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The mechanism of Bacterial resistance to antimicrobial agents:

- **A. Production of inactivator**
- **B. Decreased porins of bacterial outer membrane**
- **C. Modification of target sites**
- **D. Increased permeability of bacterial outer membrane**
- E. Decreased efflux pump

β–Lactam Antibiotics

Penicillins

Cephalosporins

Monobactams

Carbapenems

Beta-Lactam inhibitors

Section 1 Penicillins

Basic structure of penicillins

nucleus : 6-aminopenicillanic acid (6-APA)



- Natrural penicillin
 - **(Pharmacokinetics)**
 - intramuscular or intravenous therapy
 - distribute to most tissues and serosa-lined cavities,
 low concentrations appear in cerebrospinal fluid
 - Penicillin G is excreted by the kidneys

(Antibacterial activity **)**

Gram-positive coccus

Gram-negative coccus

Gram-positive bacilli

Helicoids

Gram positive coccus:

staphylococci – Staphylococcus aureus Staphylococcus epidermidis

streptococcus – Streptococcus hemolyticus Streptococcus pneumoniae Streptococcus viridans **Gram negative coccus:**

Diplococcus meningitides \ Diplococcus gonorrhoeae **Gram-positive bacilli**

Corynebacterium diphtheriae Charbon Spore-Forming Clostridium tetani, Clostridium perfringens,

Mechanism of action



Inhibition of transpeptidase:
 Increased autoenzyme activity

Clinical uses

1. Infection caused by Gram positive coccus Staphylococci: bouton, anthracia and ichorrhemia **Streptococcus hemolyticus:** pharyngitis, febris rubra, Streptococcus pneumoniae: pneumonia genuina, bronchial pneumonia Streptococcus viridans: endocarditis, ichorrhemia

- Cerebromeningitis caused by diplococcus meningitides
 Infection caused by Gram positive bacilli tetanus, diphtheria, anthracnose
 Infection caused by helicoids
 - febris hebdomadis, great pox, relapsing fever

Adverse effect

1. Allergy :

maculopapular rash, angioedema and allergic shock.

Antigenic determinant: penicilloic acid

Clinical manifestation:

laryngeal edema, bronchial spasm, low blood pressure, eclampsia,

coma

Prevention and cure



 Glucocorticoid, antihistamine drug are also chosen and supply blood volume

2. Herxheimer reaction

Chill, fever, laryngalgia, headache, tachycardia.

(Drug resistance)

1. β-lactamase activity:

Penicilin resistance: Penicillinase Cephalosporins resistance:ESBLs Lactamase inhibitors resistance: AmpC type enzyme Carbapenems resistance: Metal enzyme 2. Altered penicillin binding proteins
MRSA
(Methicillin-resistant strains of staphylococcus aureus)
PRSP
(Penicillin-resistant streptococcus pneumoniae)

3. Decreased permeability to drug

\Box , Semisynthetic penicillin

1. Oral Penicillin

- Penicillin V has a spectrum similar to penicillin G.
- It is more acid-stable than penicillin G.
- It is often employed in the treatment of upper respiratory infection caused by gram positive coccus.

2. Penicillinase-resistant penicillin

Methicillin

Oxacillin

nafillin

Cloxacillin

Dicloxacillin

flucloxacillin

Feature:

- (1) They kill penicillinase-producing staphylococci
- (2) They can't kill Methicillin-resistant strains of Staphylococcus aureus (MRSA)
- (3) They are used in treatment of infections caused by penicillinase-producing staphylococci

3. Extended spectrum penicillins

Ampicillin

Amoxicillin

Feature:

- (1) They are more effective against gramnegative bacilli.
- (2) They are inactivated by β -lactamases
- (3) They treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections.
- (4) They treat infection caused by penicillinresistance pneumococci
- (5) Ampicillin can not treat infection caused by pseudomonas aeruginosa

4. Antipseudomonal penicillins:

Carbenicillin

Piperacillin

Feature:

These antibiotics have activity against **Pseudomonas aeruginosa.** In addition these antibiotics are effective against many gramnegative bacilli, but not against penicillinaseproducing staphylococci. Piperacillin is the most potent, and used to treat serious infection caused by bacillus proteus and pseudomonas aeruginosa

Section 2 Cephalosporins

7- aminocephalosporanic acid

6-aminopenicillanic acid



B: β -lactam ring

- , First generation cephalosporin

Cefalotin Cefazolin Cefradine

Cefaloridine

[Feature of antibacterial activity]

- 1. They have strong active against Grampositive cocci
- 2. They have less active against Gramnegative bacteria;
- 3. They are resistant to staphylococcal producing penicillinase, but not resistant to gram negative bacilli producing penicillinase;

4. They are ineffective against Pseudomonas aeruginosa and anaerobic;

- 5. They are used to treat infection by Grampositive cocci.
- 6. They are nephrotoxic

\Box , Second generation cephalosporin

Cefuroxime

Cefamandole

Cefaclor

Feature of antibacterial activity

- 1. They have active against Gram-positive cocci, but antibacterial action is weaker than that of first generation;
- 2. They have extended gram-negative bacilli, their action is stronger than first generation;
- 3. They are resistant to gram negative bacilli producing penicillinase;

4. They are ineffective against Pseudomonas aeruginosa , but effective against anaerobic;
5. They often are used to treat sinusitis, otitis, lower respiratory tract infections.
6. They are less nephrotoxic.

Ξ , Third generation cephalosporin

Ceftazidime

Ceftriaxone

Cefoperazone

[Feature of antibacterial activity]

- 1. They have strongest active against gram negative bacilli among three generations;
- 2. They have weakest active against Gram-positive cocci among three generations;
- **3.** They are resistant to gram negative bacilli producing broad-spectrum β-lactamase;

- 4. They are effective against Pseudomonas aeruginosa and anaerobic;
- 5. They are used to treat a wide variety of serious infections caused by organisms that are resistant to most other drugs.
- 6 They are no nephrotoxic.

四、Fourth generation cephalosporin

Cefepime

[Feature of antibacterial activity]

- 1. Cefepime is active against Gram-positive cocci , aerobic Gram negative organisms ;
- 2. It is more resistant to chromosomal β-lactamasese and some extended spectrum β-lactamasese ;
- 3. It may be useful in treatment of infection caused by Gram negative bacilli resistance to third generation cephalosporin,

(Adverse effects of cephalosporins)

- 1. Allergy: anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, and hemolytic anemia
- Disulfiram-like effect: accumulation of acetaldehyde
 Bleeding: anti-vitamin K effects

Section 3 Other β-lactams antibiotics

Carbapenems

Monobactams

β-lactamase inhibitors

- Carbapenems

Imipenem

Meropenem

Panipenem

Imipenem

Feature:

- Imipenem resists hydrolysis by most β lactamases.
- 2. It is active against penicillinase-producing gram-positive and gram-negative organisms, anaerobes, Pseudomonas aeruginosa.

- 3. It undergoes cleavage by a dehydropeptidase found in renal tubule to form an inactive metabolite that is potentially nephrotoxic.
- 4. imipenem with cilastatin, a dehydropeptidase inhibitor, protects the parent drug from cleavage
- 5. Imipenem/cilastatin can cause nausea, vomiting, and diarrhea.

二、Monobactams

Aztreonam

Feature:

- 1. It has active against aerobic gram-negative rods
- 2. It lacks activity against gram-positive organisms and anaerobes.
- 3. It may offer a safe alternative for treating patients allergic to penicillins and/or cephalosporins.
- 4. It is relatively nontoxic,

Ξ , β -lactamase inhibitors

Clavulanic acid

Sulbactam

Tazobactam

Feature:

- 1. They do not have significant antibacterial activity
- They protect β-lactam antibiotics by inactivating β-lactamases
- **3.** They are formulated with β-lactam antibiotics to enhance latter antibacterial action
- 4. They have ineffective against bacteria which do not produce β-lactamases.