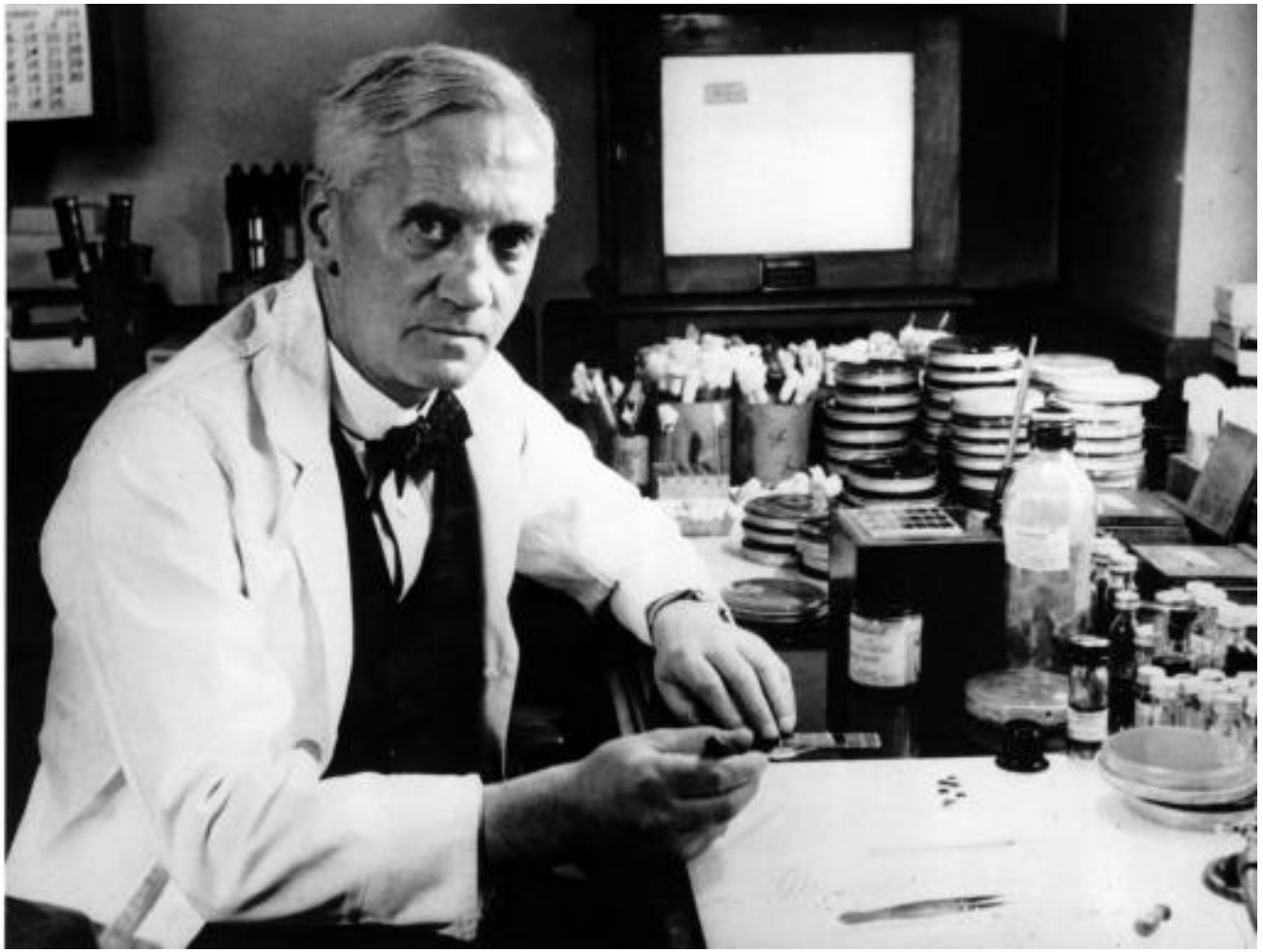
Beta-Lactam Antibiotics & Other Cell Wall Synthesis Inhibitors

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.

Alexander Fleming



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,.

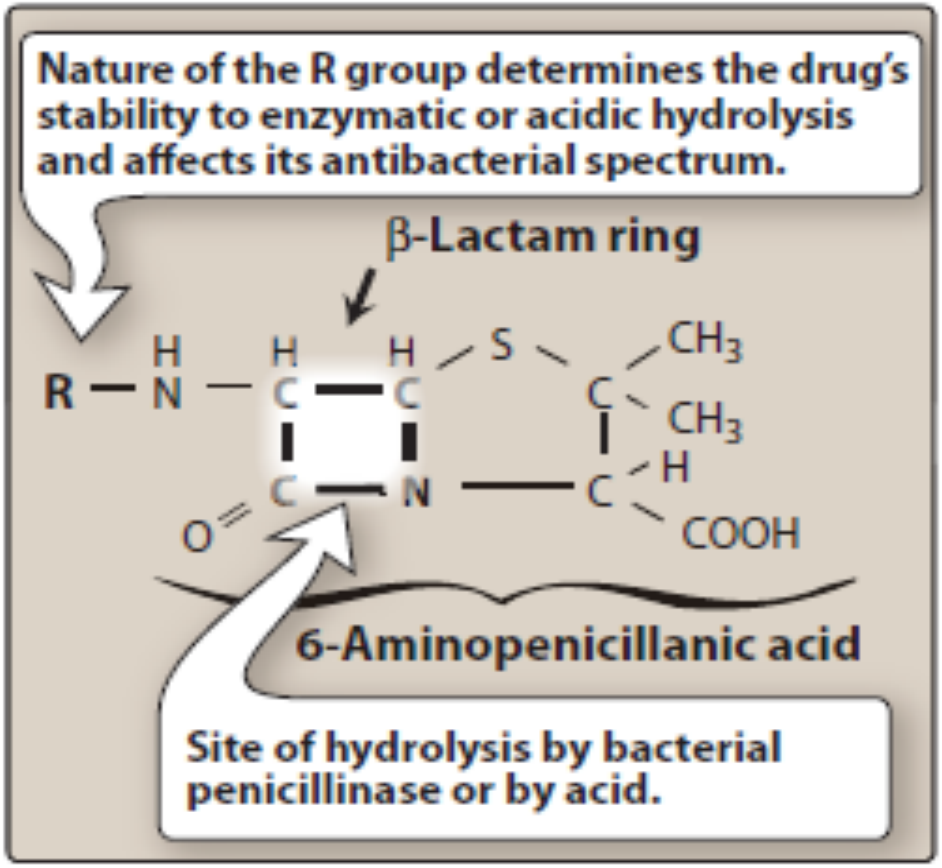


Figure 38.2
Structure of β-lactam antibiotics.

❖ 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

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.

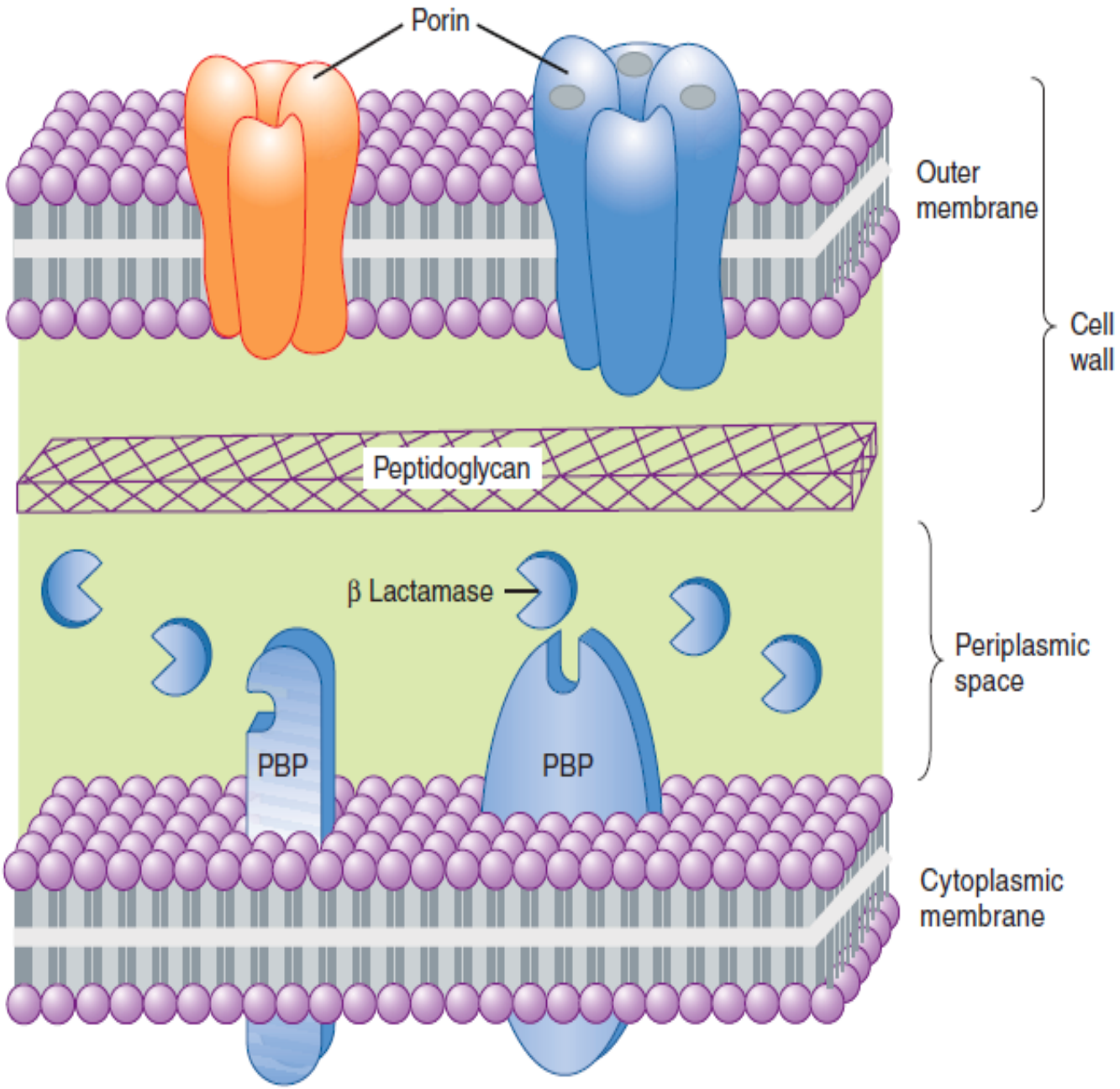


FIGURE 43–1 Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics.

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 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. 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. Toxicity

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.