بسم الله الرحمن الرحيم

Pharmacology of antibacterial drugs
Cell wall inhibitors (part 2)

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2024

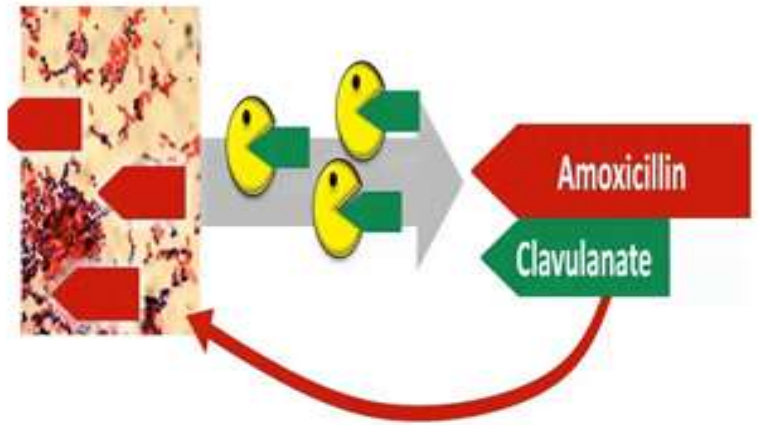
III- Aminopenicillins (broad spectrum penicillins)

Ampicillin & amoxicillin

➢ They are bactericidal for sensitive strains of **both gram positive and gram-negative bacteria.**

➢ They are destroyed by penicillinase enzyme, so, the concurrent administration of **β-lactamase inhibitors (clavulanate** or **sulbactam)** markedly expands the spectrum of activity of these agents (**synergism**).

➢ Oral and parental preparations are available.



Clavulanate, a "suicide inhibitor", is a way to block the bacterial resistance mechanism of β-lactamase

Therapeutic uses of Aminopenicillins

1- **Upper respiratory tract infection** (e.g. strept. tonsillitis, pharyngitis, otitis media, sinusitis ..etc.), and some lower respiratory infections (e.g. lobar pneumonia).

2- **Meningitis**: in combination with Vancomycin and a third-generation cephalosporin as empirical treatment to avoid resistance.

3- **Ampicillin** at high dose is effective also in shigellosis.

4- **Amoxicillin** is used with other drugs for eradication of **H. pylori infections.**

5- Augmentin (**Amoxicillin- clavulanate**) is indicated in treatment of mild cases of **cellulitis and diabetic foot infections.**

N.B. The use of **ampicillin** in treating **typhoid fever** & **Urinary tract infection** is limited now.

IV- Extended spectrum (Anti-pseudomonal) penicillins

carboxypenicillins and ureidopnicillins

➢The carboxypenicillins (**carbenicillin** and **ticarcillin**) and the ureidopenicillins (**mezlocillin** and **piperacillin**) have activity against *Pseudomonas aeroginosa* and certain *proteus* species that are resistant to ampicillin.

➢They are used for treating urinary tract infections and other infections caused by *Pseudomonas* and other gram-negative bacilli.

➢They are sensitive to destruction by β-lactamases. Adding beta lactamase inhibitor (e.g. tazobactam) would decrease bacterial resistance.

β-Lactamase inhibitors

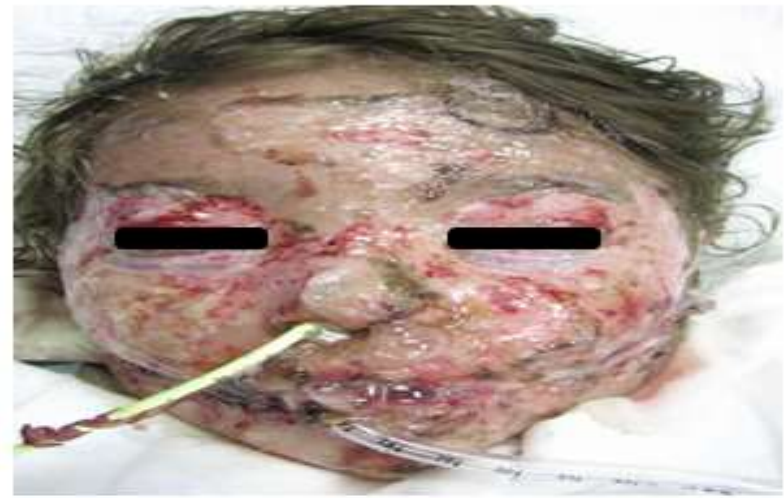
- They inactivate β-lactamases. They are active against plasmid-encoded β-lactamases but not against type I chromosomal β-lactamases induced by gram negative bacilli.
- Examples are **clavulanic acid** and **sulbactam**.
- These compounds are **suicide inhibitors** that **irreversibly** bind to β-lactamases **protecting beta lactam drugs** from hydrolysis & **synergism** occurs.

- **Augmentin = Amoxicillin + clavulanic acid**
- **Unasyn = Ampicillin + sulbactam**
- **Timentin= ticarcillin +Clavulanic acid**
- ***Zosyn= piperacillin+ tazobactam***

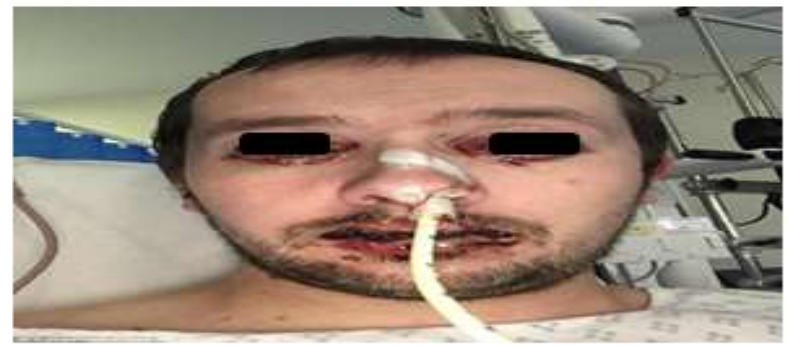
Adverse reactions to penicillins

1-Hypersensitivity reactions:

The reactions may be presented as maculopapular **rash**, **urticarial** rash, **fever**, **bronchospasm**, **vasculitis**, interstitial **nephritis**, serum sickness, **exfoliative dermatitis** and **Steven Johnson syndrome**.



The most serious reactions are **angioedema** (marked swelling of the face, tongue, lips and peri-orbital tissues accompanied commonly by asthmatic breathing) and **anaphylactic shock** (the dramatic scenario of sudden severe hypotension and rapid death). Incidence of anaphylaxis with IM penicillin is **0.05%.**



Stevens–Johnson syndrome

➢**Hemolytic anemia,** and **eosinophilia**, may occur. Drug Reaction with Eosinophilia and Systemic Symptoms (**DRESS**) syndrome is rare with beta lactams but sometimes fatal.

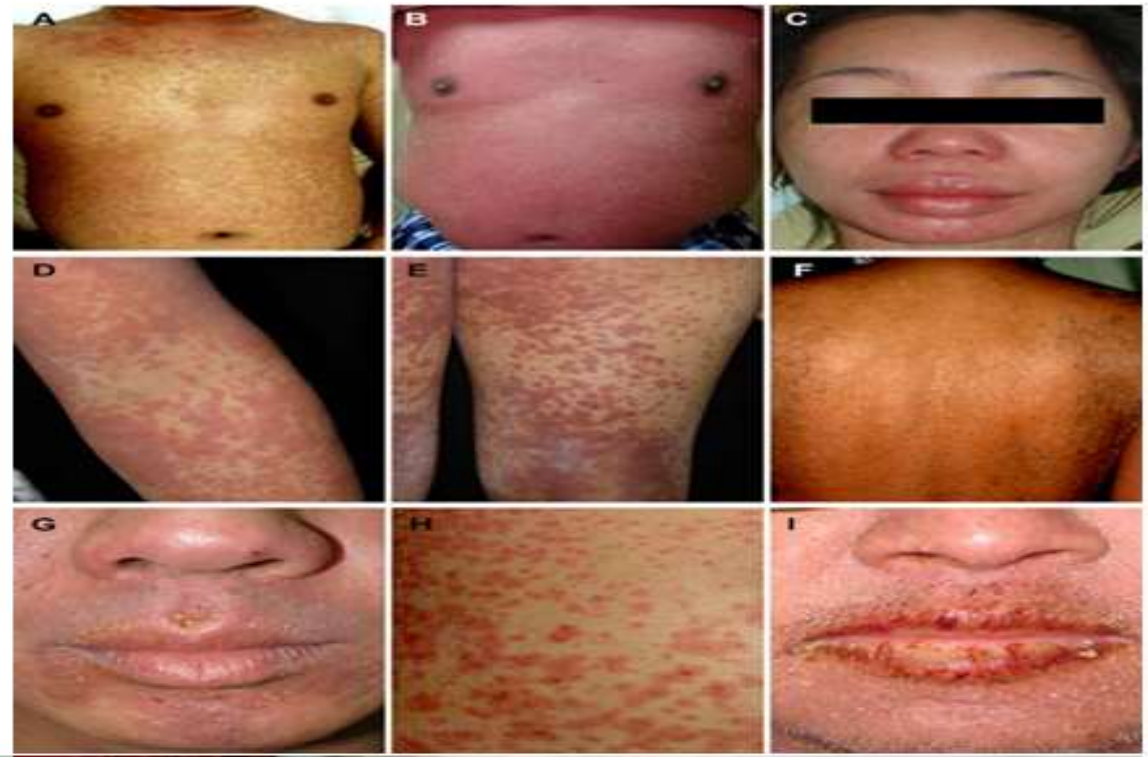
➢The incidence of all allergic reactions is about **0.7-10%** and cross hypersensitivity to the other β-lactams (e.g. cephalosporins, some carbapenems) occurs sometimes.

➢ The reactions may occur **with any dose and dosage form** of penicillin (not dose-dependent but individual dependent).

➢It is not necessary to be preceded by known previous exposure to penicillins as drugs. Unrecognized exposure to penicillin may occur in the environment e.g. in foods of animal origin or from the organisms-producing penicillins.

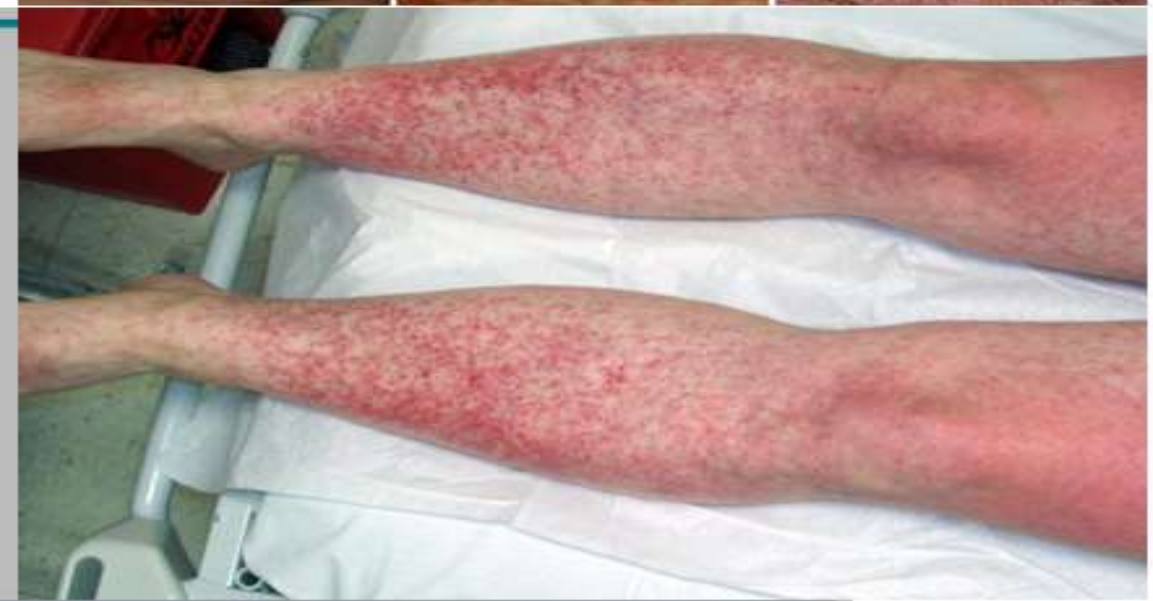
➢Penicillins and their breakdown products (penicilloyl moiety) act as haptens to which antibodies (IgE) are formed.

DRESS syndrome (previously called drug induced pseudo-lymphoma)



Hematologic abnormalities
- Eosinophilia >1500/mm^3
- Presence of atypical lymphocytes

Systemic involvement
- Adenopathies >2 cm in diameter
- Cytolytic hepatitis
- Interstitial nephritis
- Interstitial pneumonitis
- Myocarditis



➢ Taking **history** of hypersensitivity and doing **skin testing** before administration of penicillins can reduce the incidence of these reactions (namely anaphylaxis).

➢If necessary (e.g., treatment of **enterococcal endocarditis** or **neurosyphilis** in a patient with serious penicillin allergy), **desensitization** can be accomplished with gradually increasing doses of penicillin.

2- Jarisch Herxheimer reaction (JHR):

➢JHR is a transient clinical phenomenon that occurs in patients infected by spirochetes who undergo antibiotic treatment.

➢ More specifically, the reaction occurs within 8-24 hours of antibiotic therapy for spirochetal infections, including syphilis, leptospirosis, Lyme disease, and relapsing fever.

- It usually manifests as fever, chills, rigors, nausea and vomiting, headache, tachycardia, hypotension, hyperventilation, flushing, myalgia, and exacerbation of skin lesions.

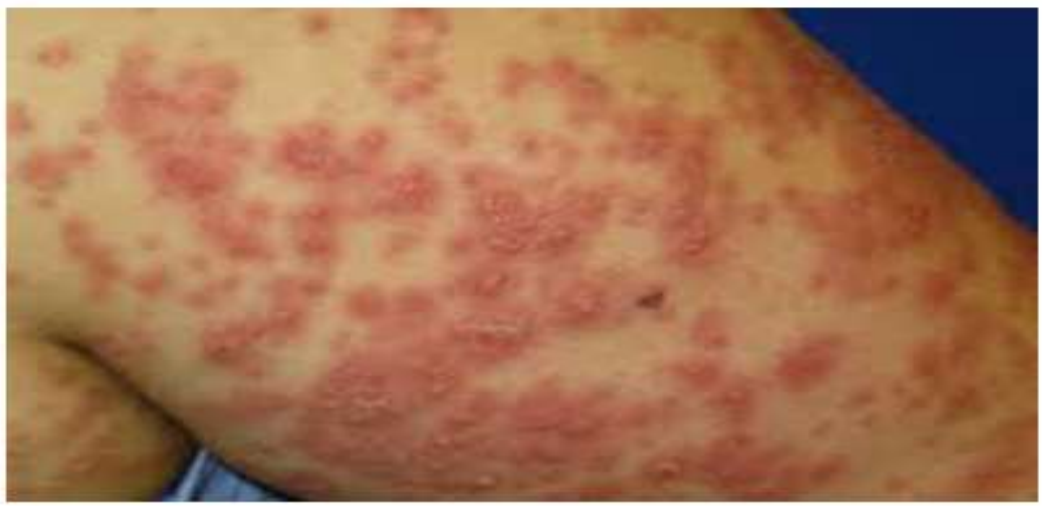
- JHR is an acute, self-limiting condition, which is important to identify in patients and to **distinguish it from allergic reactions and sepsis.**

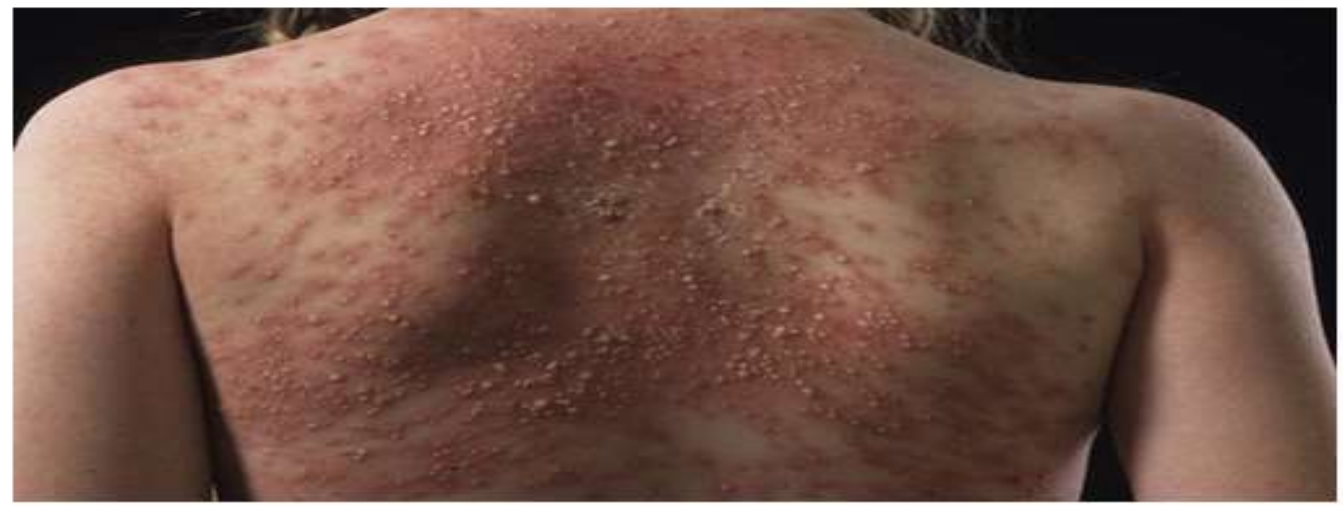
- The breakdown of the spirochete after the use of antibiotics causes the **release of toxins and cytokines** (TNF alpha, IL6 and IL8).

- TNF-alpha antibodies and, in some cases, **steroids** as well can ameliorate the reaction while **paracetamol** of limited efficacy.

3- Acute generalized exanthematous pustulosis (AGEP):

- AGEP, is an uncommon pustular drug eruption characterized by sterile superficial pustules.
- AGEP is usually classified as a **severe cutaneous adverse reaction.**
- Over 90% of cases of AGEP are provoked by medications, most often beta-lactam antibiotics (e.g., penicillins, cephalosporins).
- AGEP is associated with *IL36RN* **gene mutations**.
- These genetic abnormalities make the patient more susceptible to pustulosis when receive certain medications or viral infection.
- Treatment includes supportive care, prevention of the culprit antibiotics and the use of a potent topical steroid.





4- Other adverse effects:

1-Pain and sterile inflammation at the sites of I.M. injections.

2-Nausea, vomiting and diarrhea (dose related when given orally).

3-Carbenecillin may impair platelet aggregation and its sodium salt precipitate heart failure (withdrawn from market).

4-In renal insufficiency, parenteral administration of large doses of penicillin G may produce **seizures.**

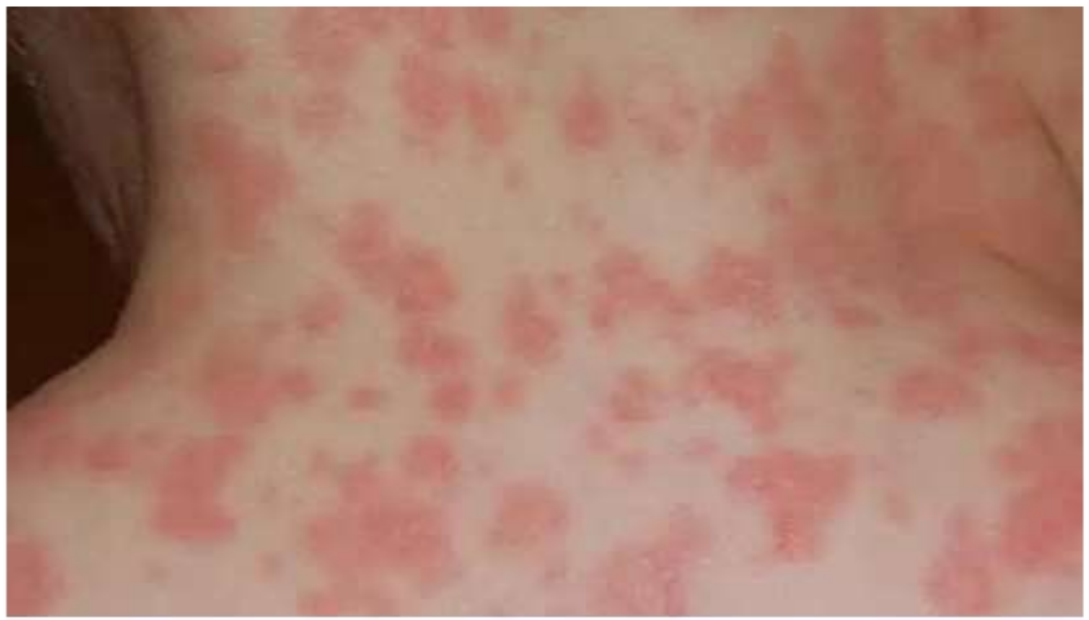
5- Alteration of normal intestinal flora when given by mouth may cause **super-infection** like oral candidiasis or pseudomembranous colitis (clostridial).

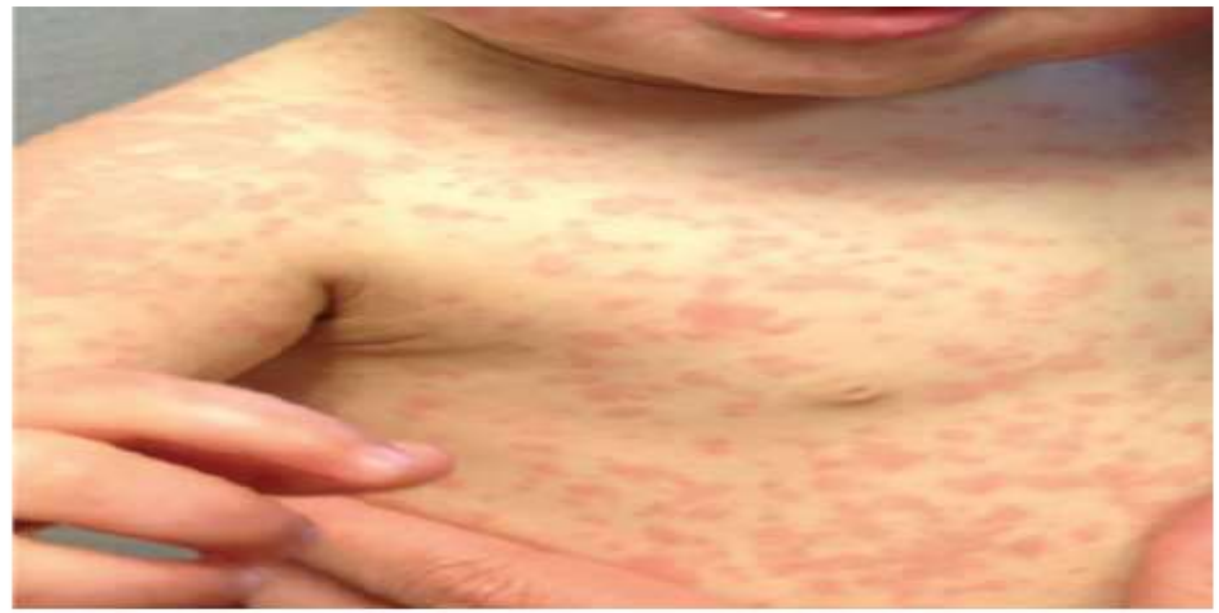
6- Nafcillin can cause neutropenia and nephritis.

7- Oxacillin may cause hepatitis.

8- Amoxicillin related maculopapular rash:

- About 5% to 10% of children will develop a morbilliform rash.
- The amoxicillin -related rash in most cases, is considered a side effect of amoxicillin and not an allergic rash.
- In a small number of cases, the rash will be a sign of an allergic reaction which means the amoxicillin will need to be stopped.





Cephalosporin Members

First generation (Gram positive mainly)

- Oral
  - Cephalexin
  - Cephradine
  - Cefadroxil
- Parenteral
  - Cephalothin
  - Cefazolin

Third generation

(More active against gram negative (Pseudomonas), Resistant to beta Lactamase, Less active against gram positive and anaerobes

- Oral
  - Cefixime
  - Cefpodoxime proxetil-
  - Cefdinir-
  - Cefditoren-
  - Ceftibuten-
  - Cefetamet pivoxil –
- Parenteral
  - Cefotaxime -
  - Ceftizoxime-
  - Ceftriaxone-
  - Ceftazidime –
  - Cefoperazone-

Second generation (Positive, Negative, Anaerobes, Not active against Pseudomonas, Least commonly used)

- Oral
  - Cefaclor
  - Cefuroxime axetil (Prodrug)
  - Cefprozil
- Parenteral
  - Cefuroxime – Crosses BBB
  - Cefoxitin (Cephamycin)-
  - Cefotetan (Cephamycin) -
  - Cefamandole

Fourth generation (Resistant to Beta Lactamase, Parenteral)

- Cefepime-
- Cefpirome –
- Cefozopran-

Fifth generation (Increase in activity against gram positive than fourth generation, Parenteral)

- Ceftobiprole-
- Ceftaroline-

Cephalosporins

Mechanism of action: inhibition of cell wall synthesis (like penicillin).

Classification

a) **First generation**: Examples: cephalexin, Cephradine, cefadroxil, and **cefazolin**. They are active against **gram positive bacteria**

➢**First generation** cephalosprins are excellent agents for **skin** and **soft tissue infections and urinary tract infections** caused by Strept. pyogenes and Methicillin sensitive Staph. aureus.

➢A single dose of cefazoline just **before surgery** is a preferred **prophylaxis** for procedures in which skin flora are possible pathogens.

Pharmacokinetics: They can be used **orally** or I.V. or I.M. (which is painful except cefazolin), they **can't cross to the brain,** and they are excreted unchanged in urine.

b) **Second generation**: Examples: cefaclor, cefuroxime, cefotetan, and cefoxitin, They are not powerful against gram positive, but active against some **gram-negative organisms** like *E coli, Klebsiella, proteus and Hemophilus Influenza* (but not active against pseudomonas). **cefoxitin and cefotetan are active against anaerobes like B. fragilis).**

Uses:

1- Cefoxitin is preferred as a **prophylaxis** in **colorectal surgery**.

2-Cefuroxime is used in community acquired pneumonia.

3- In **respiratory tract infection** (Cefaclor is used in sinusitis, otitis media, etc.,) if there is allergy or resistance to ampicillin).

4- In mixed anerobic infections, gynecological, and pelvic infections. Cefoxitin and cefotetan are used peritonitis caused by B. fragilis. They guard against **sepsis** by intestinal anaerobes.

Third generation: Examples: cefotaxime, cefixime, ceftriaxone, Cefoperazone, and ceftazidime. They are much **more active against gram negative bacteria** than second generation with extended spectrum to include *Enterobacteriaceae*

They are less active than first generation against gram positive cocci.

Cefdinir is an oral third generation cephalosporin

Pharmacokinetics:

- They are used I.V. and I.M. Cefdinir is used orally.
- They are excreted unchanged by the kidney except ceftriaxone & Cefoperazone (excreted mainly in the bile).
- All cross to the brain except Cefoperazone.

Therapeutic uses:

1- Ceftriaxone is the drug of choice in **gonorrhea**.
2- Ceftriaxone, Cefoperazone are used in **typhoid fever.**
3- Treatment of **Shigellosis.**
4-Treatment of **meningitis** (with aminoglycosides, or vancomycin, or other drugs). Cefoperazone is ineffective in meningitis.
5- Treatment of community acquired **pneumonia**.
6- Treatment of **Urinary tract infections**.
7- Serious infections caused by Klebsiella, Enterobacter, Proteus, Hemophilus, Enterobacteriaceae, and other gram negative (either alone or combined with aminoglycosides).

d) Fourth generation: Example: cefepime and cefpirome.

It is like third generation with more **resistance to some β-lactamases.**

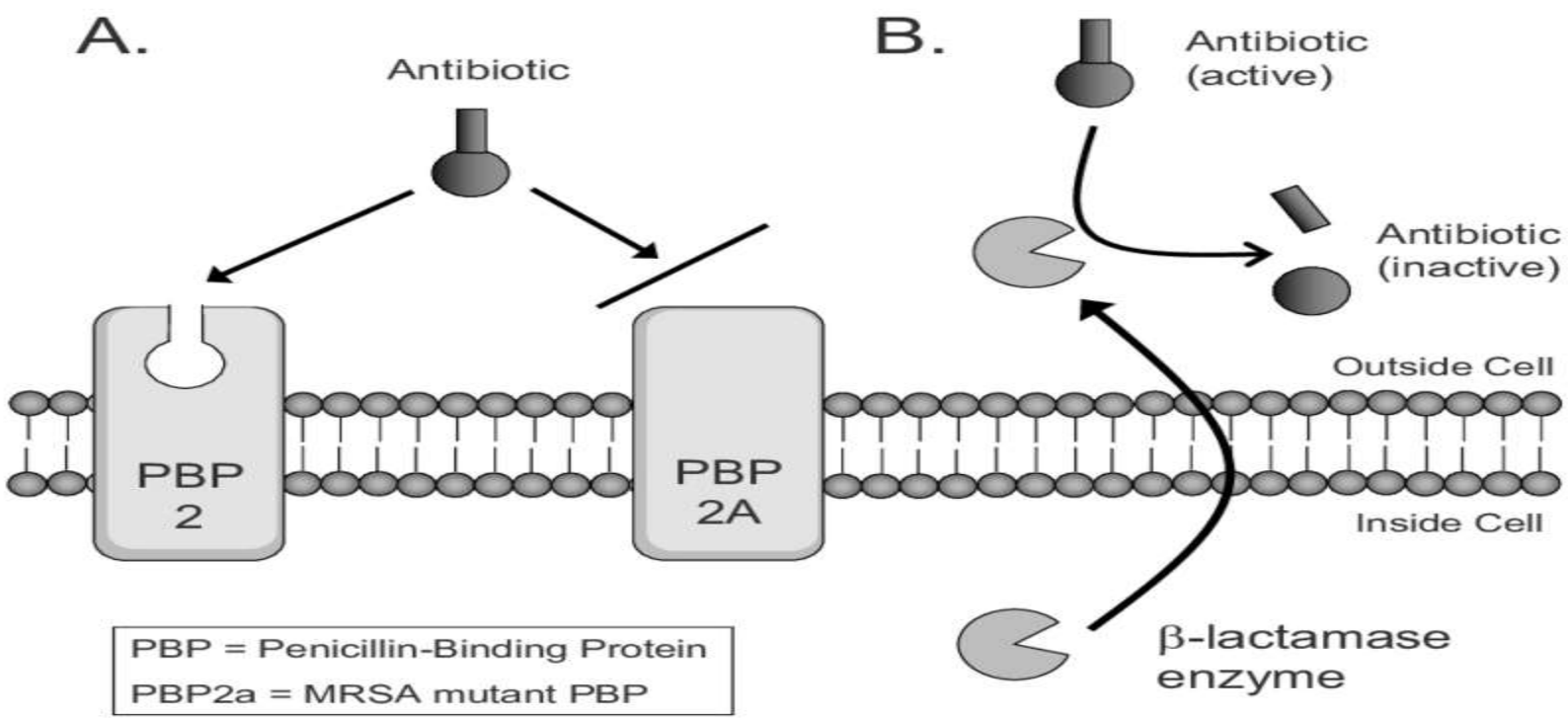
Empirically, cefepime can be used in treatment of **serious infections in hospitalized patients (nosocomial infections)** when *gram positive microorganisms*, *Enterobacteriaceae* and *Pseudomonas* are potential etiologies of infection.

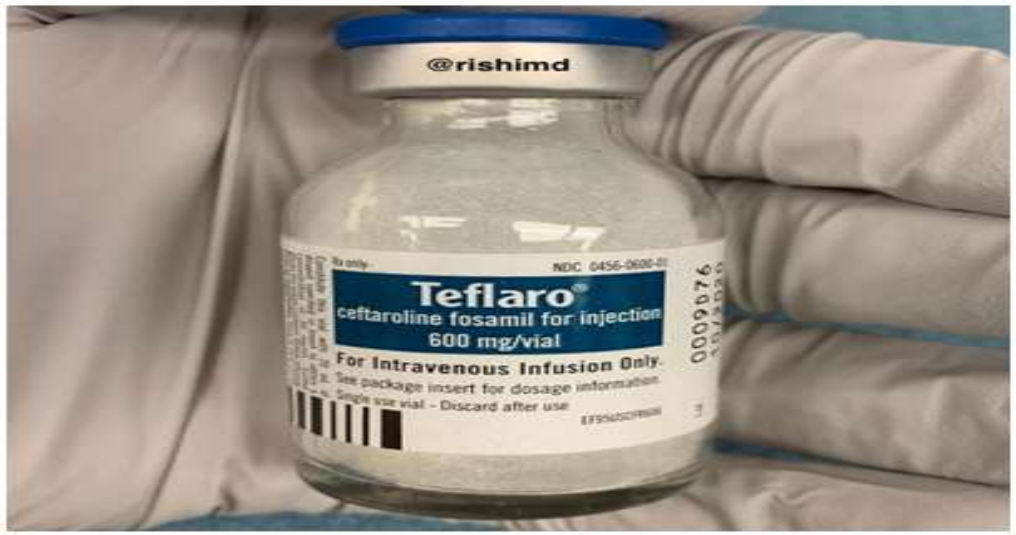
e) Fifth generation: Ceftaroline

Used by IV infusion for treatment of :

1. MRSA and some VRSA (Vancomycin resistant staph aureus) infections.
2. Community acquired pneumonia.
3. Acute bacterial skin and skin structure infections.

Side effects of fifth generation: Headache, allergic reactions and GIT upset.





Ceftaroline has the ability for binding to the penicillin-binding proteins (PBPs), including PBP2a (which confers resistance to MRSA) and PBP2x (which confers resistance to penicillin-resistant S. pneumoniae)

3- Resistance: The following mechanisms are involved:

1. Inability of the antibiotic to reach its site of action.
2. Alterations in penicillin binding proteins (PBP).
3. Destruction by β-lactamases.

➢The first generation is more susceptible to hydrolysis by β-lactamases of *Staph. aureus*.

➢Cefuroxime & cefoxitin of second generation and most third generation cephalosprins are more resistant to β-lactamases of gram-negative bacteria than first generation.

➢Fourth generations are less susceptible to β-lactamases induced by gram negative bacteria.

Combinations of cephalosporins

Ceftazidime + Avibactam

Antipseudomonal third generation cephalosporin + Anti beta lactamase For complicated intra-abdominal infections.

Ceftolozane + Tazobactam

Fifth generation cephalosporins + anti beta lactamase

- **Used for treatment of urinary tract infection.**
- Used with metronidazole for treatment of intraabdominal infections and ventilator associated pneumonia.

Siderophore Cephalosporin

- Siderophores (Greek for "iron bearer") are bacterial products which bind iron and increase its transport to inside bacterial cells.
- A novel cephalosporin called **cefiderocol** is now approved for treatment of **resistant β-lactamase-producing gram-negative organisms.**
- **Cefiderocol** works by **binding penicillin binding proteins**, thus inhibiting cell wall synthesis.
- It differs from other β-lactams, which rely on passive transport across porin channels in a bacterial cell wall, in that **cefiderocol is bound by active iron transporters** and pumped into the bacterial cell at high concentration.
- **Cefiderocol** is active against **aerobic gram-negative organisms**, including drug-resistant **Enterobacteriaceae**, **Pseudomonas** aeruginosa, and **Acinetobacter** baumannii.
- It is not expected to have activity against gram-positive or anaerobic organisms.


Thank
You