بسم الله الرحمن الرحيم

Pharmacology of antibacterial drugs

Cell wall inhibitors (part 3) & Cell membrane inhibitors

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2024

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.

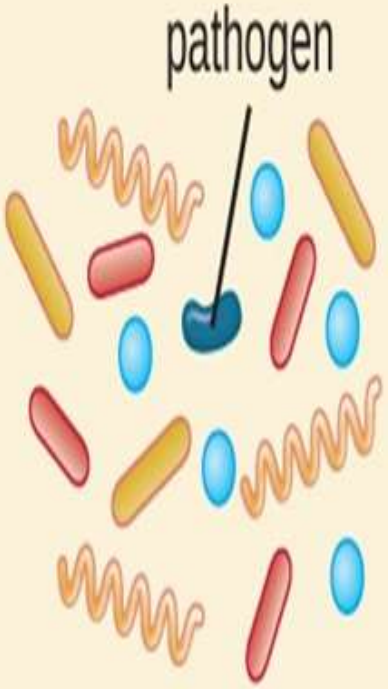
- Cephalosporin- related nephrotoxicity is more in elderly patients, in presence of previous renal dysfunction, or if the patients use other nephrotoxic drugs as aminoglycoside, vancomycin or loop diuretics.

5- Superinfection:

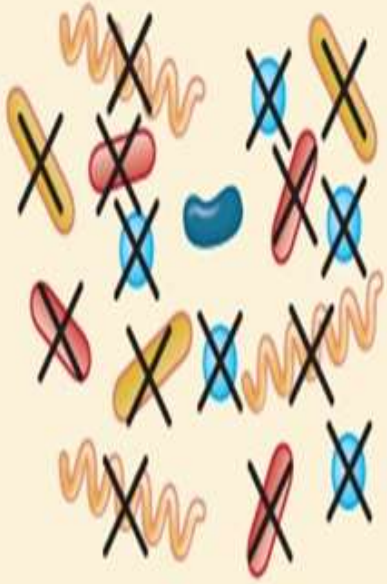
More with the second and third generations as they are broad spectrum and less effective against Staphylococcus, Enterococci and Fungi leading to their overgrowth causing superinfection. cefixime can cause pseudomembranous colitis.

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

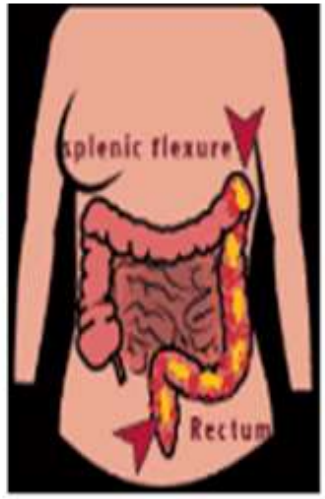
Inflammatory condition of the colon

Primarily caused by Clostridium difficile infection

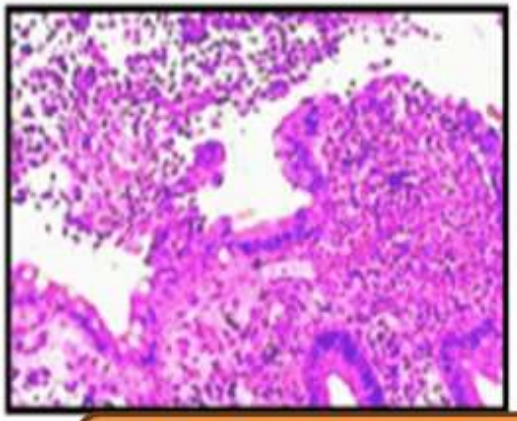
Jmportant predisposing factor is prior use of antibiotics

Increased risk of spread in hospitalized patients

Abdominal pain, diarrhea, fever, leukocytosis



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

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 lactams cell wall inhibitors

1-Glycopeptides

1- Antimicrobial activity:

Vancomycin possesses activity against gram positive bacteria. Strains are considered susceptible at MICs of ≤ 2 µg/ml for S.aureus, ≤ 4 µg/ml for S.epidermidis, and ≤ 1 µg/ml for streptococci. **It is not effective against gram negative bacilli or mycobacteria.**

Teicoplanin is effective against methicillin susceptible and methicillin resistant staphylococci which have MICs of 4 µg/ml.

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.

- 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

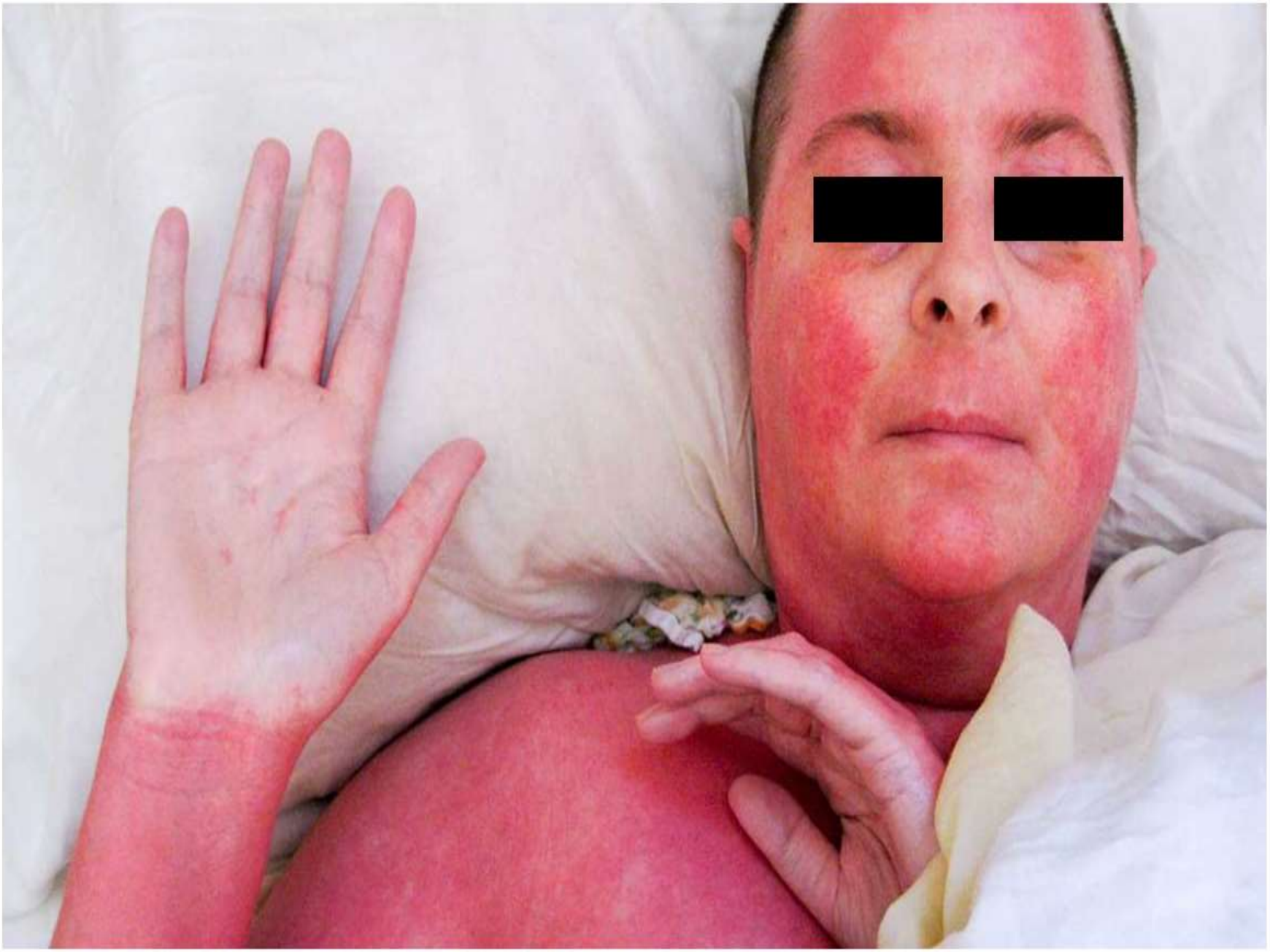
Therapeutic uses:

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.

4- Miscellaneous cell wall inhibitors

A- Cycloserine: **inhibits mycobacterial cell wall synthesis** and used with other drugs for treatment of tuberculosis.

B- Tunicamycin is a natural antibiotic consists of mixture of nucleosides that inhibit glycoprotien synthesis (thus inhibit cell wall synthesis **in Gram positive** bacteria and **inhibits viral coating**), it has **antifungal** activity and it **induces endoplasmic reticulum stress** and arrest of cell cycle in different cancers including breast carcinoma.

C- Ramoplanin inhibits early stages of bacterial cell wall.
It is absorbed in the gastrointestinal tract, although it is unstable in the bloodstream, so can be taken only **orally** against **multiple antibiotic-resistant *Clostridioides difficile*** infections of the gastrointestinal tract. Ramoplanin is "particularly useful" in cases *E. faecalis* no matter its sensitivity to Vancomycin.

D- Type B Lantibiotics.

- Lantibiotics produced by Gram-positive bacteria and inhibit peptidoglycan biosynthesis in other Gram-positive bacteria.
- They are active in very low concentrations.
- Lantibioics have become attractive candidates for use in **food preservation** (by inhibiting pathogens that cause food spoilage) and the **pharmaceutical industry** (to prevent infections in humans or animals).

Antibacterial drugs inhibiting bacterial cell membrane functions

1-Polymyxins

Mechanism of action: polymyxins **disrupt both the outer and inner bacterial membranes.**

The combination (**trimethoprim/polymyxin**) broaden the effective spectrum of polymyxin. It is used for **topical treatment of acute bacterial conjunctivitis.**

- Polymyxins B are **not absorbed from the gastrointestinal tract**, so they are only administered orally if the goal is to disinfect the GI tract.

- For systemic effects; the **intravenous or inhalation** routes are used.
- They are also used externally as a **cream or drops** to treat **Otitis externa** (swimmers ear), and to treat and prevent **skin infections.**

- Polymyxin antibiotics are relatively neurotoxic and nephrotoxic, so are usually used only as a last resort if other antibiotics are ineffective or are contraindicated.

- Typical uses are for infections caused by strains of multiple drug-resistant Pseudomonas aeruginosa or carbapenemase producing Enterobacteriaceae.

- Polymyxins have less effect on Gram-positive organisms.

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