Cell Wall inhibitors

Cell Wall inhibitors

- The bacterial cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.

- To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms.

- The most important members of this group of drugs are the
  - β-lactam antibiotics (named after the β-lactam ring that is essential to their activity),
  - vancomycin, and
  - daptomycin.

PENICILLINS

- The penicillins are among the most widely effective and the least toxic drugs known,

but increased resistance has limited their use.

- Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 38.2).

- The nature of this side chain affects the
  - antimicrobial spectrum,
  - stability to stomach acid,
  - crosshypersensitivity, and
  - susceptibility to bacterial degradative enzymes (β-lactamases).

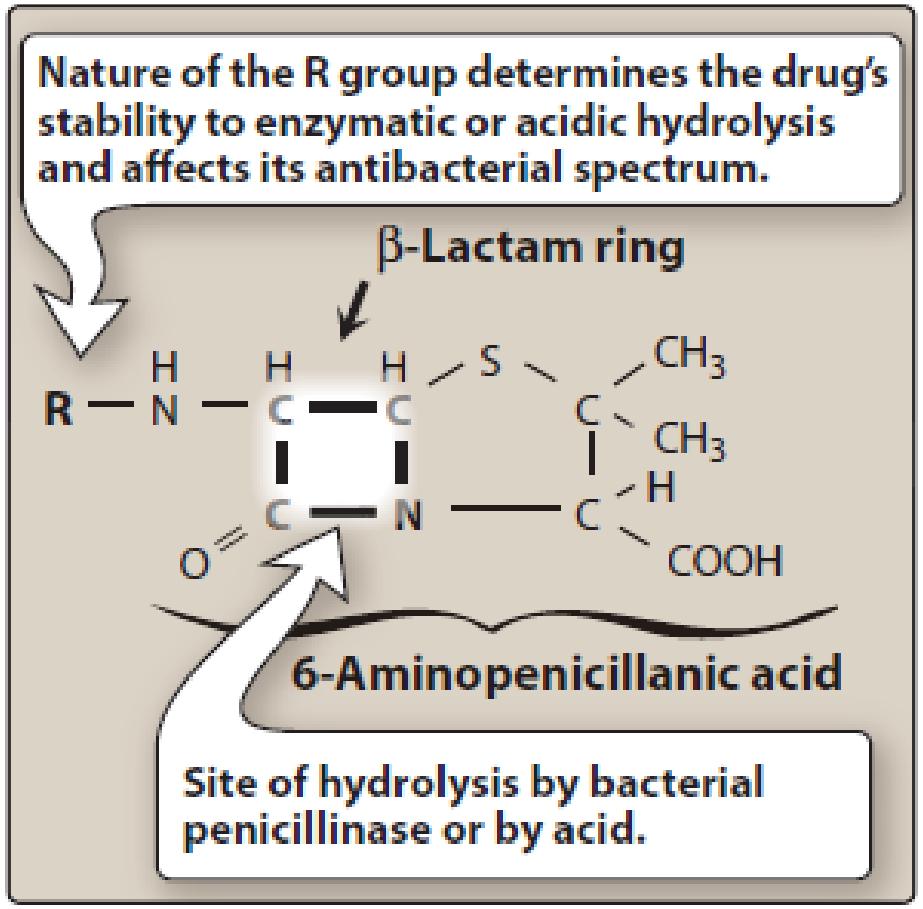


Figure 38.2

Structure of β-lactam antibiotics.

A. Mechanism of action

- The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane.

Mechanism of action

- Penicillin-binding proteins:
- Penicillins also inactivate numerous proteins on the bacterial cell membrane.
- These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of

the cell wall and in the maintenance of the morphologic features of the bacterium.

Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria

The number of PBPs varies with the type of organism. Alterations in some of these PBPs provide the organism with resistance to the penicillins.

Mechanism of action

- **Inhibition of transpeptidase:**
- Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains (Figure 38.3).

- Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.

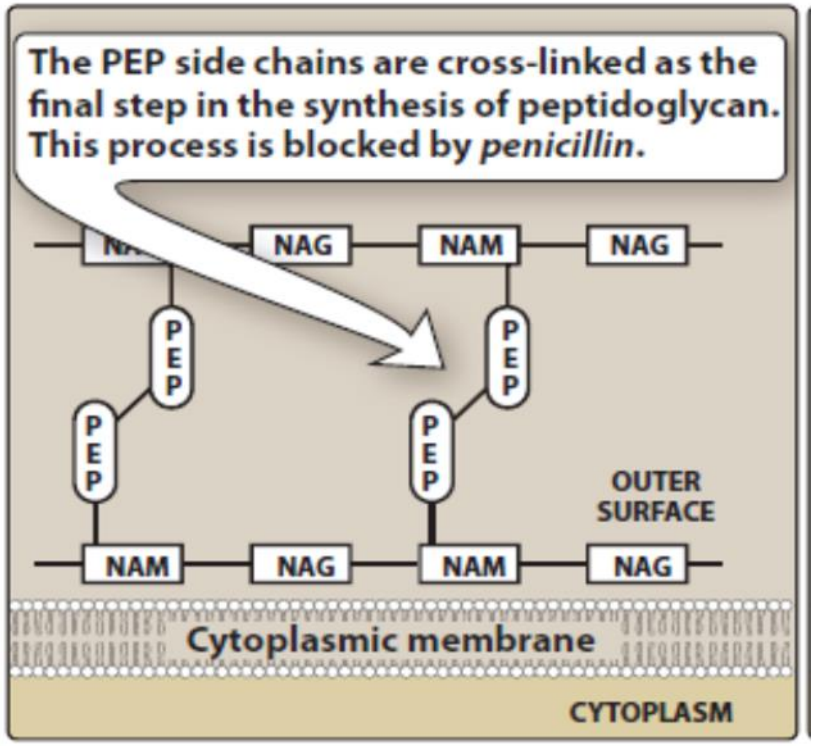


Figure 38.3
Bacterial cell wall of gram-positive bacteria. (NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.)

Mechanism of action

- **Production of autolysins:**
- Many bacteria, particularly the gram positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall.

- In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis.
- Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

Antibacterial spectrum

- 1. Natural penicillins: Natural penicillins (penicillin G and penicillin V) are obtained from fermentations of the fungus Penicillium chrysogenum.

- Penicillin [pen-i-SILL-in] G (benzyl-penicillin) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes (Figure 38.4).

- Penicillins are susceptible to inactivation by β-lactamases (penicillinases) that are produced by the resistant bacteria.

- Despite widespread use and increase in resistance to many types of bacteria, *penicillin* remains the drug of choice for the treatment of
  - gas gangrene (Clostridium perfringens) and
  - syphilis (Treponema pallidum).

- *Penicillin V* has a similar spectrum to that of *penicillin G*

- *Penicillin V* is more acid stable than *penicillin G* and is often employed orally in the treatment of infections.

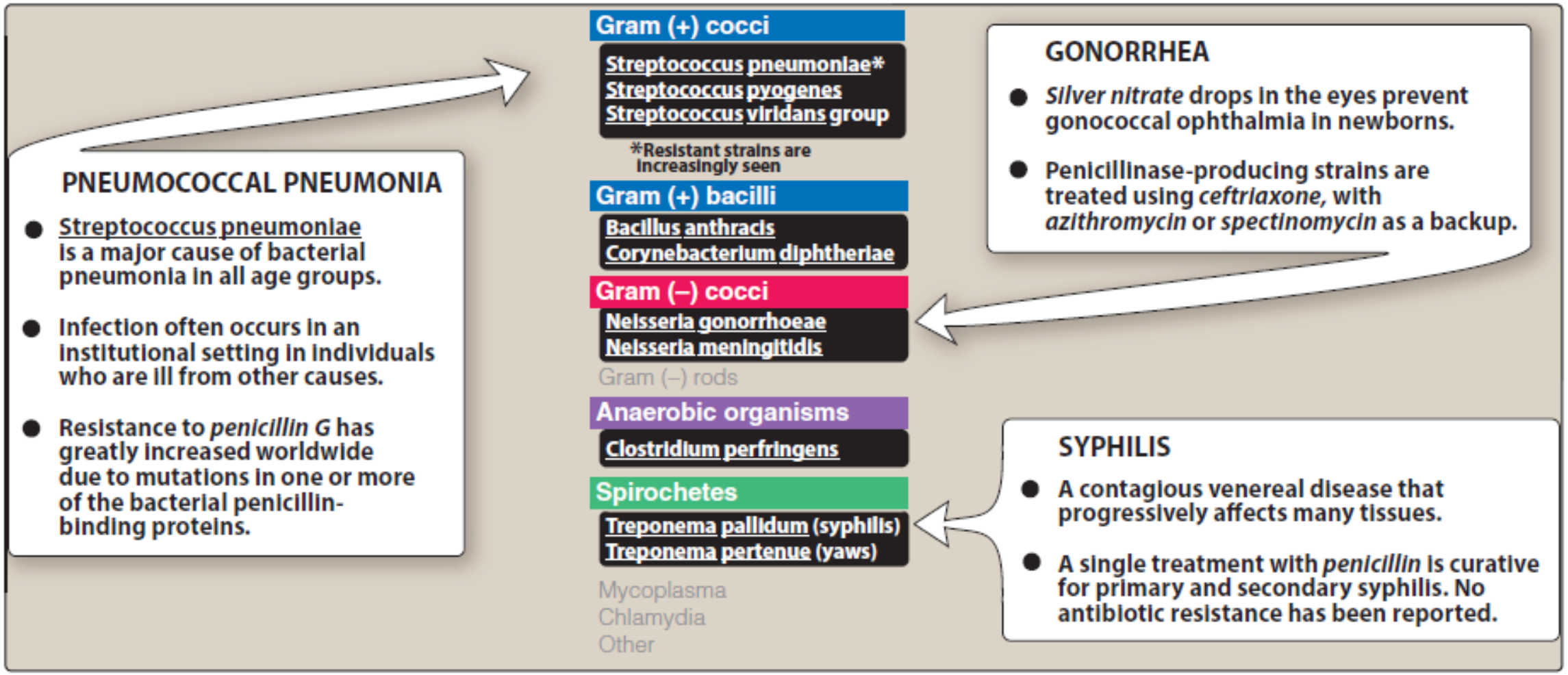


Figure 38.4
Typical therapeutic applications of *penicillin G*.

- **2. Antistaphylococcal penicillins:**
  - *Methicillin* [meth-i-SILL-in],
  - *Nafcillin* [naf-SILL-in],
  - *oxacillin* [ox-a-SILL-in], and
  - *Dicloxacillin* [dye-klox-a-SILL-in]
- are β-lactamase (penicillinase)-resistant penicillins.

- Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including *methicillin* sensitive Staphylococcus aureus (MSSA).

- [Note: Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus.

- MRSA is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to most commercially available β-lactam antibiotics.]

- The penicillinase- resistant penicillins have minimal to no activity against gram-negative infections.

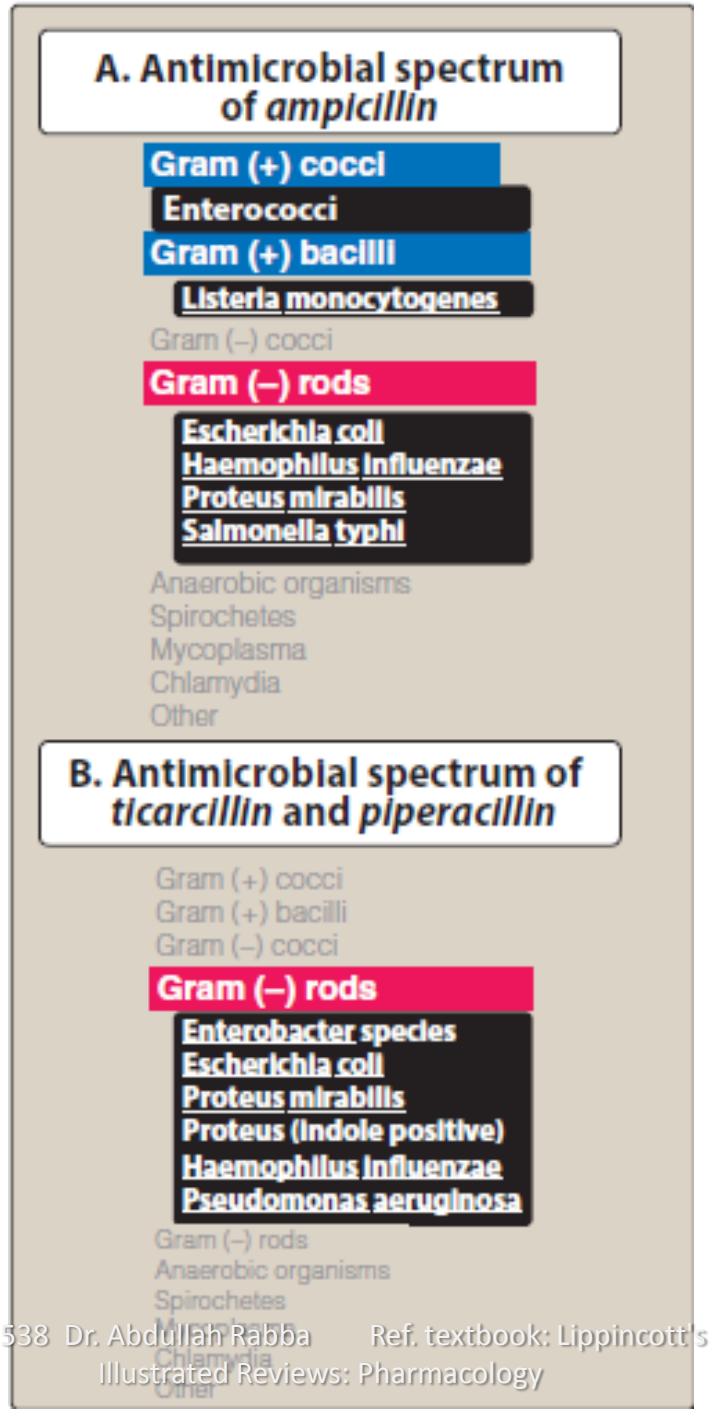
- **3. Extended-spectrum penicillins:**
  - *Ampicillin* [am-pi-SILL-in] and
  - *amoxicillin* [a-mox-i-SILL-in]
- have an antibacterial spectrum similar to that of *penicillin G* but are more effective against gram negative bacilli

- These extended-spectrum agents are also widely used in the treatment of respiratory infections,

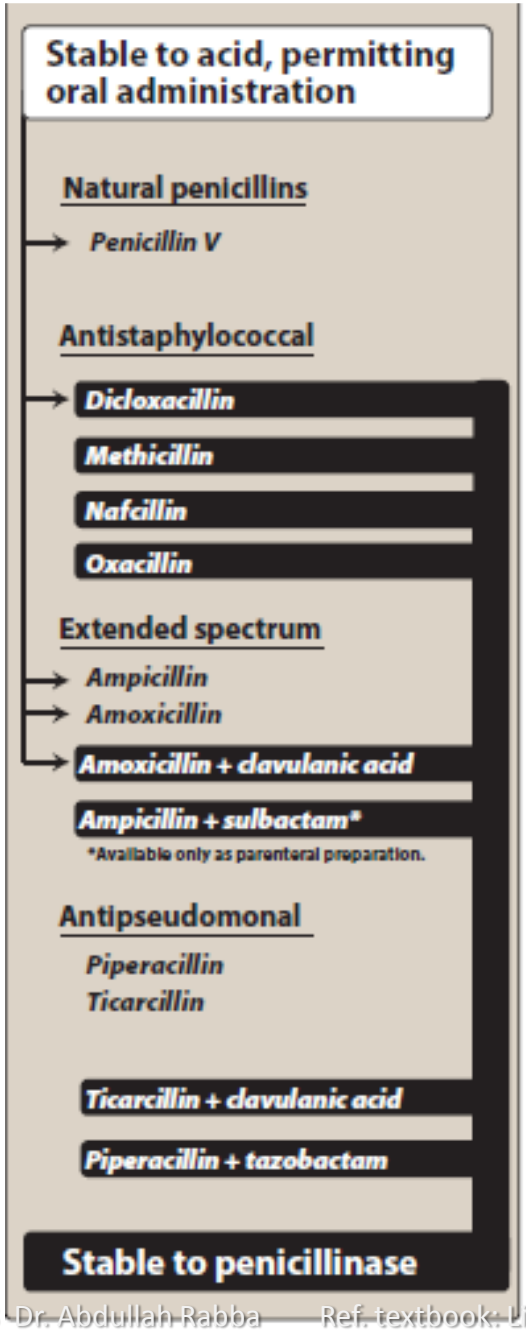
- *amoxicillin* is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis.

- Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinases.

- Formulation with a β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin,* respectively, from enzymatic hydrolysis and extends their antimicrobial spectra.



- **4. Antipseudomonal penicillins:**
  - *Piperacillin* [pip-er-a-SILL-in] and
  - *ticarcillin* [tye-kar-SILL-in]
- are called antipseudomonal penicillins because of their activity against Pseudomonas aeruginosa
- These agents are available in parenteral formulations only.
- *Piperacillin* is the most potent of these antibiotics.
- They are effective against many gram-negative bacilli, but not against Klebsiella because of its constitutive penicillinase.
- Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms (for example, most Enterobacteriaceae and Bacteroides species).



Resistance

- Natural resistance to the penicillins occurs in organisms that either
  - lack a peptidoglycan cell wall (for example, Mycoplasma pneumoniae) or
  - have cell walls that are impermeable to the drugs.
- Acquired resistance (plasmid-mediated) significant clinical problem. Multiplication of resistant strains leads
  - **1. β-Lactamase activity:**
  - **2. Decreased permeability to the drug**
  - **3. Altered PBPs:**

β-Lactamase activity:

- This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity .

- They are the major cause of resistance to the penicillins and are an increasing problem.
- β-Lactamases either are
  - constitutive, mostly produced by the bacterial chromosome or,
  - more commonly, are acquired by the transfer of plasmids.

2. Decreased permeability to the drug:

- Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs.

- The presence of an efflux pump can also reduce the amount of intracellular drug (for example, Klebsiella pneumoniae).

3. Altered PBPs:

- Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth.

- This explains MRSA resistance to most commercially available β-lactams.

Pharmacokinetics

- **1. Administration:**
- The route of administration of a β-lactam antibiotic is determined by
  - the stability of the drug to gastric acid and by
  - the severity of the infection.

- **a. Routes of administration:**
- 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).

- **B. 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.

- **2. 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.

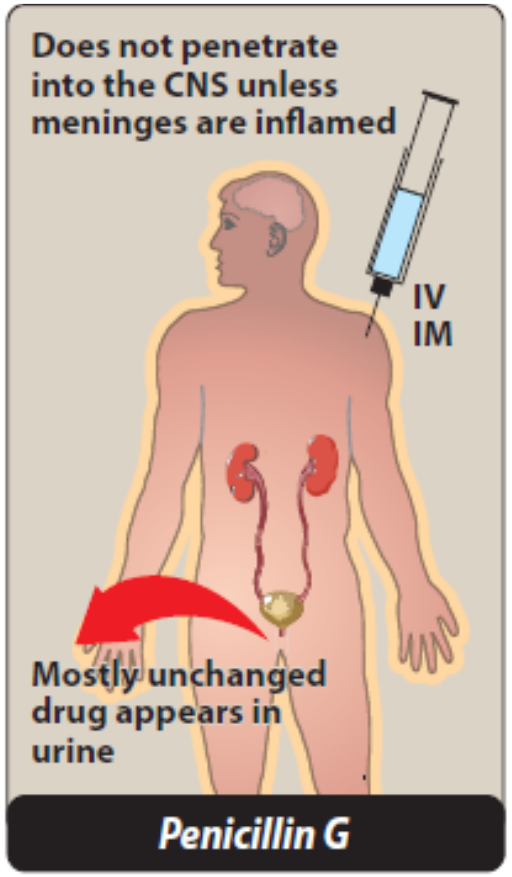
- Therefore, they should be taken on an empty stomach.

- **3. Distribution:**
- The β-lactam antibiotics distribute well throughout the body.

- All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects.

- However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed (Figures 38.7 and 38.8).
  - [Note: Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.]

- Penicillin levels in the prostate are insufficient to be effective against infections.



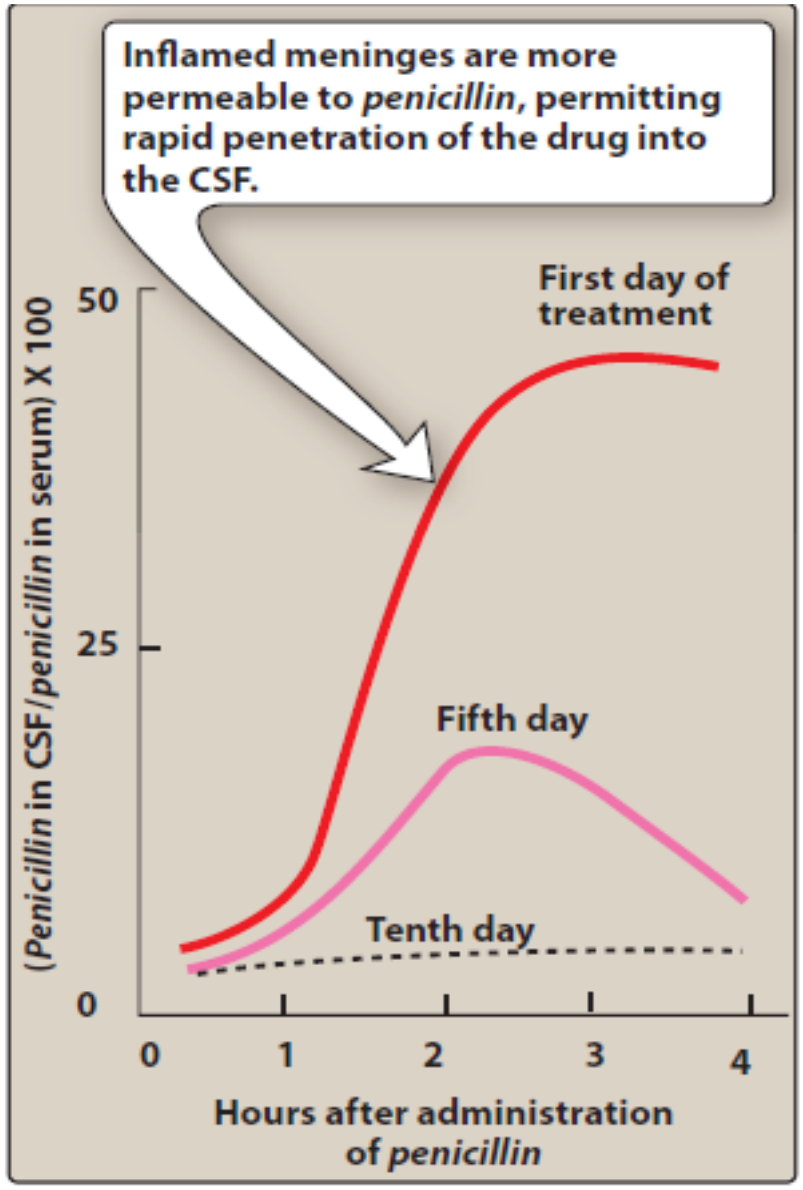


Figure 38.8

Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF)

- **4. Metabolism:**

- Host metabolism of the β-lactam antibiotics is usually insignificant,

- but some metabolism of *penicillin G* may occur in patients with impaired renal function.

- **5. Excretion:**
- The primary route of excretion is through the
  - organic acid (tubular) secretory system of the kidney as well as by
  - glomerular filtration.

- Patients with impaired renal function must have dosage regimens adjusted.
  - *Nafcillin* and *oxacillin* are exceptions to the rule.
  - They are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency.
- *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels.

- The penicillins are also excreted in breast milk.

E. Adverse reactions

- Penicillins are among the safest drugs, and blood levels are not monitored.
- However, adverse reactions may occur

- **1. Hypersensitivity:**
- Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis.

- Cross-allergic reactions occur among the β-lactam antibiotics.

- To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

- **2. Diarrhea:**
- Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms.

- It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.

- Pseudomembranous colitis from *Clostridium difficile* and other organisms may occur with penicillin use.

- **3. Nephritis:**
- Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis.

- [Note: *Methicillin* is therefore no longer used clinically.]

- **4. Neurotoxicity:**
- The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached.

- Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

- **5. Hematologic toxicities:**
- Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin*, and *nafcillin* (and, to some extent, with *penicillin G*).

- Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

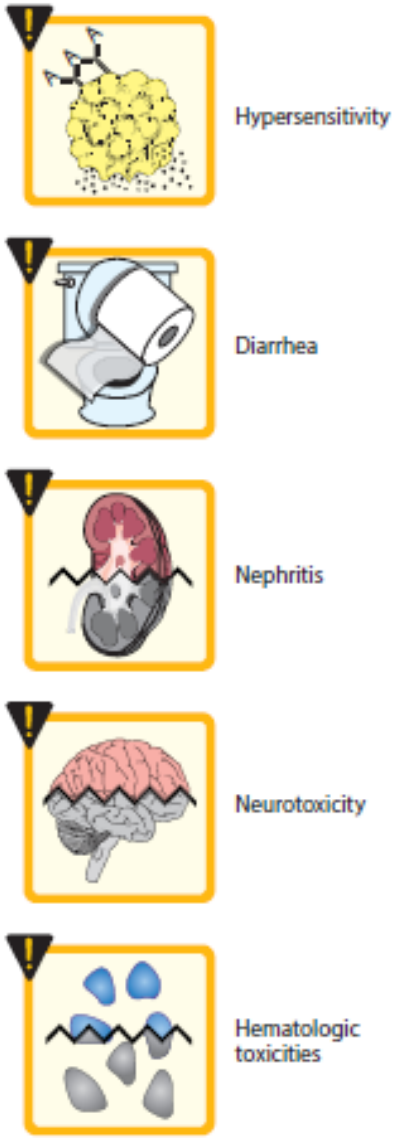


Figure 38.9
Summary of the adverse effects of *penicillin*.