بسم الله الرحمن الرحيم

Pharmacology
Lecture 29-Anti bacterial drugs (V) cephalosporins and other cell wall inhibitors

Dr. Mohammad Salem Hareedy

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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.**

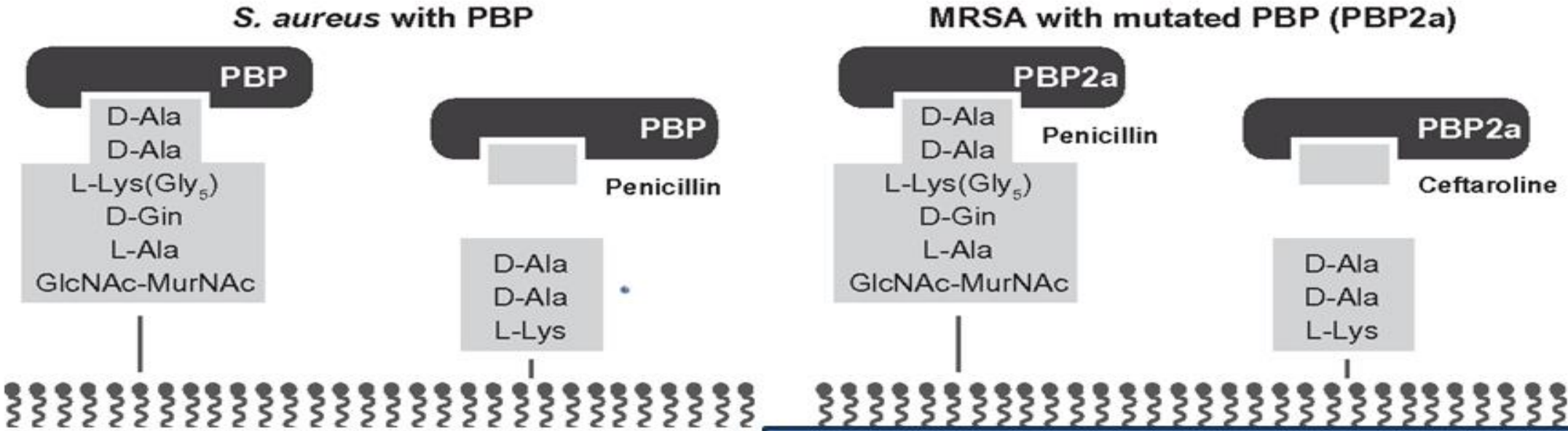
Empirically, cefepime can be used in treatment of **serious infections in hospitalized patients (nosocomial infections)** when *gram positive microorganisms*, *Enterobacteriaceae* and *Pseudomonas* are potential etiologies of infection.

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.

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.

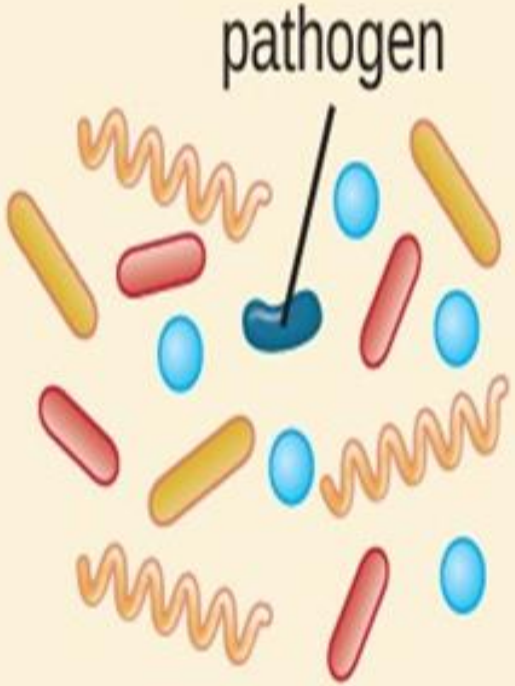
- Cephalosporin- related nephrotoxicity is more in elderly patients, in presence of previous renal dysfunction, or if the patients use other nephrotoxic drugs as aminoglycoside, vancomycin or loop diuretics.

5- Superinfection:

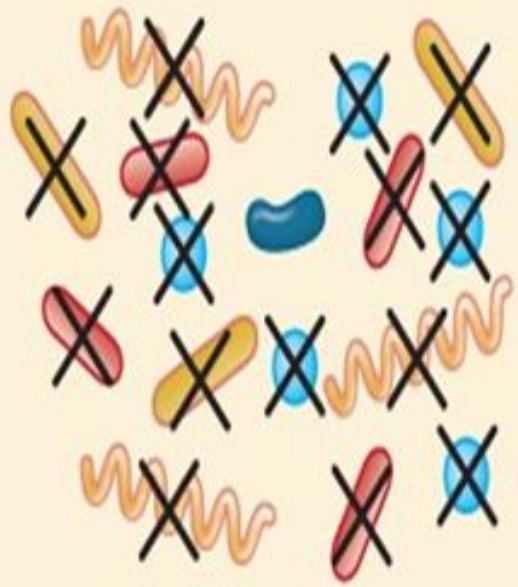
More with the second and third generations as they are broad spectrum and less effective against Staphylococcus, Enterococci and Fungi leading to their overgrowth causing superinfection. cefixime can cause pseudomembranous colitis.

Antibiotic induced superinfection

1 Normal microbiota keeps opportunistic pathogens in check.



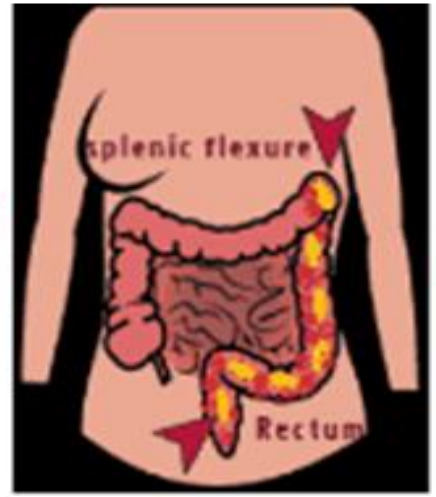
2 Broad-spectrum antibiotics kill nonresistant cells.



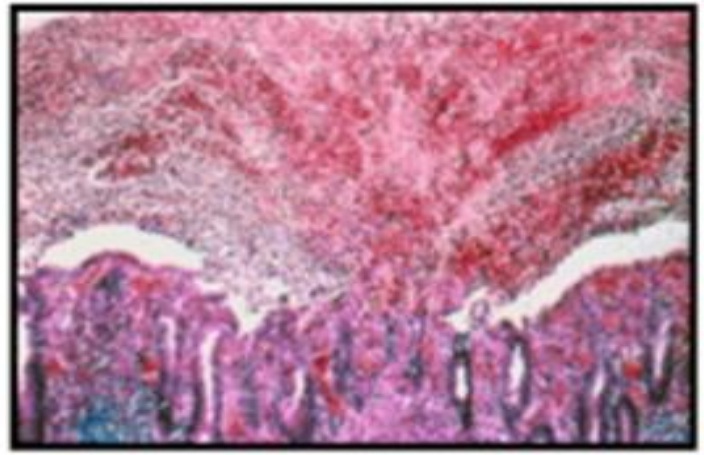
3 Drug-resistant pathogens proliferate and can cause a superinfection.

Pseudomembranous Colitis

Inflammatory condition of the colon
Primarily caused by Clostridium difficile infection



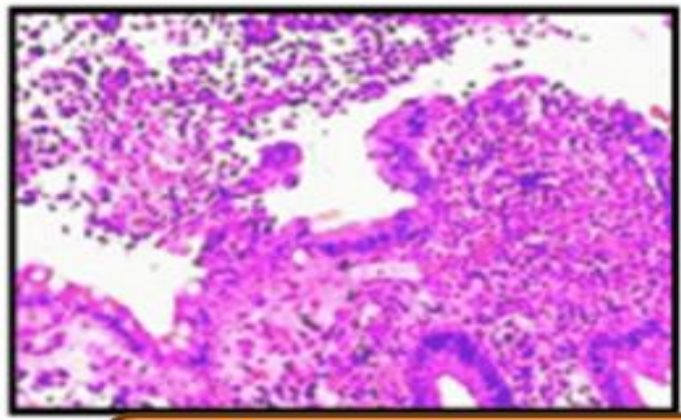
Jmportant predisposing factor is prior use of antibiotics



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

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.

Carbapenems

This class of antibiotics has a broad spectrum of activity than most other β-lactam antibiotics.

1- Imipenem:

- It is marketed in combination with cilastatin, a drug that inhibits the degradation of imipenem by a renal tubular **dehydropeptidase**.

- Like other β-lactam antibiotics, it binds to PBP, disrupt bacterial cell wall synthesis, but it is **very resistant to hydrolysis by most β-lactamases.**

-Anti-microbil activity

It has antibacterial activity against penicillinase producing strains of Staph. aureus but **MRSA** are not susceptible.

Most strains of **Pseudomonas** are inhibited. Activity was excellent against the Enterobacteriaceae but not the carbapenemase-producing strains.

- Pharmacokinetics:

- It is given **i.v.** and is hydrolyzed by dehydropeptidase found in the brush border of the proximal renal tubule. That is why Cilastatin is added.

* Side effects: nausea, **vomiting** and possibly **seizures** (in CNS lesions & renal failure). Patients with penicillin allergy are liable to **allergy** from imipenem also.

Therapeutic uses of imipenem-cilastatin:

1-Urinary tract infection.

2- lower respiratory tract infection.

3- intra-abdominal and gynecological infection.

4- soft tissue, bone and joint infection.

5- Treatment of Cephalosporin-resistant nosocomial infection.

2- Meropenem:

- It does not require cilastatin as it is not sensitive to renal dehydropeptidase.
- It is less likely to cause seizure.
- Similar antimicrobial activity like imipenem with activity against some imipenem-resistant P. aeruginosa. Same therapeutic uses of imipenem.

Monobactam

Aztreonam

- It is a monocyclic β-lactam that differs from other β-lactam antibiotics in that it has antimicrobial activity against gram negative organisms (**like aminoglycosides**) like Pseudomonas aeruginosa, H. influenza & Enterobacteriaceae but no activity against gram positive organisms or anaerobes.
- It is resistant to many β-lactamases except the β-lactamases of Enterobacteriaceae.
- **Patients who are sensitive to penicillins or cephalosporins do not react to aztreonam.**
- **Used in severe infections caused by gram negative bacteria.**

Non-β lactam cell wall inhibitors

1-Glycopeptides (vancomycin and teicoplanin)

Antimicrobial activity:

Vancomycin possesses activity against a broad spectrum of gram-positive bacteria. **It is not effective against gram negative bacilli or mycobacteria.**

Teicoplanin is effective against methicillin susceptible and methicillin resistant staphylococci.

Mechanism of action:

Vancomycin and teicoplanin inhibit the synthesis of the cell wall in sensitive bacteria by binding to **D –alanyl-D-alanine** terminus of cell wall precursor units and block linkage to the glycopeptide polymer within the cell wall. They are **bactericidal** drugs.

Resistance to glycopeptides:

- Vancomycin A-type resistance: Enterococcal resistance to glycopeptides is developed by **substituting a terminal D-lactate for D-alanine**, reducing the binding affinity of vancomycin by 1000 times.
- S. aureus resistance may be intermediate when minimal inhibitory conc. (MIC) required of vancomycin is 4-8 µg/ml or high-level resistance when **MIC ≥ 16 µg/ml** and it may be related to abnormally thick cell wall.

- Pharmacokinetics:

-Vancomycin is poorly absorbed orally, and is usually given I.V., **but not I.M**. On the other hand, teicoplanin can be given I.M. or I.V.

-While vancomycin in circulation is 30 % bound to plasma protein, **teicoplanin is 90-95% bound**.

- Vancomycin has an elimination half-life of about 6 hours while teicoplanin half life is long; about 100 hours. They both depend on the kidney in elimination.

-vancomycin is one of the drugs where **Therapeutic drug monitoring** (TDM) is required

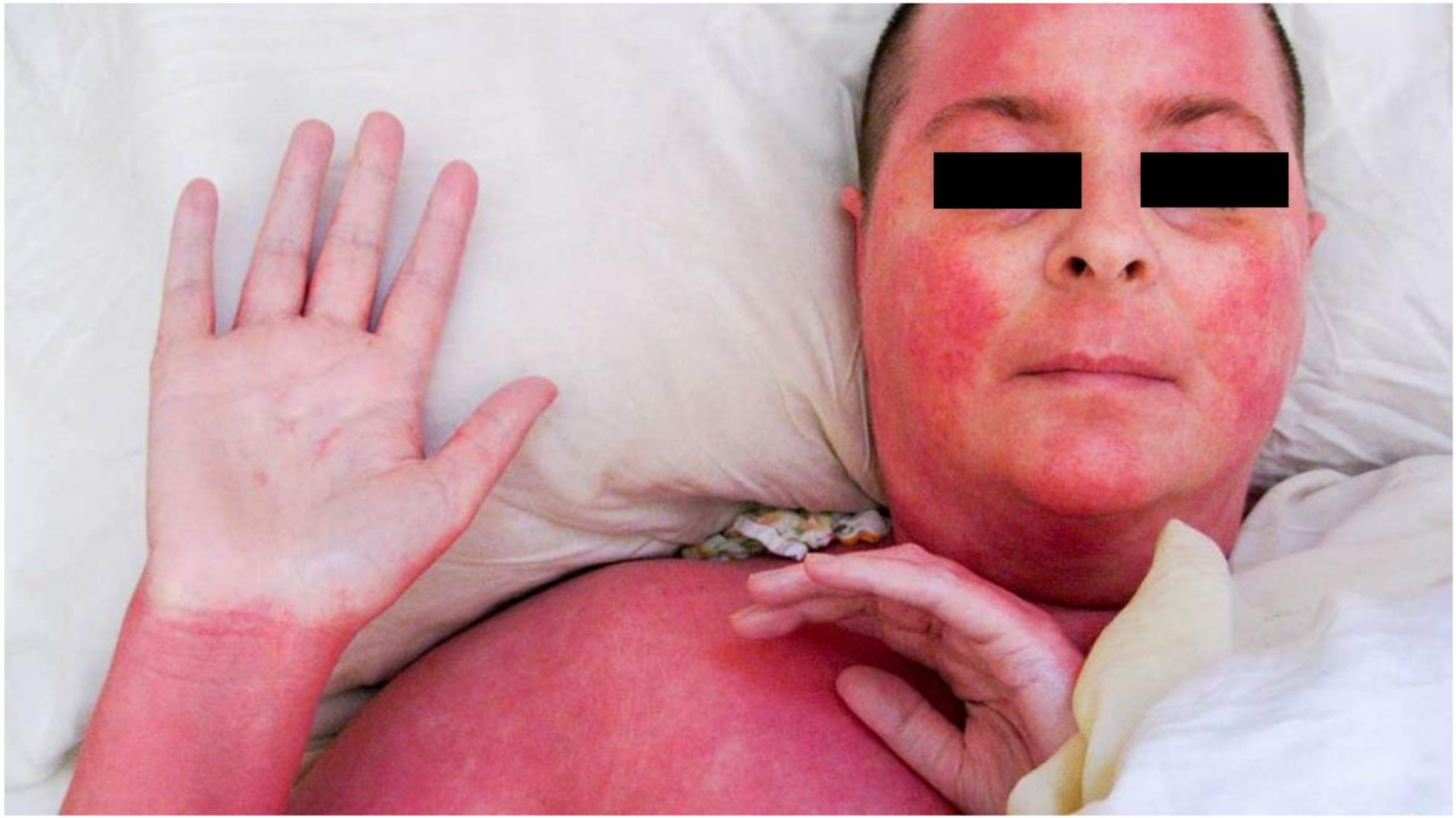
Therapeutic uses:

1. **Pneumonia** when **MRSA** is suspected
2. **Skin, soft tissue, bone and joint infection** especially when **MRSA** is the leading pathogen.
3. **Meningitis** caused by penicillin resistant Streptococcus pneumonia.
4. **Endocarditis** by **MRSA**, enterococci or when patients have severe **penicillin allergy.**
5. **Pseudomembranous colitis** caused Clostridium difficile (Vancomycin is given orally)

Adverse effects:

- **Hypersensitivity** reactions as skin rash and **anaphylaxis**.
- **Red man syndrome**: Rapid I.V. infusion of vancomycin may cause extreme flushing in the body, hypotension, and tachycardia due to a toxic effect of vancomycin on mast cell causing **histamine release**. **It does not occur with teicoplanin.**

- **Nephrotoxicity** especially with trough serum vancomycin concentration > 20 ug/ml.
- **Ototoxicity**



2- Topical cell wall inhibitors

1- Bacitracin

It is polypeptide antibiotic that inhibits bacterial cell wall synthesis.
It is used **topically** for **ophthalmic** and **dermatological** infections with gram positive cocci and bacilli. It is also used by neurosurgeons to irrigate the meninges intraoperatively as an alternative to vancomycin.

2- Mupirocin

It is used **topically** for treatment of **dermatological** infections, like traumatic skin lesions and impetigo caused by Staph. aureus and Strept. pyogenes.

The **nasal ointment** of the drug is used for **eradication of S aureus nasal carriage**

3- Fosfomycin

- Fosfomycin is a bactericidal agent that inhibits cell wall synthesis.
- It is used for the treatment of uncomplicated cystitis by E coli and Enterococcus faecalis.
- Little cross-resistance between Fosfomycin and other antibiotics exists.
- It is excreted unchanged in the urine, and concentrations remain high for 24-48 hours after a single dose of 3 grams.

Common side effects include diarrhea, nausea, headache, and vaginal yeast infections. Severe side effects may include anaphylaxis and *Clostridioides difficile*-associated diarrhea.

Daptomycin

- It is a **lipopeptide antibacterial** drug (bactericidal) used to treat vancomycin resistant gram-positive bacterial infection.
- It binds to bacterial membranes resulting in depolarization, loss of membrane potential and cell death.
- It is given by I.V. route.
- Myopathy is a side effect.


Thank you