

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# **Cell wall inhibitors (2)**

## **Penicillins & cephalosporins**

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# 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  $\beta$ -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  $>1500/\text{mm}^3$

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.



# 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: cefactor, 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** (**Cefactor** 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 **gonorrhoea**.
- 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  $\beta$ -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.

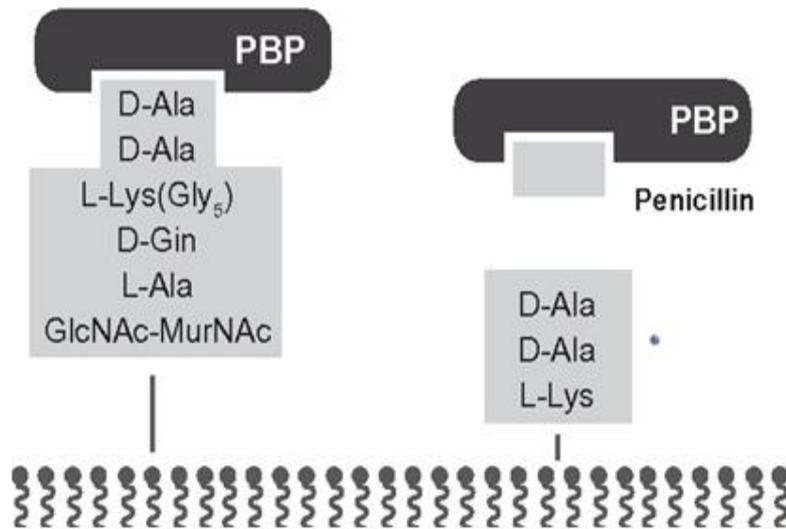
**e) Fifth generation: Ceftaroline**

Used by IV infusion for treatment of :

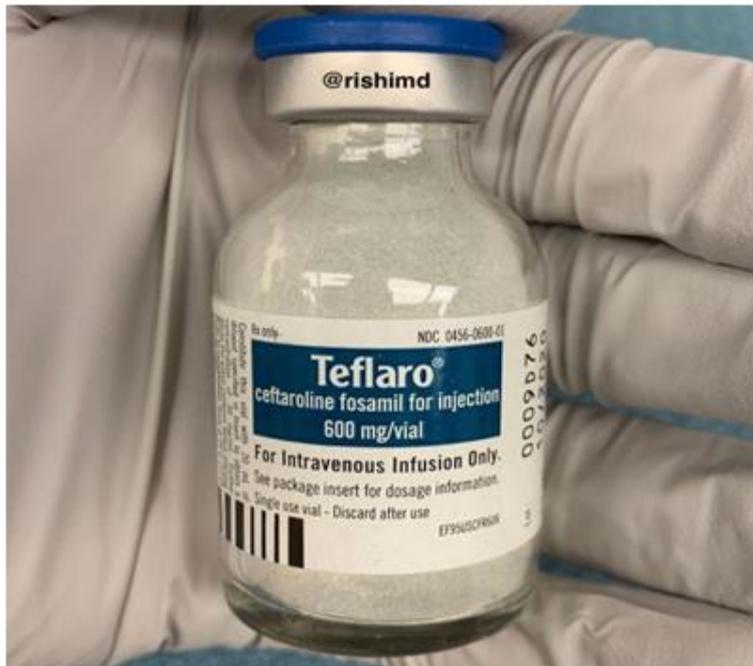
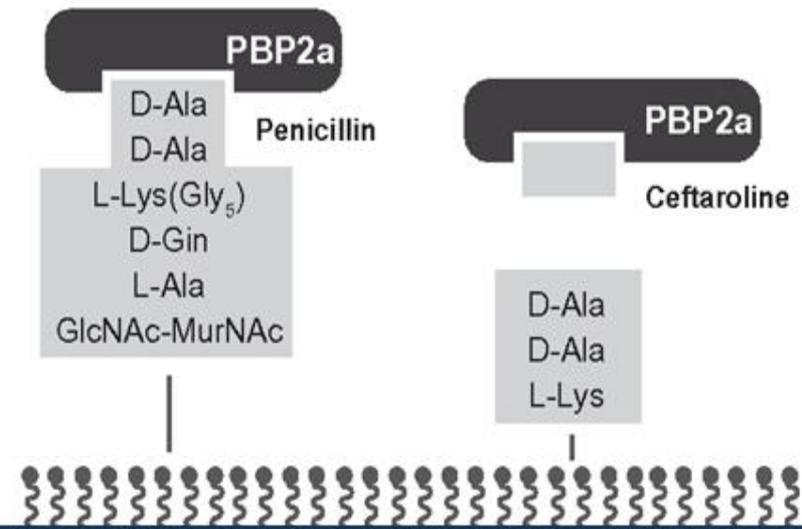
1. **MRSA** and some **VRSA** (Vancomycin resistant staph aureus) infections.
2. Community acquired pneumonia.
3. Acute bacterial skin and skin structure infections.

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

### *S. aureus* with PBP



### MRSA with mutated PBP (PBP2a)



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  $\beta$ -lactamases.

➤ The first generation is more susceptible to hydrolysis by  $\beta$ -lactamases of *Staph. aureus*.

➤ Cefuroxime & cefoxitin of second generation and most third generation cephalosprins are more resistant to  $\beta$ -lactamases of gram-negative bacteria than first generation.

➤ Fourth generations are less susceptible to  $\beta$ -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**.

# Adverse Effects of Cephalosporins

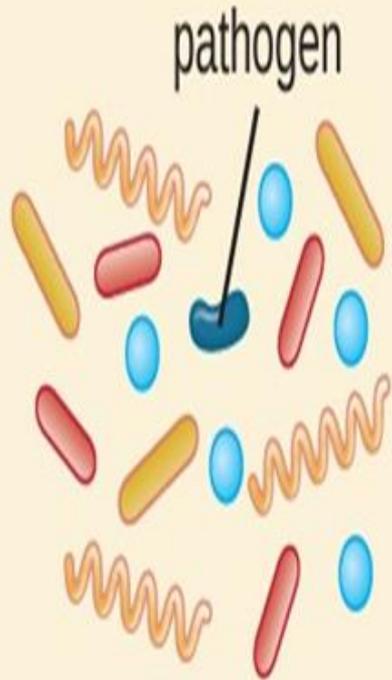
**1- Hypersensitivity reactions** like penicillins including urticaria, bronchospasm and anaphylaxis. Testing for allergy is mandatory before ceftriaxone.

- Because of the similar structures of penicillins and cephalosporins, patients who are allergic to one class of agents may manifest *cross-reactivity* to a member of the other class.
- Patients with a mild or a temporarily distant reaction to penicillin are at low risk of cephalosporin hypersensitivity reactions.
- Patients who had recent severe immediate reaction to penicillin should be given cephalosporin with great caution.

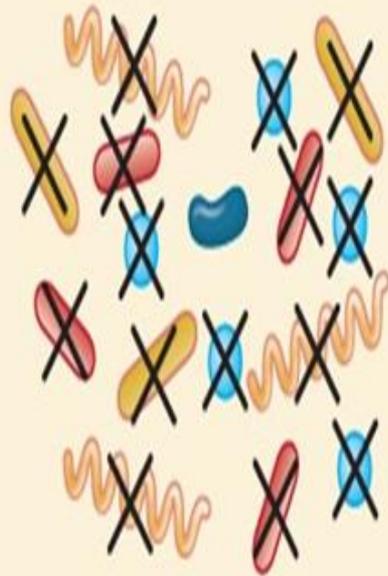
- 2- **Diarrhea** (more with Cefoperazone which is excreted in bile).
- 3- **Bleeding tendency** due to hypoprothrombinemia (**Cefoperazone**, **cefamandole**, and **cefotetan**).
- 4- Some cephalosporins (like **cephalothin**) are **nephrotoxic** especially when combined aminoglycosides. **Nephritis and tubular necrosis** with the third generation is a serious problem.
  - ❑ Cephalosporin- related nephrotoxicity is more in **elderly** patients, in presence of previous **renal dysfunction**, or if the patients use other nephrotoxic drugs as **aminoglycoside**, **vancomycin** or loop **diuretics**.
- 5- **Superinfection:**  
More with the second and third generations as they are broad spectrum and less effective against Staphylococcus, Enterococci and Fungi leading to their overgrowth causing superinfection.  
**cefixime** can cause **pseudomembranous colitis**.

## Antibiotic induced superinfection

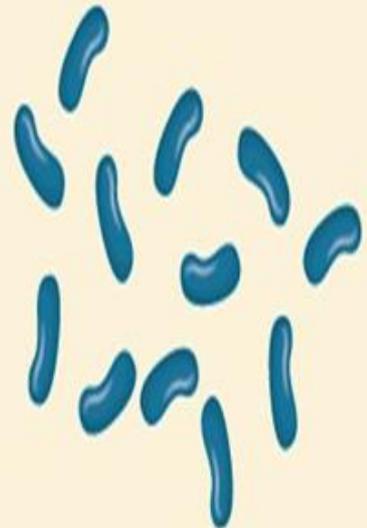
1 Normal microbiota keeps opportunistic pathogens in check.



2 Broad-spectrum antibiotics kill nonresistant cells.



3 Drug-resistant pathogens proliferate and can cause a superinfection.

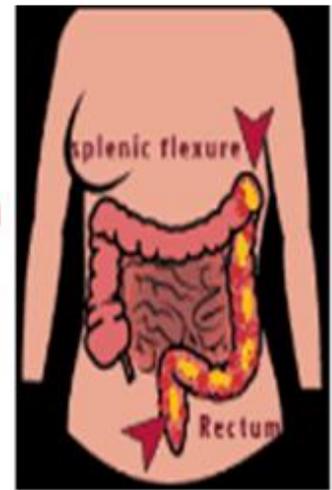




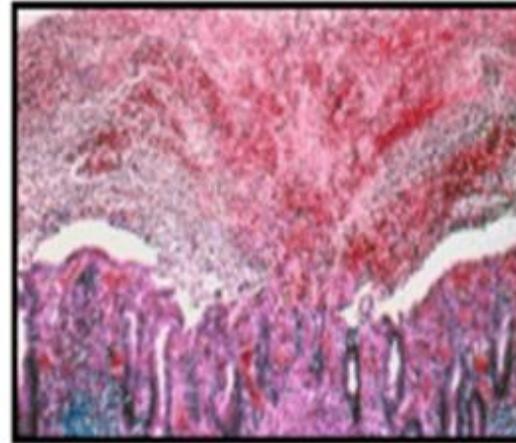
# Pseudomembranous Colitis

Inflammatory condition of the colon

Primarily caused by *Clostridium difficile* infection



Important predisposing factor is prior use of antibiotics

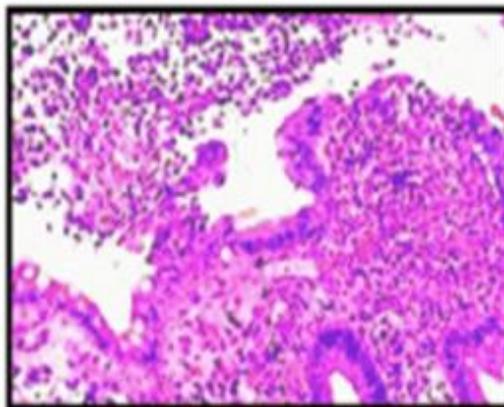


Abdominal pain, diarrhea, fever, leukocytosis

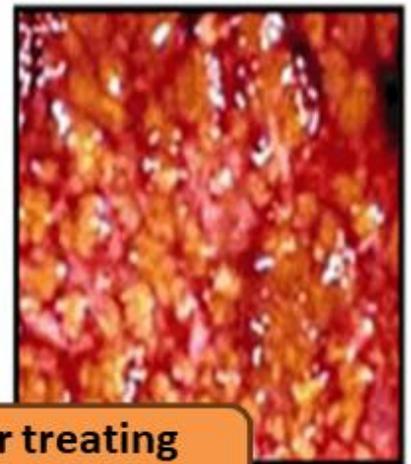
Increased risk of spread in hospitalized patients



Volcanic-like eruption with superficial pseudomembrane formation



Raised yellow-white plaques that coalesce to form pseudomembrane on mucosa



Oral vancomycin or IV metronidazole are used for treating Pseudomembranous colitis

*Thank you*