Cefprozil* CEFZIL
- *Ceftaroline* TEFLARO
- *Ceftazidime* FORTAZ
- *Ceftibuten* CEDAX
- *Ceftizoxime* CEFIZOX
- *Ceftriaxone* ROCEPHIN
- *Cefuroxime* CEFTIN
- *Cephalexin* KEFLEX

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM

MONOBACTAMS

Aztreonam AZACTAM

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Clavulanic acid + amoxicillin AUGMENTIN
Clavulanic acid + ticarcillin TIMENTIN
Sulbactam + ampicillin UNASYN
Tazobactam + piperacillin ZOSYN

OTHER ANTIBIOTICS

Colistin COLOMYCIN, COLY-MYCIN M
Daptomycin CUBICIN
Fosfomycin MONUROL
Polymyxin B AEROSPORIN
Telavancin VIBATIV
Vancomycin VANCOCIN

PENICILLINS

Classification

All penicillins are derivatives of *6-aminopenicillanic acid* and contain a beta-lactam ring structure that is essential for antibacterial activity.

Penicillin subclasses have additional chemical substituents that confer differences in antimicrobial activity, susceptibility to acid and enzymatic hydrolysis, and biodisposition.

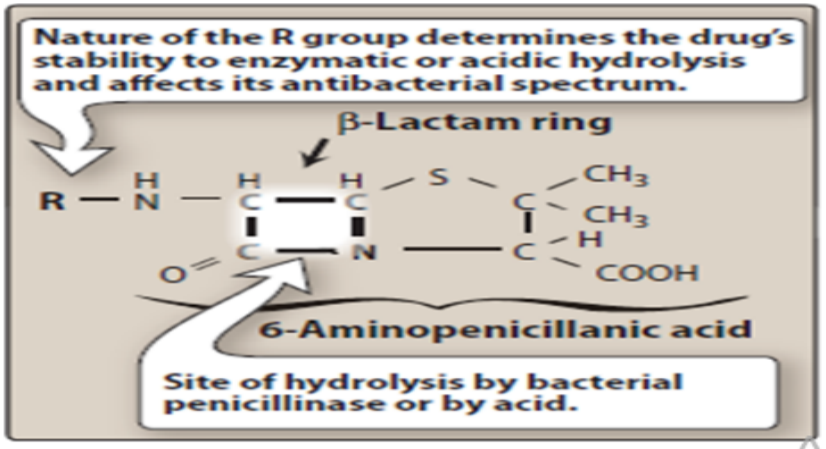


Figure 38.2
Structure of β-lactam antibiotics.

Pharmacokinetics

A. Routes of administration:

1-The combination of *ampicillin with sulbactam*, *ticarcillin with clavulanic acid*, and *piperacillin with tazobactam*, and the antistaphylococcal penicillins *nafcillin and oxacillin* must be administered intravenously (IV) or intramuscularly (IM).

Penicillin V, amoxicillin, and dicloxacillin are available only as oral preparations. Others are effective by the oral, IV, or IM routes.

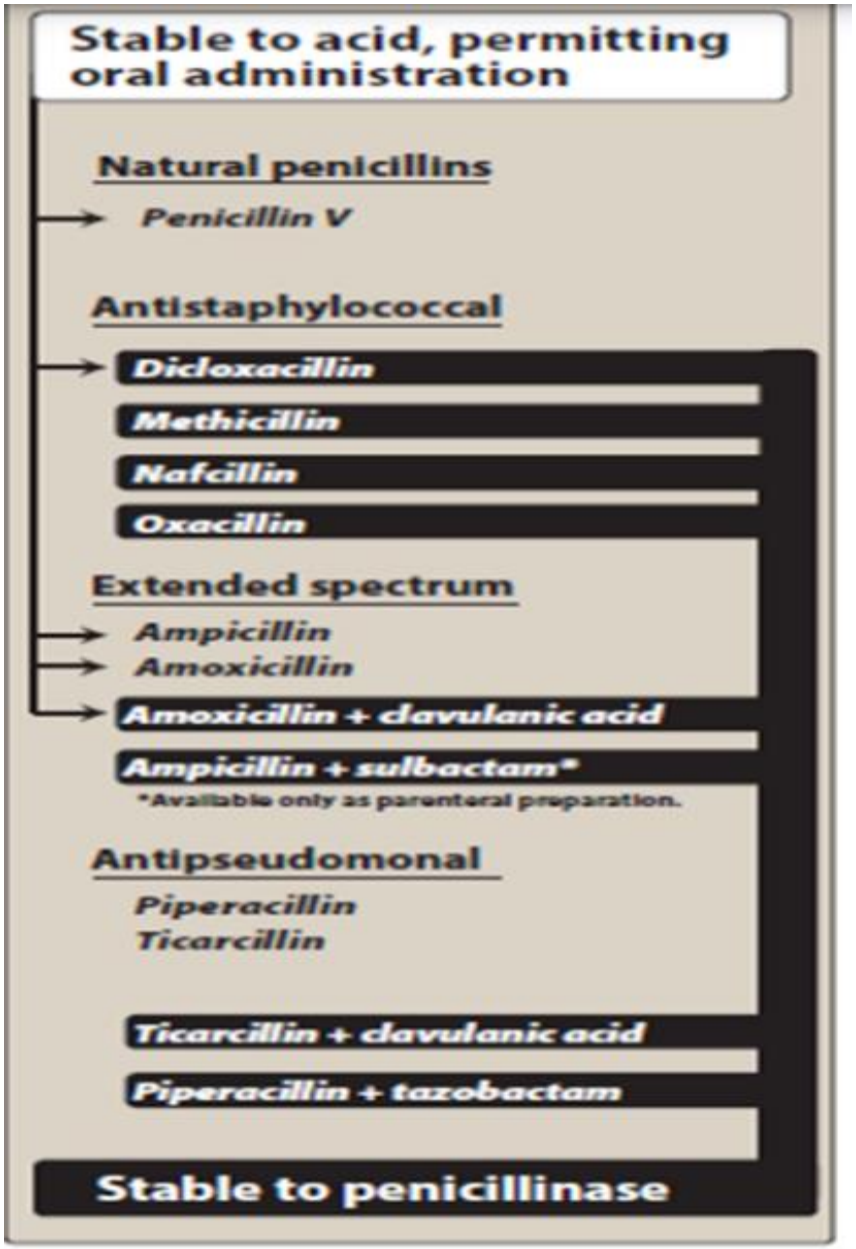


Figure 38.6
Stability of the penicillins to acid or the action of penicillinase.

2- Depot forms:

Procaine penicillin G and benzathine penicillin G

are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

B. Absorption:

Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora.

Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

C. Distribution:

All the penicillins distribute well & cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or (CSF) is insufficient for therapy unless these sites are inflamed.

D. Excretion:

The primary route of excretion is by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Nafcillin and oxacillin are metabolized in the liver.

Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels.

Mechanisms of Action and Resistance

Beta-lactam antibiotics are bactericidal drugs. They *act to inhibit cell wall synthesis* by the following steps:

(1) Binding of the drug to specific enzymes (penicillin-binding proteins [PBPs]) located in the bacterial cytoplasmic membrane;

(2) inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan
chain constituents of the cell wall; and

(3) activation of autolytic enzymes that cause lesions in the bacterial cell wall.

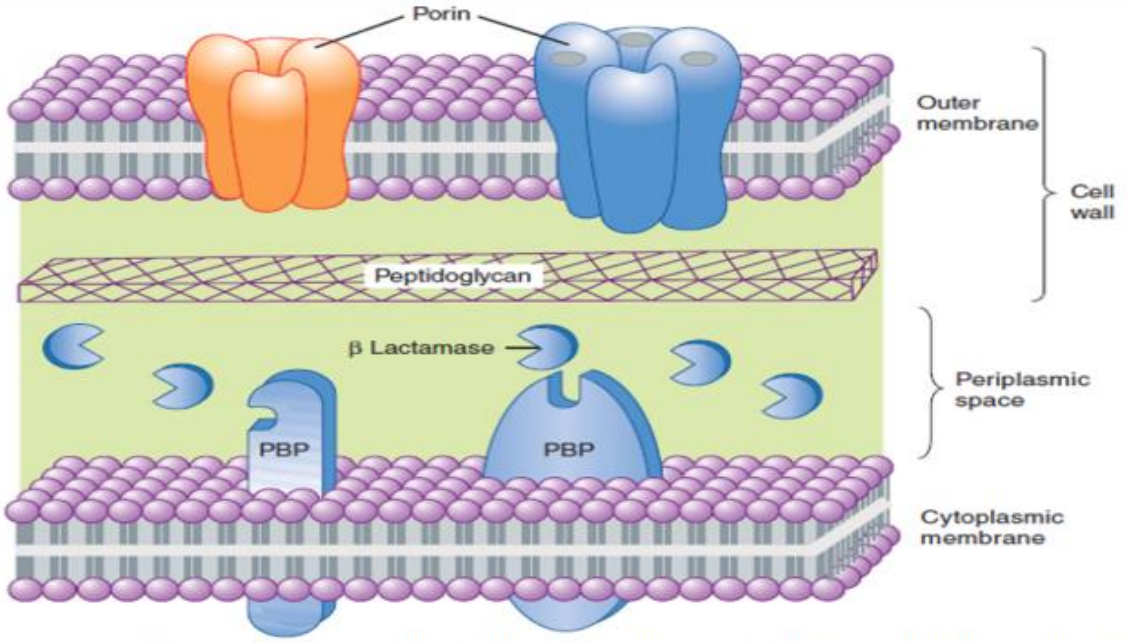


FIGURE 43–1 Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics.

Mechanism of bacterial resistance:

- The formation of beta-lactamases (penicillinases) by most staphylococci and many gram-negative organisms.

- ✓ Inhibitors of these bacterial enzymes (eg, clavulanic acid, sulbactam, tazobactam) are often used in combination with penicillins to prevent their inactivation.

- Structural change in target PBPs is responsible for methicillin resistance in staphylococci (MRSA) and for resistance to penicillin G in pneumococci (eg, PRSP, penicillin resistant *Streptococcus pneumoniae*) and *enterococci*.

- In some gram-negative rods (eg, *Pseudomonas aeruginosa*), changes in the porin structures in the outer cell wall membrane may contribute to resistance by impeding access of penicillins to PBPs.

Clinical Uses

1. Narrow-spectrum penicillinase-susceptible agents— Penicillin G is the prototype of a subclass of penicillins.

Clinical uses include therapy of infections caused by common streptococci, meningococci, gram-positive bacilli, and spirochetes.

Many strains of pneumococci (penicillin-resistant *S. pneumoniae* [PRSP] strains). *Staphylococcus aureus* and *Neisseria gonorrhoeae* are resistant via production of beta-lactamases.

penicillin G remains the drug of choice for syphilis. Activity against enterococci is enhanced by coadministration of aminoglycosides.

Penicillin V is an oral drug used mainly in oropharyngeal infections.

2. Very-narrow-spectrum penicillinase-resistant drugs—

This subclass of penicillins includes methicillin (the prototype, but rarely used owing to its nephrotoxic potential), nafcillin, and oxacillin.

Their primary use is in the treatment of known or suspected staphylococcal infections.

Their primary use is in the treatment of known or suspected staphylococcal infections.

Methicillin-resistant (MR) staphylococci (*S. aureus* [MRSA] and *S. epidermidis* [MRSE]) are resistant to all penicillins and are often resistant to multiple antimicrobial drugs.

3. Wider-spectrum penicillinase-susceptible drugs

a. Ampicillin and amoxicillin has a wider spectrum of antibacterial activity than penicillin G. Their clinical uses include indications similar to penicillin G as well as infections resulting from *enterococci, Listeria monocytogenes, Escherichia coli, Proteus mirabilis, Haemophilus influenzae, and Moraxella catarrhalis*, although resistant strains occur.

When used in combination with inhibitors of penicillinases (eg, clavulanic acid), their antibacterial activity is often enhanced. In enterococcal and listerial infections, ampicillin is synergistic with aminoglycosides.

b. Piperacillin and ticarcillin

These drugs have activity against several gram-negative rods, including *Pseudomonas, Enterobacter,* and in some cases *Klebsiella species*.

Most drugs in this subgroup have synergistic actions with aminoglycosides against such organisms.

Piperacillin and ticarcillin are susceptible to penicillinases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

E. Adverse effects

1. Allergy—Allergic reactions include urticaria, severe pruritus, fever, joint swelling, hemolytic anemia, nephritis, and anaphylaxis.

Methicillin causes interstitial nephritis, and nafcillin is associated with neutropenia.

Complete cross-allergenicity between different penicillins should be assumed.

2. Gastrointestinal disturbances— Nausea and diarrhea may occur with oral penicillins, especially with ampicillin. Gastrointestinal upsets may be caused by direct irritation or by overgrowth of gram-positive organisms or yeasts.

CEPHALOSPORINS:

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins.

Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to *7-aminocephalosporanic acid*.

Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be *more resistant than the penicillins to certain β-lactamases*.

Pharmacokinetics:

Several cephalosporins are available for oral use, but most are administered parenterally.

Cephalosporins with side chains may undergo hepatic metabolism, but the *major elimination mechanism* for drugs in this class is *renal excretion via active tubular secretion.*

Cefoperazone and ceftriaxone are excreted mainly in the bile.

Most *first- and second-generation cephalosporins* do *not enter the cerebrospinal fluid* even when the meninges are inflamed.

Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. *Cephalosporins are bactericidal* against susceptible organisms.

Cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of *other betalactamases* that can inactivate cephalosporins.

Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs.

Methicillin-resistant staphylococci are also resistant to cephalosporins.

Clinical Uses

1. **First-generation drugs**—Cefazolin (parenteral) and cephalexin (oral) are examples of this subgroup.

They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive.

Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions.

2. **Second-generation**

have slightly less activity against gram-positive organisms than the first-generation drugs but *have an extended gram-negative coverage*.

Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses *include infections caused by the anaerobe Bacteroides fragilis* (cefotetan, cefoxitin) and sinus, ear, and respiratory infections caused by *H influenzae or M catarrhalis* (cefamandole, cefuroxime, cefaclor).

3. **Third-generation drugs**: (eg, ceftazidime, cefoperazone, cefotaxime)

include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier (EXCEPT cefoperazone and cefixime).

- Most are active against *Providencia, Serratia marcescens*, and beta-lactamase producing strains of *H influenzae and Neisseria*.
- Ceftriaxone and cefotaxime are currently the most active cephalosporins against penicillin-resistant pneumococci (PRSP strains)
- Also have activity against *Pseudomonas* (cefoperazone, ceftazidime) and *B fragilis* (ceftizoxime)
- Ceftriaxone (parenteral) and cefixime (oral), currently drugs of choice in gonorrhea.

4. Fourth-generation drugs

- Cefepime is more *resistant to beta-lactamases* produced by gram-negative organisms, including *Enterobacter, Haemophilus, Neisseria*, and some *penicillin resistant pneumococci*.
- Cefepime combines the gram-positive activity of first-generation agents with the wider gram-negative spectrum of third-generation cephalosporins.
- Ceftaroline has activity in infections caused by methicillin-resistant staphylococci.

Adverse effects

1. Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur *less frequently with cephalosporins than with penicillins*.

Complete cross-hypersensitivity between different cephalosporins should be assumed. Cross-reactivity between penicillins and cephalosporins is incomplete (5–10%).

2- Cephalosporins may cause *pain at intramuscular* injection sites and *phlebitis* after I.V administration.

3-They may *increase the nephrotoxicity of aminoglycosides* when the two are administered together.

OTHER BETA-LACTAM DRUGS:

A. Aztreonam

- Aztreonam is a monobactam that is *resistant to beta-lactamases* produced by certain gram-negative rods, including *Klebsiella, Pseudomonas, and Serratia*. *The drug has no activity against gram positive bacteria or anaerobes*.
- Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure.
- *Adverse effects include* gastrointestinal upset with possible superinfection, vertigo and headache, and rarely hepatotoxicity, skin rash (NO cross allergenicity with penicillins).

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- These drugs are carbapenems (chemically different from penicillins but retaining the beta-lactam ring structure)
- They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes.

For *pseudomonal infections*, they are often used in combination with an aminoglycoside.

- MRSA strains of staphylococci are resistant.
- Imipenem is rapidly *inactivated by renal dehydropeptidase-I* and is administered in fixed combination with cilastatin, an inhibitor of this enzyme. *Cilastatin increases the plasma half life of imipenem and inhibits the formation of potentially nephrotoxic metabolite*.
    - Adverse effects of imipenem-cilastatin include *gastrointestinal distress, skin rash*, and, at very high plasma levels, CNS toxicity (confusion, encephalopathy, seizures).
    - *There is partial cross allergenicity with the penicillins.*

C. Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins.

- They are most active against plasmid-encoded beta-lactamases such as those produced by *gonococci, streptococci, E coli*, and *H influenzae*.
- They are NOT good inhibitors of inducible chromosomal beta-lactamases formed by *Enterobacter, Pseudomonas, and Serratia*.