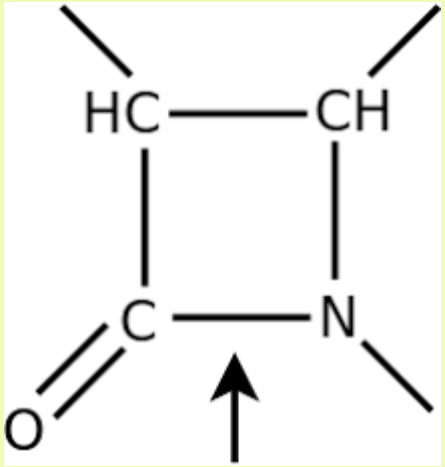
Poltava State Medical University
Department of Pharmacology, Clinical pharmacology and Pharmacy

PHARMACOLOGY OF BETA-LACTAM ANTIBIOTICS



CONTENTS

ANTIBIOTICS:

Common concepts

Antibiotics are substances produced by some microbes for their antagonism with other organisms.

The history of antibiotics.

The first antibiotic was penicillin. It was discovered by ***A.Fleming*** in 1928.

Florey, Fleming and Chain shared a Nobel Prize in 1945 for their work on penicillin.

The second antibiotic streptomycin was discovered by Vaxman. He also proposed the name “antibiotics”.

Antibiotics are divided:

1. On type of action

– bactericidal

– bacteriostatic

2. On spectrum of action

– antibiotics of wide spectrum

– antibiotics of narrow spectrum

3. On clinical use

– basis antibiotics (antibiotics of choice)

– alternative antibiotics

Main principles of therapy by antibiotics

- Early beginning of the treatment
- Choice of antibiotic on its spectrum of action
- Choice of antibiotic on the susceptibility of microbes in this patient
- Use of wide spectrum antibiotic if the cause of infection is not known
- Duration of the treatment no less than 5-7 days
- Usage of big doses of antibiotics
- Supporting of therapeutic concentration of the drug in the organism
- Combination of antibiotics with one another, as well as with drugs from other groups
- Continuation of treatment after the normalization of clinical status and body temperature for 2-3 days
- Allergic history and allergic test before the start of treatment
- Attention to age, physiological status of patient, concomitant diseases, location and severity of infection.

Common mechanisms of action

The remarkably powerful and specific activity of antimicrobial drugs is due to their selective toxicity for targets that are either unique to microorganisms or much more important in them than in humans. Among these targets are bacterial cell wall-synthesizing enzymes, the bacterial ribosome, the enzymes required for nucleic acid synthesis that is a basis for antibiotics classification

β-lactams, Glycopeptides

Polymyxins

Rifampicin

30S: Aminoglycosides
30S: Tetracyclines
50S: Chloramphenicol
50S: Macrolides, Lincosamides
50S: Linezolide, Streptogramins

Classification of antibiotics

A. Inhibitors of cell wall synthesis

1. Penicillins
2. Cephalosporins
3. Carbapenems and monobactams
4. Glycopeptides

B. Protein synthesis inhibitors acting on ribosomal subunits 30S

1. Aminoglycosides
2. Tetracyclines

C. Protein synthesis inhibitors acting on ribosomal subunits 50S

1. Macrolides and azalides
2. Chloramphenicols
3. Lincosamides

D. Antibiotics which disturb functions of nucleic acids

1. Rifampicins

E. Antibiotics which disturb structure and functions of cell membranes

1. Polienes
2. Cyclic polypeptides (polymyxins).

Common side effects

- direct host toxicity (aminoglycosides, peptides)
- toxic interactions with other drugs
- interference with protective effects of normal host microflora
- tissue lesions at injection sites (tetracyclines)
- impairment of host immune or defense mechanisms (chloramphenicol)

- reduced phagocytosis, and chemotactic activity of neutrophils (tetracyclines)
- inhibition of phagocytosis (aminoglycosides)
- hypersensitivity reactions (beta-lactams, aminoglycosides)
- hepatic microsomal enzyme induction (rifampin) or inhibition (chloramphenicol) that interferes with their own metabolism as well as that of concurrent medications,

Selection or promotion of resistance

Antibiotics do not cause bacteria to become resistant but their use selects resistant populations of bacteria.

Some genes that code for resistance are identified in bacterial cultures.

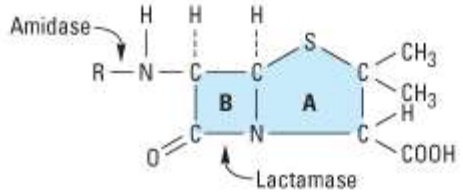
The most important for resistance are plasmids.

They carry genes of the antibacterial resistance transmitted from one bacterium to another, especially in many Gram-negative pathogens.

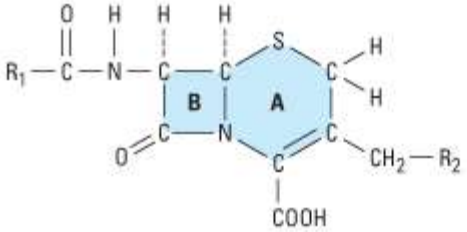
BETA-LACTAM ANTIBIOTICS
(inhibitors of cell wall synthesis)

Their structure contains a beta-lactam ring.
The major subdivisions are:

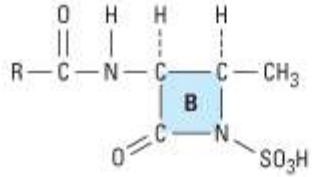
(a) **penicillins** whose official names usually include or end in “cillin”
(b) **cephalosporins** which are recognized by the inclusion of “cef” or “ceph” in their official names.
(c) **carbapenems** (e.g. meropenem, imipenem)
(d) **monobactams** (e.g. aztreonam)
(e) **beta-lactamase inhibitors** (e.g. clavulanic acid, sulbactam).



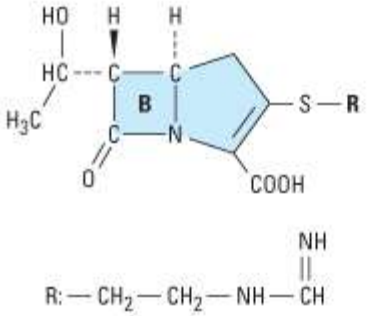
Substituted 6-aminopenicillanic acid



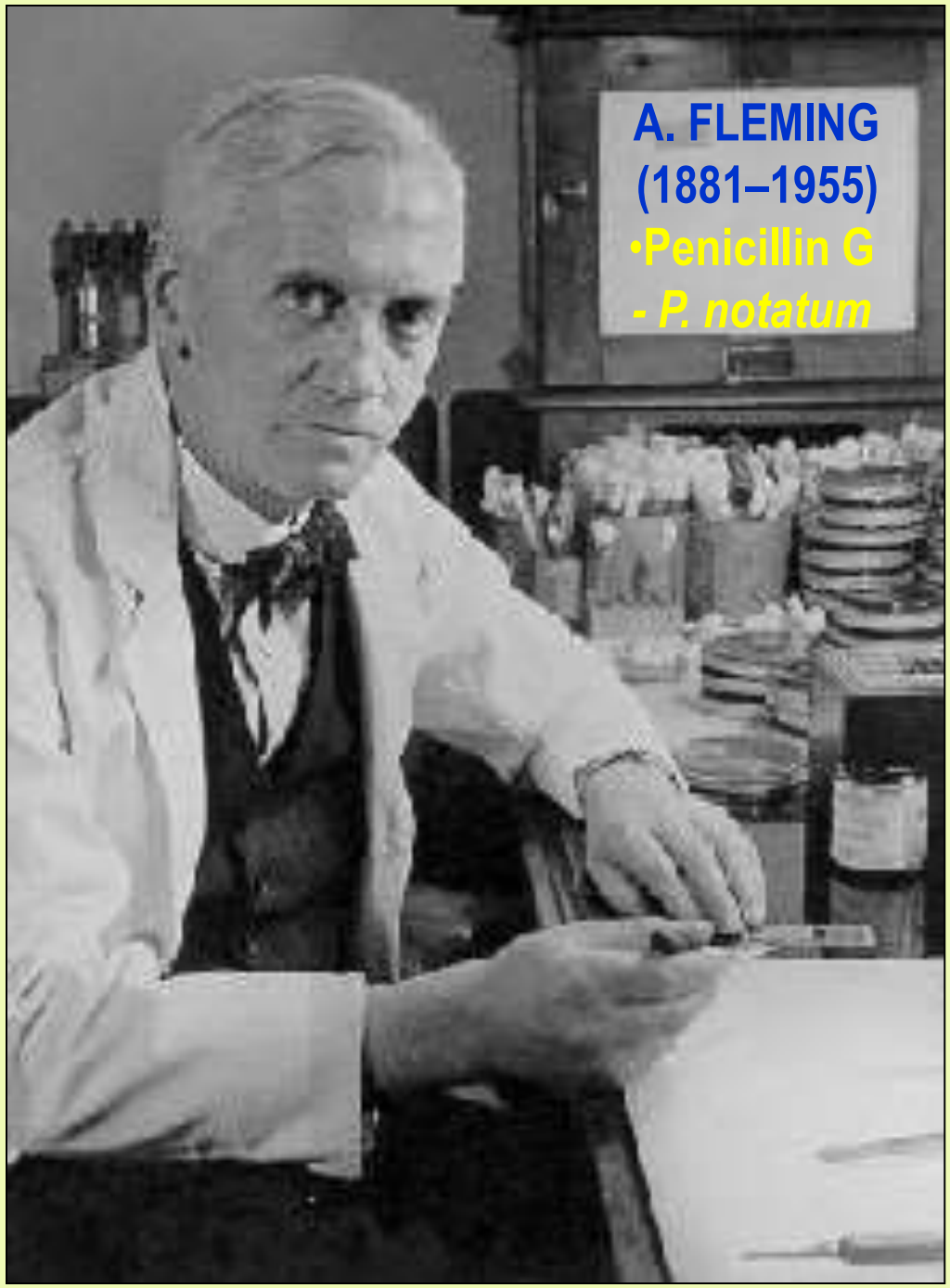
Substituted 7-aminocephalosporanic acid



Substituted 3-amino-4-methylmonobactamic acid (aztreonam)

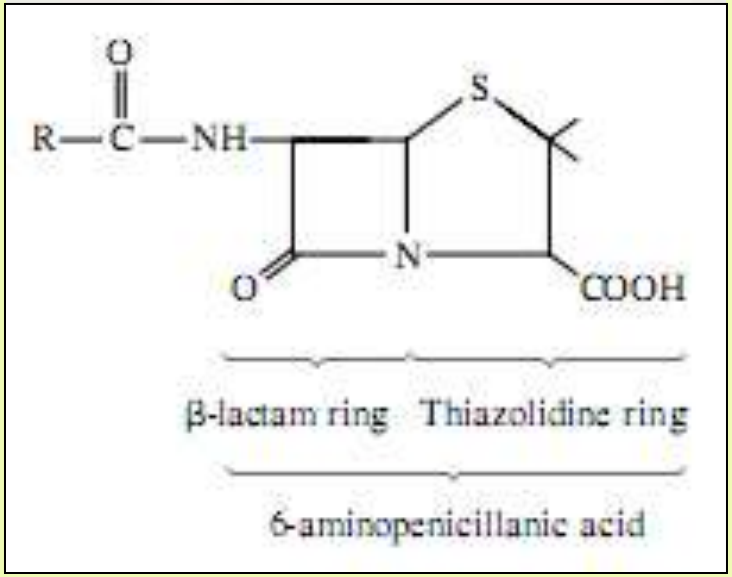


Substituted 3-hydroxyethylcarbapenemic acid (imipenem)



I. PENICILLINS

(1928)



Penicillium chrysogenum

Structure and function of cell wall

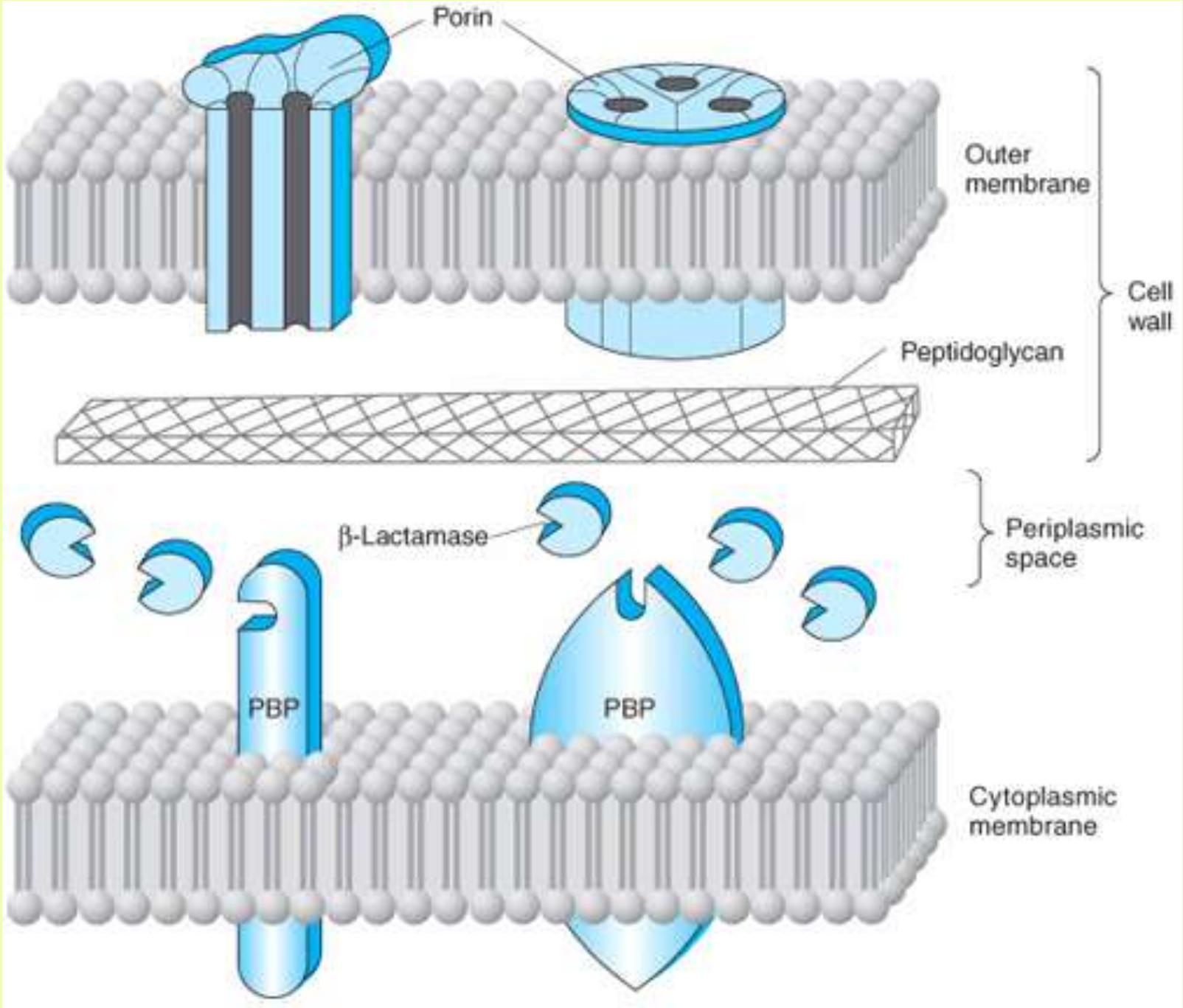
- The cell wall surrounds the cytoplasmic membrane, maintains cell shape and integrity.
- The cell wall is composed of a complex cross-linked polymer of polysaccharides and polypeptides, peptidoglycan (murein, mucopeptide).
- The polysaccharide contains amino sugars, *N*-acetylglucosamine, and *N*-acetylmuramic acid.
- A five-amino-acid peptide is linked to the *N*-acetylmuramic acid sugar. This peptide terminates in D-alanyl-D-alanine.

Mechanism of action

Penicillin-binding protein (PBP, an enzyme) removes the terminal alanine in the process of forming a cross-link with a nearby peptide.

Beta-lactam antibiotics covalently bind to the active site of PBPs. This inhibits the transpeptidation reaction, halting peptidoglycan synthesis, and the cell dies.

Beta-lactams kill only growing and synthesizing cell wall bacteria .


Porin
Outer membrane
Cell wall
Peptidoglycan
Periplasmic space
β-Lactamase
PBP
PBP
Cytoplasmic membrane

NARROW SPECTRUM PENICILLINS

- Biosynthetic (natural) penicillins
- Antistaphylococcal beta-lactamase resistant penicillins

BROAD SPECTRUM PENICILLINS

- Aminopenicillins
- Antipseudomonal penicillins
  - Carboxypenicillins
  - Ureidopenicillins

Side effects of penicillins

The main hazard with the penicillins is allergic reaction. These include itching, rashes, fever, and angioedema, and rarely anaphylactic shock which can be fatal. Allergies are least likely when penicillins are given orally.

Metabolic opening of the β-lactam ring creates a highly reactive penicilloyl group which polymerizes and binds with tissue proteins to form the major antigenic determinant.

The anaphylactic reaction involves specific IgE antibodies which can be detected in the plasma of susceptible persons.

There is a cross-allergy between all the various forms of penicillin due to their common structure and to the degradation products common to them all.
Partial cross-allergy exists between penicillins and cephalosporins (a maximum of 10%).
Carbapenems and monobactams have a much lower risk of cross-reactivity.

When the history of allergy is not clear and it is necessary to prescribe a penicillin,
the presence of gE antibodies in serum
is a useful indicator of reactions mediated by these antibodies.
An intradermal test for allergy may be performed; appearance of a flare and wheal reaction indicates a positive response.
Only about 10% of patients with a history of “penicillin allergy” respond positively.

Nonallergic side effects include diarrhoea due to alteration in normal intestinal flora which may progress to *Clostridium difficile*-associated diarrhoea (for wide spectrum penicillins).

Neutropenia is a risk if penicillins or other β-lactams which are used in high dose and longer than 10 days.

Rarely penicillins cause anemia, and thrombocytopenia or interstitial nephritis.

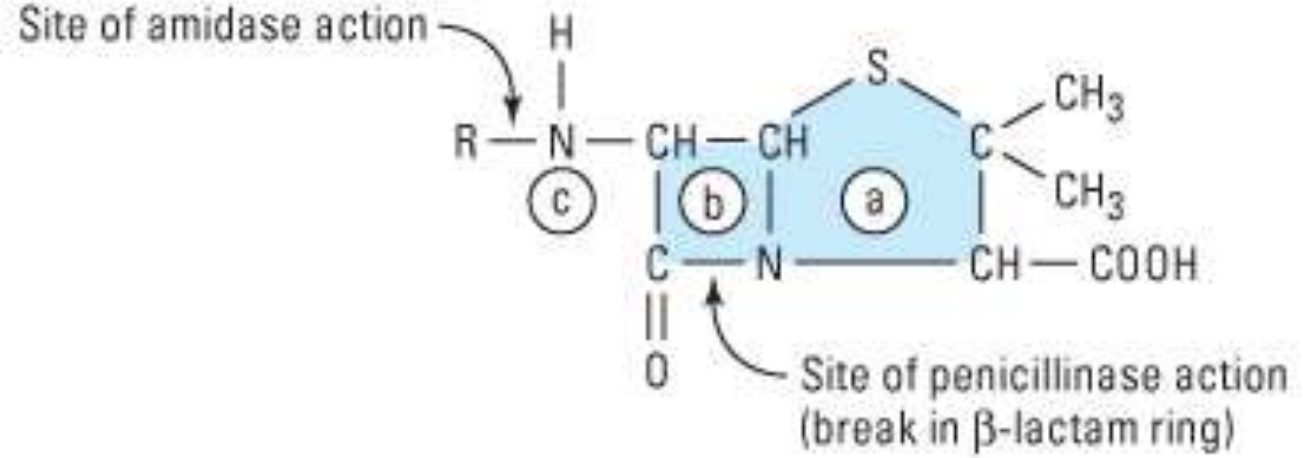
Extremely high plasma penicillin concentrations cause convulsions.

Co-amoxiclav, flucloxacillin, or oxacillin given in high doses for prolonged periods in the elderly may cause hepatic toxicity.

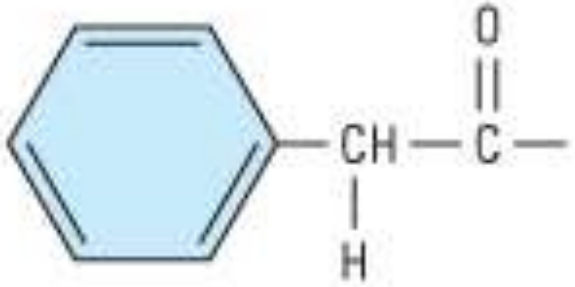
1. NARROW SPECTRUM PENICILLINS

a) Biosynthetic (natural) penicillins

▼**Benzylpenicillin (Penicillin G)** is used when high plasma concentrations are required. The short $t_{1/2}$ (0.5 h) means that doses have to be large to maintain a therapeutic concentration.
The large therapeutic ratio of penicillin allows the resulting fluctuations to be tolerable.
Benzylpenicillin is eliminated by the kidney (about 80%).
Effective doses range is between 4 and 24 million units per day administered IM or IV in 4 to 6 divided doses; Penicillin G Sodium can be given as IV infusion.



6-Aminopenicillanic acid



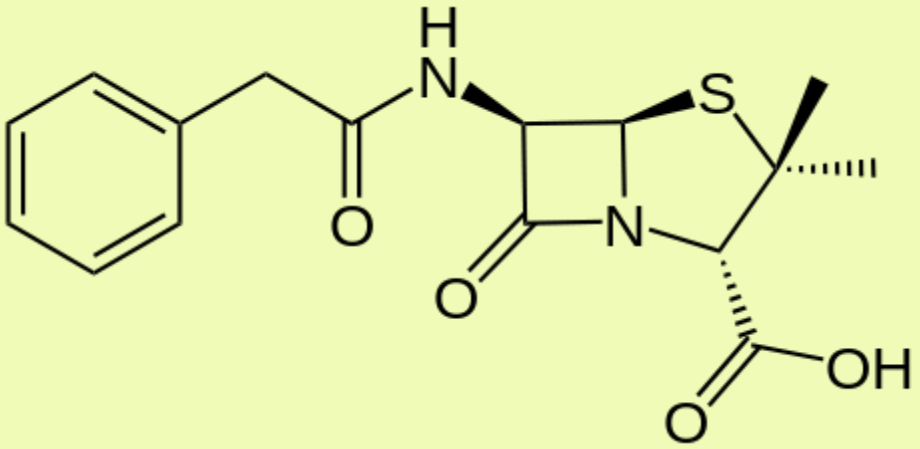
Penicillin G (benzylpenicillin):

High activity against gram-positive bacteria. Low activity against gram-negative bacteria. Acid-labile. Destroyed by β-lactamase. 60% protein-bound.

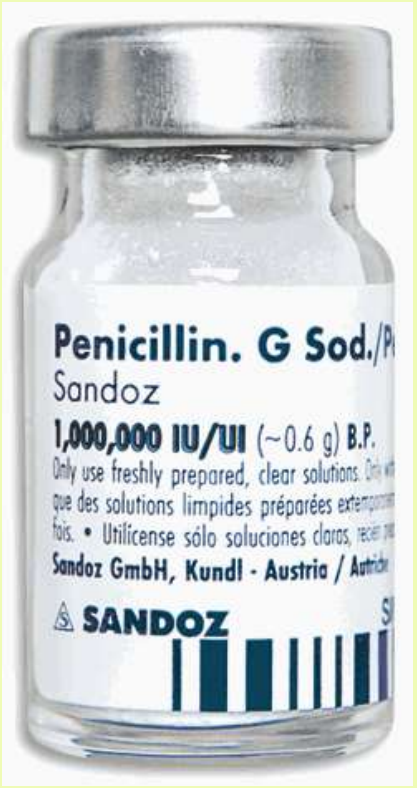
Penicillin G is a drug of choice for infections caused by streptococci, meningococci, enterococci, penicillin-susceptible pneumococci, non-β-lactamase-producing staphylococci, *T. pallidum* and many other spirochetes, clostridium species, actinomyces, and other Gram-positive rods and non-β-lactamase-producing Gram-negative anaerobic organisms.

▼**Phenoxymethylpenicillin Potassium** (Penicillin-VK)
the oral form of penicillin, is indicated only in minor infections (e.g. tonsillitis) because of its poor bioavailability, short action and narrow antibacterial spectrum.

▼**Benzathine penicillin** and **Procaine Penicillin G**
maintain low but prolonged drug levels.
A single IM injection is an effective treatment for β-hemolytic streptococcal pharyngitis,
2.4 million units IM once a week for 1–3 weeks, is effective in the treatment of syphilis.



Penicilline G Sodium®

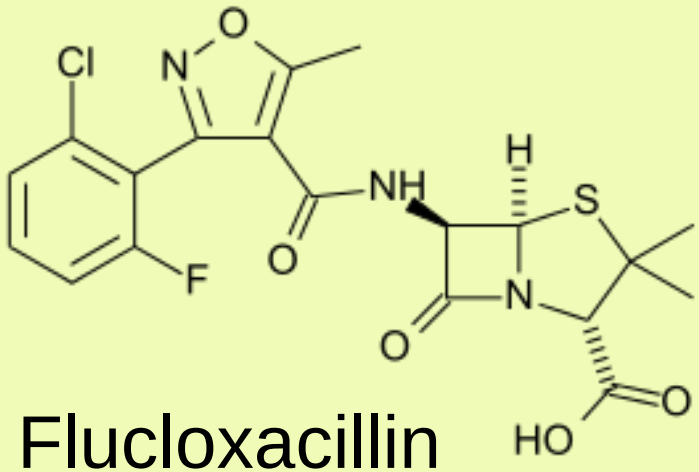


Phenoxymethylpenicillin Potassium (Penicillin-VK®)

▼**Procaine penicillin G** is rarely used nowadays because many strains are penicillin-resistant.

b) Antistaphylococcal penicillins

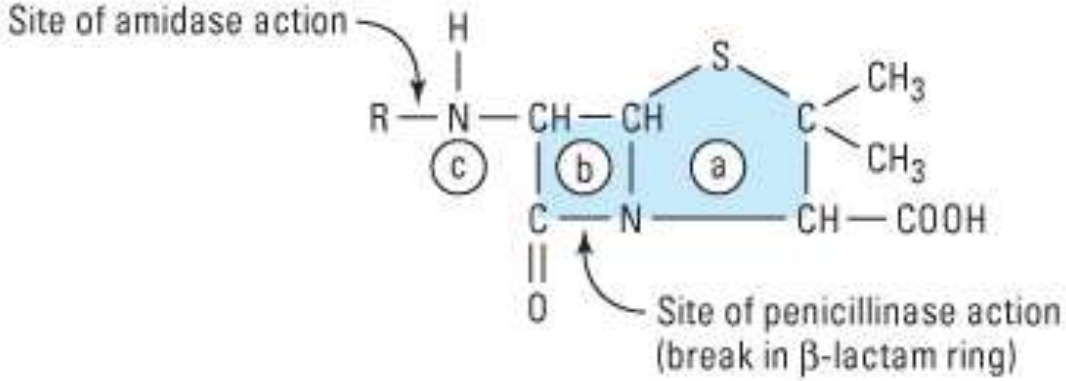
- **Isoxazolyl penicillins**
  - **Cloxacillin, Dicloxacillin**
  - **Flucloxacillin, Oxacillin**
- **Others**
  - **Methicillin**
  - **Nafcillin**



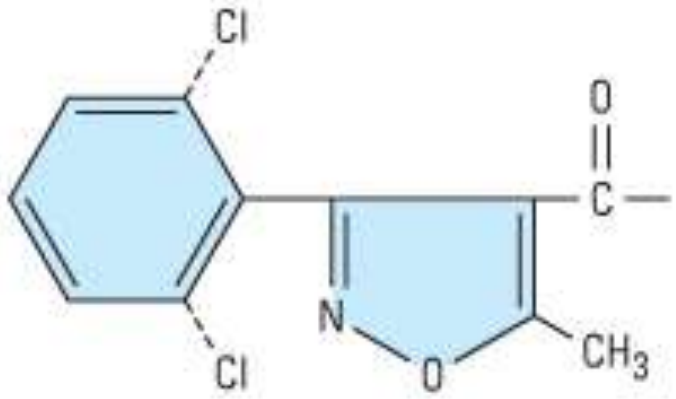
Flucloxacillin

These semisynthetic penicillins are indicated for infection by beta-lactamase-producing staphylococci, although penicillin-susceptible strains of streptococci and pneumococci are also susceptible.

An **isoxazolyl penicillin** (*cloxacillin, dicloxacillin, or oxacillin*), 250–500 mg orally every 4 to 6 h is suitable for the treatment of mild to moderate localized staphylococcal infections.
All are relatively acid-stable but food interferes with their absorption.



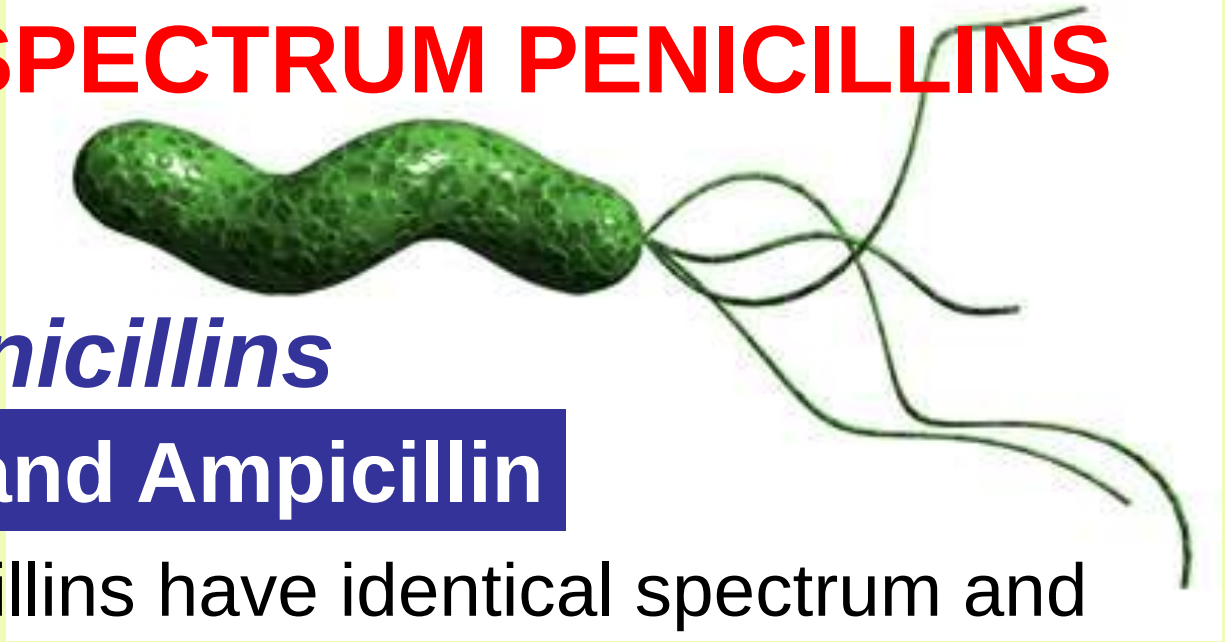
6-Aminopenicillanic acid



Oxacillin (no Cl atoms); cloxacillin (one Cl in structure); dicloxacillin (2 Cls in structure); flucloxacillin (one Cl and one F in structure) (isoxazolyl penicillins):

Similar to methicillin in β-lactamase resistance, but acid-stable. Can be taken orally. Highly protein-bound (95–98%).

2. BROAD-SPECTRUM PENICILLINS



a) Aminopenicillins

Amoxicillin and Ampicillin

The aminopenicillins have identical spectrum and activity, but amoxicillin is better absorbed orally (70–90%). They are ***effective against streptococci, enterococci, and some Gram-negative organisms (including H. pylori)*** but have variable activity against staphylococci and are ineffective against P. aeruginosa.

These drugs are given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections. Aminopenicillins are the most active of the oral beta-lactams against penicillin-resistant pneumococci and are the preferred beta-lactams for treating infections suspected to be caused by these resistant strains.

Ampicillin (but not amoxicillin) is effective for *shigellosis*.
Ampicillin (IV) is useful for treating serious infections caused by penicillin-susceptible organisms, including anaerobes, enterococci, *L. monocytogenes*, and beta-lactamase-negative strains of Gram-negative cocci and bacilli such as *E. coli*, and salmonella species.
Non-beta-lactamase-producing strains of *H. influenzae* are generally susceptible.

b) Antipseudomonal penicillins

These drugs retain activity against streptococci and possess additional effects against Gram-negative organisms, including *Enterobacteriaceae and Pseudomonas*.

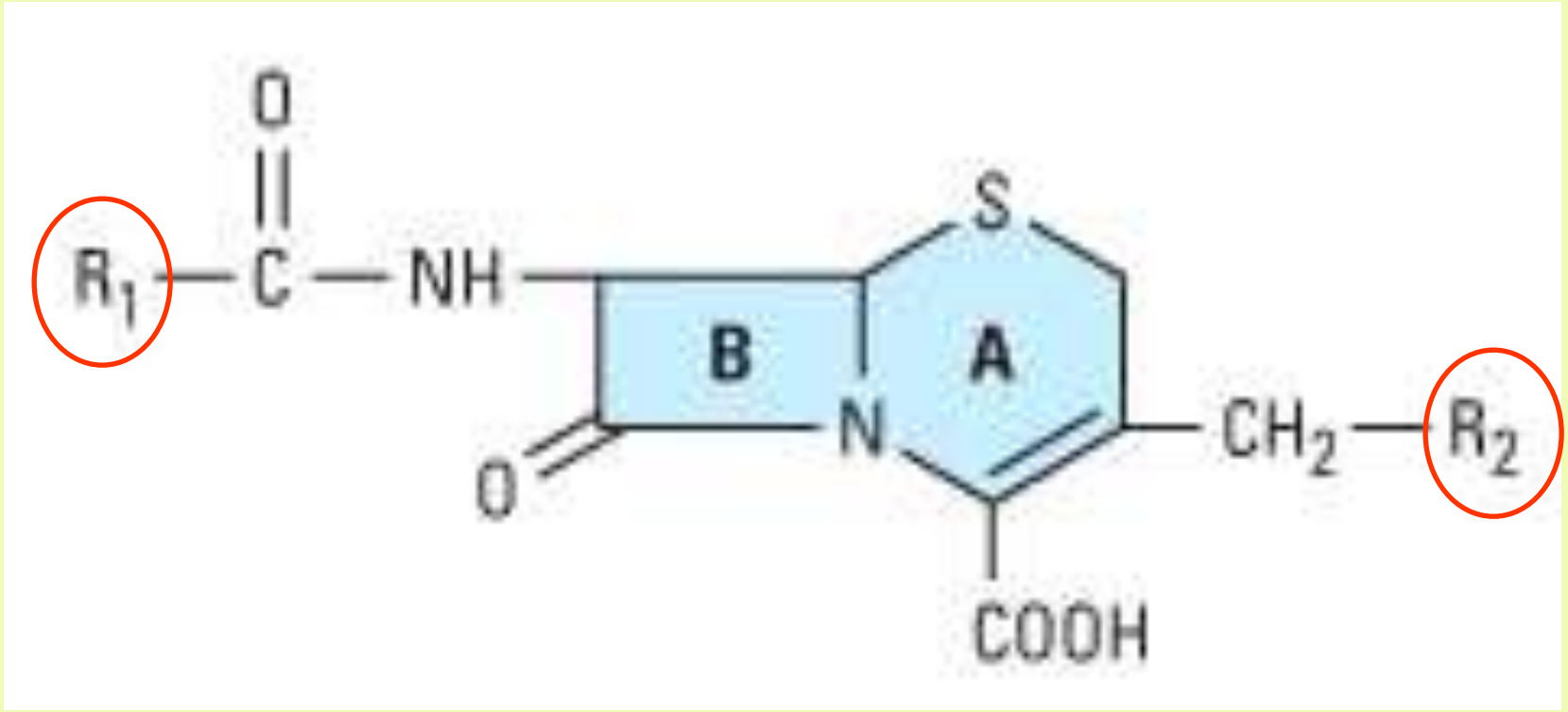
- **Carboxypenicillins**
  - **Carbenicillin**
  - **Ticarcillin**
- **Ureidopenicillins**
  - **Azlocillin**
  - **Mezlocillin**
  - **Piperacillin**

II. CEPHALOSPORINS

The nucleus of the cephalosporins, *7-aminocephalo-sporanic acid*, bears a close resemblance to *6-amino-penicillanic acid*.

The intrinsic antimicrobial activity of natural cephalosporins is low, but the attachment of various R_1 and R_2 groups has yielded hundreds of potent compounds of low toxicity.

Cephalosporins can be classified into 4 generations, depending mainly on the spectrum of their antimicrobial activity.



7-Aminocephalosporanic acid nucleus

Cephalosporins are similar to penicillins, but more stable to many bacterial beta-lactamases and have a broader spectrum of activity.

However, strains of *E. coli* and *Klebsiella* species expressing extended-spectrum beta-lactamases that can hydrolyze most cephalosporins are becoming a problem.

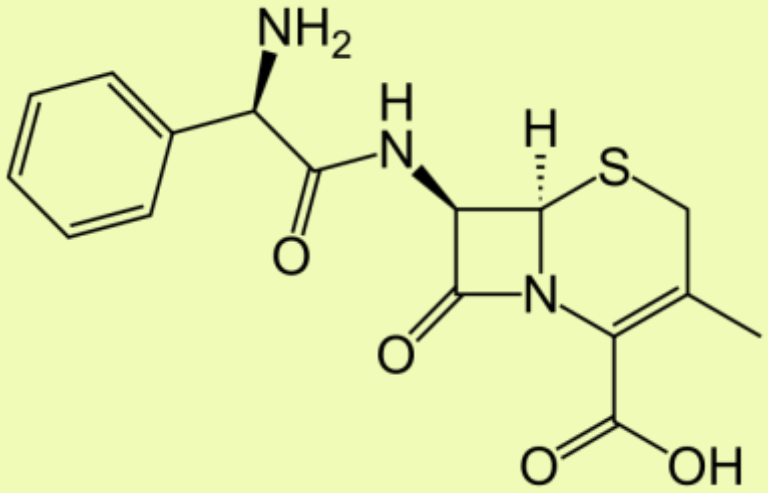
Cephalosporins are *not active* against *enterococci* and *L. monocytogenes.*

1. 1st-generation cephalosporins

- **cefadroxil, cefazolin, cefalexin,**
- **cefalothin, cefapirin, cefradine**

These drugs are very active against Gram-positive cocci (pneumococci, streptococci, staphylococci). Cephalosporins are not active against methicillin-resistant strains of staphylococci. *E. coli, K. pneumoniae*, and *P. mirabilis* are often sensitive. Anaerobic cocci are usually sensitive, but *Bacteroides fragilis* is not.


60 mL
CEFALEXIN
125 mg / 5mL
Powder for Suspension
ANTIBACTERIAL
cherry flavor
Manufactured by:
LUMAR PHARMACEUTICAL LABORATORY
For:
INTERPHARM MARKETING
60 mL
CEFALEXIN
ANTIBACTERIAL


NH2
H
N
O
H
S
N
O
O
OH

Cefalexin

Although the 1st -generation cephalosporins are broad spectrum and relatively nontoxic, they are rarely the drug of choice for any infection.

Oral cephalosporins (cefalexin, cefadroxil, and cefradine) are absorbed from the gut to a variable extent. They are used for the treatment of urinary tract infections, for staphylococcal, or streptococcal infections including cellulitis or soft tissue abscess. However, oral cephalosporins should not be relied on in serious systemic infections (because they do not cross blood-brain barrier).

Cefazolin penetrates well into most tissues.
It is a drug of choice for surgical prophylaxis.
Cefazolin (IM,IV) may be a choice in infections for which it is the least toxic drug (eg, *K. pneumoniae*).
Cefazolin does not penetrate the CNS and cannot be used to treat meningitis.
Cefazolin is an alternative to an antistaphylococcal penicillin for patients who are allergic to penicillin.

2. 2nd-generation cephalosporins

- **cefaclor, cefamandole, cefprozil,**
- **cefotetan, cefuroxime, cefoxitin**

They are active against organisms inhibited by 1st -generation drugs, but in addition they have extended Gram-negative coverage.

Klebsiellae are usually sensitive.

Cefamandole, cefuroxime, and cefaclor are active against *H. influenzae* but not against serratia or *B. fragilis*.

Cefoxitin and cefotetan are active against *B. fragilis* and some serratia strains but are less active against *H. influenzae*.

Cefaclor, cefuroxime axetil, and cefprozil can be given orally (10-15 mg/kg/d in 2 to 4 divided doses). Except for cefuroxime axetil, these drugs are not predictably active against penicillin-resistant pneumococci and should be used cautiously to treat suspected or proved pneumococcal infections. Cefaclor is more susceptible to β-lactamase hydrolysis compared with the other agents, and its usefulness is correspondingly diminished.

The oral 2nd-generation cephalosporins are active against beta-lactamase-producing *H. influenzae* or *Moraxella catarrhalis* and are used to treat sinusitis, otitis, or lower respiratory tract infections, in which these organisms have an important role.
Because of their activity against anaerobes (*B. fragilis*), cefoxitin or cefotetan, can be used for mixed anaerobic infections such as peritonitis or diverticulitis.
Cefuroxime is used to treat community-acquired pneumonia because it is active against β-lactamase-producing *H. influenzae, K. pneumoniae* and penicillin-resistant pneumococci. it is less effective in the treatment of meningitis than ceftriaxone or cefotaxime, and should not be used.

Cefuroxime

- Zinacef™

Cefoxitin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2.0g
注射用头孢西丁钠
Cefoxitin Sodium for Injection
瑞阳制药有限公司


CEFOXITIN
FOR INJECTION, USP
10 g*
CEFOXITIN
FOR INJECTION, USP
2 g*
CEFOXITIN
FOR INJECTION, USP
1 g*

3. 3rd-generation cephalosporins

- **cefixime, cefoperazone, cefotaxime,**
- **cefdinir, cefpodoxime, ceftriaxone**

Compared with 2nd-generation agents, these drugs have expanded Gram-negative coverage, and some are able to cross theblood-brain barrier.

3rd-generation drugs are active against *Citrobacter*, *Serratia marcescens*, and *Providencia*.

They are also effective against β-lactamase-producing strains of Haemophilus and Neisseria.

Ceftazidime and cefoperazone are the only two drugs with useful activity against *P. aeruginosa*.

Like the 2nd-generation drugs, 3rd-generation cephalosporins are hydrolyzable by constitutively produced beta-lactamase, and they are not reliably active against enterobacter species. *Serratia*, *Providencia*, and *Citrobacter* also produce a chromosomally encoded cephalosporinase that can confer resistance to 3rd-generation cephalosporins. Cefixime, cefdinir, and cefpodoxime are oral agents.

3rd-generation cephalosporins are used to treat serious infections caused by organisms resistant to most other drugs.

Strains expressing extended-spectrum beta-lactamases, are not susceptible and 3rd –generation cephalosporins should be avoided in the treatment of *Enterobacter* infections.

Ceftriaxone and cefotaxime are approved for the treatment of meningitis, including meningitis caused by pneumococci, meningococci, *H. influenzae*, and susceptible enteric Gram-negative rods, but not by *L. monocytogenes*.

Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections caused by these strains (meningitis caused by highly penicillin-resistant strains of pneumococci may not respond).
Other potential indications include empirical therapy of sepsis of unknown cause in both the immuno-competent and the immunocompromised patient.

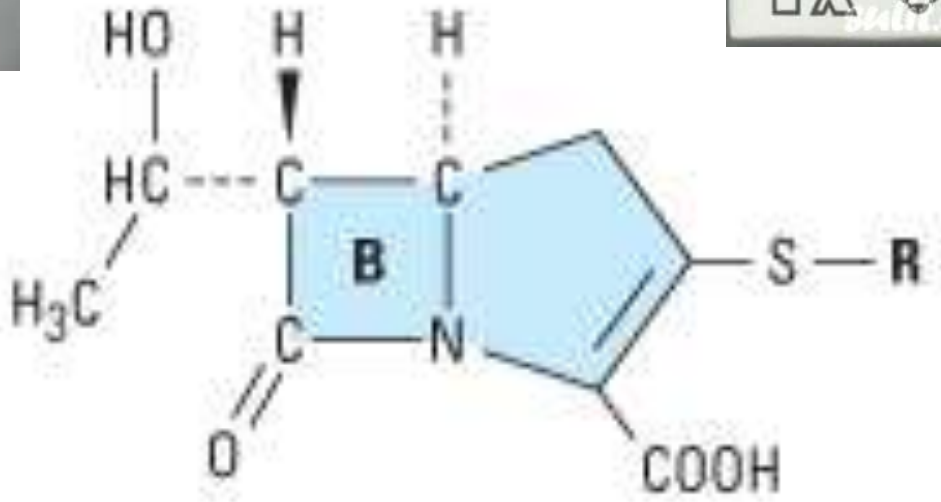
Ceftriaxone

4. 4th-generation cephalosporins

- **cefepime, cefpirome**

Cefepime is more resistant to hydrolysis by chromosomal beta-lactamases.
It has good activity against *P. aeruginosa*, *Enterobacteriaceae*, *S. aureus*, and *S. pneumoniae*.
Cefepime is highly active against *Haemophilus* and *Neisseria*.
It has good activity against most penicillin-resistant strains of streptococci.

III. CARBAPENEMS



- Doripenem
- Ertapenem
- Meropenem
- Tienam® (imipenem/cilastatin)

Carbapenems penetrate body tissues and fluids well, including the cerebrospinal fluid. All are cleared renally, and the dose must be reduced in patients with renal insufficiency.

Imipenem has a wide spectrum with good activity against many Gram-negative rods, including *P. aeruginosa*, Gram-positive organisms, and anaerobes.

It is resistant to most β-lactamases but not metallo-beta-lactamases.

E. faecium, MRS of staphylococci, *C. difficile* and some others microorganisms are resistant.

Imipenem is inactivated by dehydropeptidases in renal tubules, resulting in low urinary concentrations. It is administered together with an inhibitor of renal dehydropeptidase, Cilastatin.

Meropenem is similar to imipenem but has slightly greater activity against Gram-negative aerobes and slightly less activity against Gram-positives. It is not significantly degraded by renal dehydropeptidase and does not require an inhibitor.

Ertapenem is less active than meropenem or imipenem against *P. aeruginosa* and *Acinetobacter* species. It is not degraded by renal dehydropeptidase.

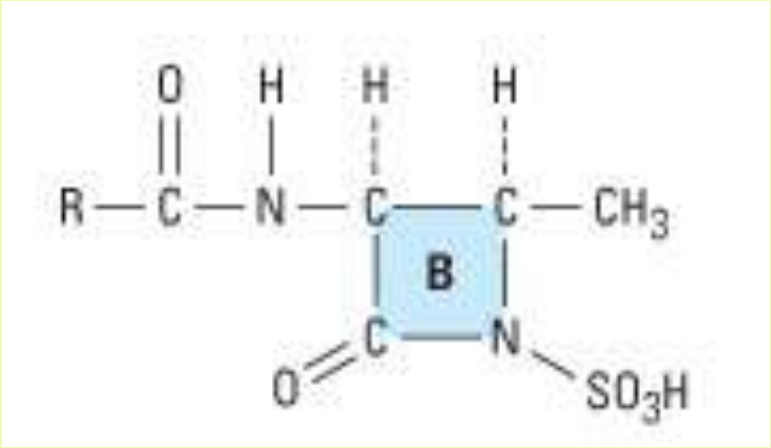
Carbapenems are indicated for infections caused by susceptible organisms, e.g. *P. aeruginosa*, which are resistant to other available drugs and for the treatment of mixed aerobic and anaerobic infections.
Carbapenems are active against many highly penicillin-resistant strains of pneumococci.
A carbapenem is the beta-lactam of choice for the treatment of Enterobacter infections (it is resistant to destruction by the beta-lactamase of these organisms).
Imipenem or meropenem may be an effective treatment for febrile neutropenic patients.

Side effects of carbapenems

They are nausea, vomiting, diarrhea, skin rashes, and reactions at the infusion sites.
Excessive levels of imipenem in patients with renal failure may lead to seizures.
Patients allergic to penicillins may be allergic to carbapenems.

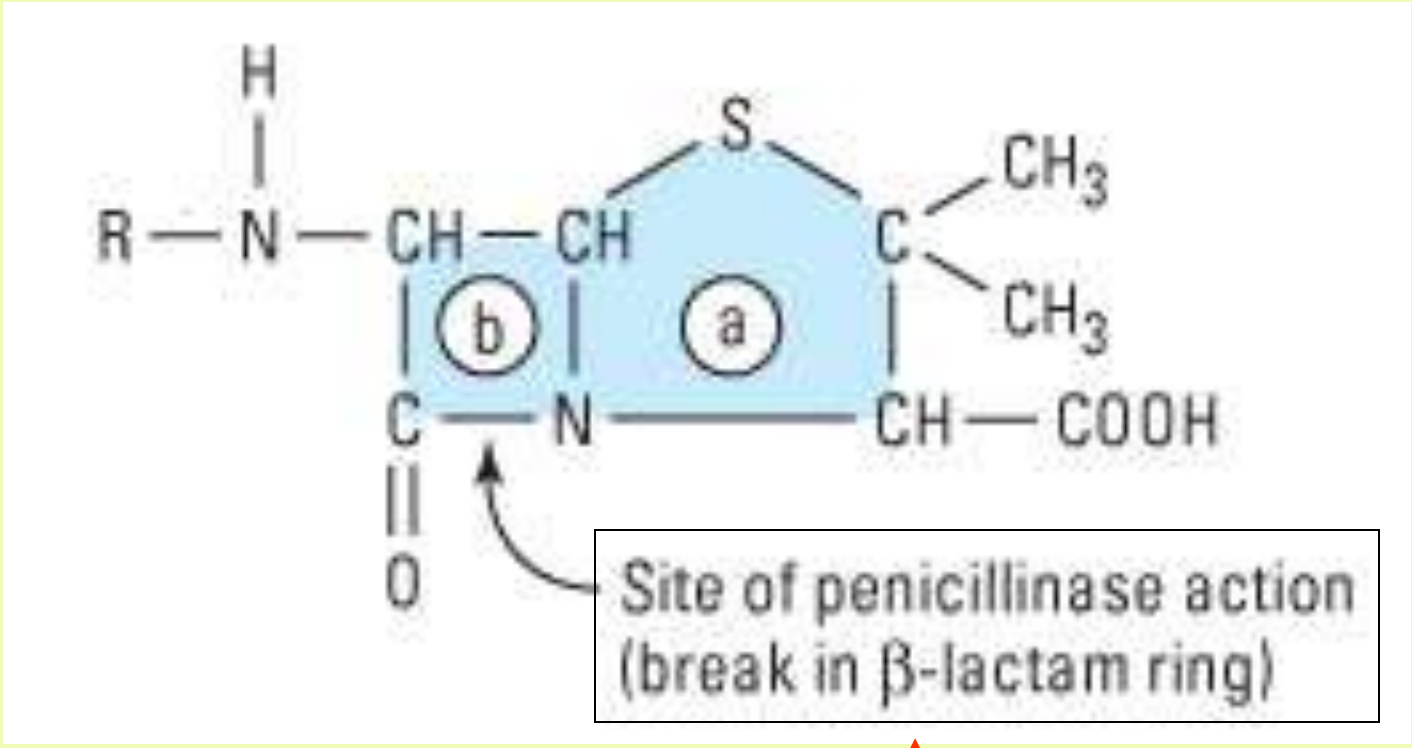
IV. MONOBACTAMS

- **Aztreonam**



Monobactams are drugs with a monocyclic β-lactam ring. They are relatively resistant to beta-lactamases and active against Gram-negative rods (including *Pseudomonas* and *Serratia*). They have no activity against Gram-positive bacteria or anaerobes. Aztreonam is given IV. The half-life is 1–2 h and is greatly prolonged in renal failure. Penicillin-allergic patients tolerate aztreonam without reaction.

BETA-LACTAMASE INHIBITORS



(–)

- Clavulanic acid
- Sulbactam
- Tazobactam

Resistance to penicillins and other beta-lactams is due to one of some general mechanisms:
(1) inactivation of the antibiotic by beta-lactamase;
(2) modification of the target PBPs;
(3) impaired penetration of the drug to the target PBPs;
(4) efflux of the drug from bacterial cells.
Beta-lactamase production is the most common mechanism of resistance. Many hundreds of different beta-lactamases have been identified. Some, such as those produced by *Staphylococcus aureus, Haemophilus* spp., and *Escherichia coli*, are relatively narrow in substrate specificity, preferring penicillins to cephalosporins. They are called penicillinases and cephalosporinases.

Other β-lactamases produced by *P. aeruginosa* and *Enterobacter* spp., and extended-spectrum beta-lactamases, hydrolyze both cephalosporins and penicillins.

Carbapenems are highly resistant to hydrolysis by penicillinases and cephalosporinases but they are hydrolyzed by metallo-beta-lactamase and carbapenemases.

Ampicillin, amoxicillin, ticarcillin, and piperacillin are also available in combination with one of several **beta-lactamase inhibitors: clavulanic acid, sulbactam, or tazobactam**.

The addition of a beta-lactamase inhibitor extends the activity of these penicillins to include beta-lactamase-producing strains of *S. aureus* as well as some beta-lactamase-producing Gram-negative bacteria *(E. coli, K. pneumoniae, P. aeruginosa, Proteus, H. influenzae*).

Co-Amoxiclave:
Amoxicillin & Clavulanate
Augmentin®

Gram positive aerobes	Gram negative aerobes
Obligate anaerobes	Penicillinase-producing *Staphylococcus**

Antibacterial spectrum for amoxicillin-clavulanate

*** MRSA are resistant**

Amoxicillin & Clavulanate (Augmentin®)

CONTROL TASKS

- A patient twice a year receives a seasonal prophylaxis of a rheumatic attack. For this purpose an antibiotic from long-acting natural penicillins is given intramuscularly once per week. Which preparation is used?

A. Bicillin-1 B.Benzylpenicillin-sodium C. Bicillin-5 D. Ampicillin E. Oxacillin. (A)

- A patient has staphylococcal pneumonia caused by penicillin-resistant strain. Alternative antibiotic from the first generation of cephalosporins is prescribed to him. Which preparation is probably used for the treatment of this patient?

A. Ceftriaxone B. Benzylpenicillin-sodium C. Amoxiclav D. Ampicillin E. Cefazolin. (E)

- A patient has severe infection caused by unknown microbe. The third generation cephalosporin is administered intravenously to the patient till the results of bacteriological study will be obtained. Which drug is suitable in this case? (A)

A. Ceftriaxone B. Cefalexin C. Cefazolin D. Meropenem. E. Aztreonam.

- A child with pneumonia due to pneumococci was treated with ampicillin. What is a mechanism of action of this antibiotic?

A. Inhibition of protein synthesis B. Inhibition of cell wall synthesis C. Inhibition of topoisomerase II D. Folate antagonism E. Denaturation of proteins. (B)

THE END

Thank you

for attention!