Major Cell Wall Synthesis Inhibitors

1. **Beta-Lactams**
    - Types: Penicillins, cephalosporins, monobactams, and carbapenems.
    - Mechanism: Block formation of the peptidoglycan layer.
    - Structure: Common beta-lactam ring, labile to hydrolysis.
    - Action: Bactericidal, active only against growing cells; variable spectrum.
2. **Glycopeptides**
    - Examples: Vancomycin and teicoplanin.
    - Mechanism: Disrupt assembly of the peptidoglycan precursor lipid II.

Chemistry of Beta-Lactam Antibiotics

- **Basic Structure of Penicillins**: Thiazolidine ring (A) connected to a beta-lactam ring (B) with an attached side chain (R).
    - **Beta-Lactam Ring**: Responsible for biological activity, targeted by penicillinase.
    - **Side Chain (R)**: Cleaved by amidase to create 6-aminopenicillanic acid, allowing for new side chains in semi-synthetic penicillins.

Mechanism of Action of Penicillins

- **Bactericidal Effect**: Inhibits cell wall synthesis in growing bacteria.
- **Bacterial Cell Wall Structure**: Glycopeptides linked by peptide bridges.
- **Penicillin Binding Proteins (PBPs)**: Sites for transpeptidases in the periplasmic space.
- **Trans-Peptidation Reaction**: Provides cell wall rigidity; inhibition leads to bacterial death.

Mechanisms of Resistance to Penicillins

1. **Enzymatic Hydrolysis**: Bacteria produce beta-lactamases to destroy beta-lactams.
2. **Limited Penetration**: Drug cannot reach PBPs, especially in Gram-negative bacteria.
3. **Efflux Pumps**: Actively remove the antibiotic from action sites.
4. **Altered PBPs**: Decreased affinity for beta-lactams.
5. **Intrinsic Resistance**: Seen in bacteria without cell walls, like Mycoplasma.

Types of Penicillins

1. **Narrow Spectrum (Natural) Penicillins**:
    - Examples: Penicillin G (benzyl penicillin), Penicillin V (phenoxymethyl penicillin).
    - Active Against: Gram-positive cocci; ineffective against most Staphylococcus aureus strains.
2. **Penicillinase-Resistant Penicillins (Anti-Staph)**:
    - Examples: Methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin.
    - Spectrum: Narrow; active against staphylococci producing penicillinase (not MRSA).
    - Ineffective Against: Gram-negative bacteria and bacilli.
    - Combinations: (flucloxacillin+amoxicillin),(dicloxacillin and ampicillin)
    - For MRSA we use vancomycin or linezolid
3. **Broad Spectrum Penicillins (Aminopenicillins)**:
    - Examples: Ampicillin, amoxicillin.
    - Activity: Gram-positive cocci and some Gram-negative bacteria like H. influenzae, E. coli.
    - Can be taken orally or parentally
    - They are destroyed by penicillinase
    - Often Combined With: Beta-lactamase inhibitors (e.g., clavulanate or sulbactam).
    - **Therapeutic uses of Aminopenicillins:**
        1. Therapeutic uses of Aminopenicillins
        2. Upper respiratory tract infection (e.g. strept. tonsillitis, pharyngitis, otitis media, sinusitis ..etc.), and some lower respiratory infections (e.g. lobar pneumonia).
        3. Meningitis: in combination with Vancomycin and a third-generation cephalosporin as empirical treatment to avoid resistance.
        4. Ampicillin at high dose is effective also in shigellosis.
        5. Amoxicillin is used with other drugs for eradication of H. pylori infections.
        6. Augmentin (Amoxicillin- clavulanate) is indicated in treatment of mild cases of cellulitis and diabetic foot infections.
        7. N.B. The use of ampicillin in treating typhoid fever & Urinary tract infection is limited now.
    - Combinations:
        1. Augmentin = Amoxicillin + clavulanic acid
        2. Unasyn = Ampicillin + sulbactam
4. **Extended Spectrum Penicillins (Anti-Pseudomonal)**:
    - Examples: Carbenicillin, mezlocillin, piperacillin, ticarcillin.
    - Activity: Includes Pseudomonas, Enterobacter, and Proteus species.
    - They are destroyed by penicillinase
    - Often Combined With: Beta-lactamase inhibitors (e.g., tazobactam).
    - They are used for treating UTI and other infections caused by pseudomonas and other gram negative bacteria.

1.Natural Penicillins

Pharmacokinetics of Natural Penicillins

- **Penicillin G**:
  - Not used orally; given IV/IM due to acid lability.
  - Short half-life, requiring frequent dosing.
  - Excretion: Mainly renal; probenecid prolongs duration by inhibiting renal secretion.
  - Repository forms (e.g., benzathine) used for long-lasting effects (e.g., monthly for rheumatic fever).
- **Penicillin V**:
  - Stable in acidic conditions, suitable for oral administration.
  - Short-acting, needing frequent dosing.

Therapeutic Uses of Penicillin G

1. Pneumococcal infections (pneumonia, meningitis).
2. Streptococcal infections (e.g., pharyngitis, rheumatic fever prevention).
3. Meningococcal infections (acute meningitis).
4. Gonococcal infections (alternative: ceftriaxone).
5. Anaerobic infections (e.g., brain abscess).
6. Syphilis and diphtheria carrier state.
7. Clostridial infections (gas gangrene) and anthrax.

Chemoprophylaxis with Penicillin G

- **Rheumatic Fever Prevention**: Monthly IM injection of benzathine penicillin G.
- **Other Prophylaxis**: For syphilis contacts, and bacterial endocarditis prevention in rheumatic valve disease patients.

Penicillin and Aminoglycoside Combination

- **Synergistic Effect**: Cell wall inhibitors (penicillins) facilitate aminoglycoside entry into bacterial cells.

Adverse Reactions to Penicillins

1. **Hypersensitivity**:
    - Includes rash, fever, bronchospasm, vasculitis, interstitial nephritis, and anaphylaxis.
    - Serious reactions: Angioedema and anaphylactic shock.
    - DRESS Syndrome (Drug-Induced Pseudo-Lymphoma)

      • Characteristics: Potentially life-threatening hypersensitivity reaction.

      • Features include eosinophilia (>1500/mm³), atypical lymphocytes, and systemic involvement: Enlarged lymph nodes (>2 cm). Hepatitis, nephritis, pneumonitis, myocarditis. Skin manifestations like rash, redness, or swelling.

      • Incidence & Causes: Rare with beta-lactam antibiotics but can occur. Independent of dose or dosage form; depends on individual susceptibility.

      • Prevention: Skin testing before administration in hypersensitive patients.

      • Trigger Factors: Unrecognized environmental exposure to penicillin in food or organisms.

2. **Jarisch-Herxheimer Reaction (JHR)**:
    - Occurs in response to spirochete infection treatment (e.g., syphilis).
    - Symptoms: Fever, chills, hypotension; self-limiting.
    - Caused by spirochete breakdown and toxin release.
3. **Acute Generalized Exanthematous Pustulosis (AGEP)**:
    - Rare pustular reaction, mostly due to beta-lactams.
    - Linked to genetic mutations
    - Treatment: Supportive care and discontinuation of the offending drug.
4. **Other Adverse Effects**:
    - Injection site pain, GI upset, seizures in renal insufficiency, and super-infections (e.g., oral candidiasis).
    - Specific Drugs: Nafcillin may cause neutropenia and nephritis; oxacillin may cause hepatitis. carbenecillin may impair platelet aggregation
    - Amoxicillin-associated rash: Often benign, but may indicate allergy in rare cases

Cephalosporins Overview

Mechanism of Action

- Inhibits bacterial cell wall synthesis (similar to penicillin).

Classification and Generations

1. **First Generation**
    - **Examples:** Cephalexin, Cephradine, Cefadroxil, Cefazolin.
    - **Activity:** Effective against gram-positive bacteria (e.g., *Streptococcus pyogenes*, *Methicillin-sensitive Staphylococcus aureus*).
    - **Uses:**
        - Skin, soft tissue infections, and UTIs.
        - Cefazolin is preferred for pre-surgical prophylaxis (single dose).
    - **Pharmacokinetics:**
        - Administered orally, IV, or IM(which is painful except cefazolin); excreted in urine; does not cross the blood-brain barrier.

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2. **Second Generation**
    - **Examples:** Cefaclor, Cefuroxime, Cefoxitin, Cefotetan.
    - **Activity:** Effective against some gram-negative organisms (e.g., *E. coli*, *Klebsiella*, *Proteus*, *H. influenzae*), and cefoxitin and cefotetan are active against anaerobes like B. fragilis).They are not powerful against gram positive
    - **Uses:**
        - Prophylaxis in colorectal surgery (Cefoxitin).
        - Community-acquired pneumonia (Cefuroxime).
        - Sinusitis, otitis media (Cefaclor).
        - Pelvic, gynecological, and peritonitis infections. (Cefoxitin and cefotetan)

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3. **Third Generation**
    - **Examples:** Cefotaxime, Cefixime, Ceftriaxone, Cefoperazone, Ceftazidime.

- **Activity:** Broader gram-negative coverage (*Enterobacteriaceae*); limited activity against gram-positive cocci.
- **Pharmacokinetics:**
  - IV, IM; Cefdinir is oral.
  - Most are excreted renally, except Ceftriaxone and Cefoperazone (biliary excretion).
  - All cross to the brain except Cefoperazone
- **Uses:**
  - Gonorrhea (Ceftriaxone).
  - Typhoid fever (Ceftriaxone, Cefoperazone).
  - Meningitis (except Cefoperazone).
  - Treatment of Shigellosis and Urinary tract infections.
  - Serious gram-negative infections (Klebsiella, Proteus, *H. influenzae*).

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4. **Fourth Generation**
   - **Examples:** Cefepime, Cefpirome.
   - **Activity:** Similar to third generation but with more resistance to beta-lactamases.
   - **Uses:** Empirical treatment for nosocomial infections involving gram-positive, *Enterobacteriaceae*, and *Pseudomonas*.

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5. **Fifth Generation**
   - **Example:** Ceftaroline.
   - **Activity:** Effective against MRSA, some VRSA, and *penicillin-resistant Streptococcus pneumoniae*.
   - **Uses:**
     - MRSA infections.
     - Community-acquired pneumonia.
     - Acute bacterial skin infections.
   - **Side Effects:** Headache, GI upset, allergic reactions.

- 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)

Resistance Mechanisms

1. Inability of the drug to reach its target site.
2. Alterations in penicillin-binding proteins (PBPs).
3. Destruction by beta-lactamases:
    - First generation is more susceptible.
    - Later generations (second, third, fourth) have increasing resistance.

Special Combinations

- **Ceftazidime + Avibactam:** Combines beta-lactamase inhibitor for complicated intra-abdominal infections.

Siderophore Cephalosporin

- **Cefiderocol:**
    - Novel mechanism utilizing bacterial iron transporters.
    - Active against resistant gram-negative organisms (*Enterobacteriaceae*, *Pseudomonas*, *Acinetobacter*).
    - Ineffective against gram-positive or anaerobic organisms.

Adverse Effects of Cephalosporins

1. **Hypersensitivity Reactions**: Similar to penicillins, ranging from mild urticaria to severe anaphylaxis. Cross-reactivity between penicillins and cephalosporins may occur. Testing for allergies is advised before administration.
2. **Diarrhea**: More common with cefoperazone (excreted in bile).
3. **Bleeding Tendency**: Due to hypoprothrombinemia (seen with cefoperazone, cefamandole, cefotetan).
4. **Nephrotoxicity**: Increased risk with elderly patients, renal dysfunction, or concurrent use of nephrotoxic drugs.

5. **Superinfection**: Broad-spectrum cephalosporins (2nd and 3rd generation) may lead to fungal or resistant bacterial overgrowth

   e.g., *C. difficile*, causing pseudomembranous colitis, we treat pseudomembranous colitis with oral vancomycin or IV metronidazole.

Carbapenems

- Broad-spectrum β-lactam antibiotics with high resistance to β-lactamases.
- **Imipenem**: It is given i.v. Combined with cilastatin to prevent renal degradation by dehydropeptidase . Effective against *Pseudomonas* and Enterobacteriaceae but not carbapenemase-producing strains.
- side effects: nausea, vomiting, seizures (in CNS lesions & renal failure). Patients with penicillin allergy are liable to allergy from impenem also.
- Uses: UTIs, respiratory, abdominal, gynecological, bone, and nosocomial infections resistant to cephalosporins.
- **Meropenem**: Similar to imipenem but does not require cilastatin and is less likely to cause seizures.

Monobactams

Aztreonam

- Active against gram-negative bacteria (e.g., *Pseudomonas aeruginosa*), no activity against gram-positive organisms or anaerobes.
- It is resistant to many B-lactamases except the B-lactamases of Enterobacteriaceae
- Safe for patients allergic to penicillins/cephalosporins.

Glycopeptides (Vancomycin, Teicoplanin)

Antimicrobial Activity

- **Vancomycin**: Effective against gram-positive bacteria (*S. aureus*, *S. epidermidis*, streptococci).
    - Ineffective against gram-negative bacilli and mycobacteria.
- **Teicoplanin**: Effective against methicillin-susceptible and resistant staphylococci .

Mechanism of Action

- Inhibit bacterial cell wall synthesis by binding to the *D-alanyl-D-alanine* terminus of precursor units, blocking glycopeptide polymerization.

- **Resistance Mechanisms**:
    - Enterococcal resistance: *D-lactate* substitution reduces vancomycin binding affinity by 1000x.
    - *S. aureus* resistance: Thickened cell wall.

Pharmacokinetics

- **Vancomycin**:
    - Poor oral absorption not IM; administered IV.
    - 30% plasma protein-bound; half-life ~6 hours.
- **Teicoplanin**:
    - Can be given IV or IM.
    - 90-95% protein-bound; long half-life (~100 hours).
- Both drugs are renally excreted.
- **Therapeutic Drug Monitoring (TDM)** required for vancomycin.

Therapeutic Uses

1. MRSA-related pneumonia, skin, soft tissue, bone, and joint infections.
2. Meningitis caused by penicillin-resistant *S. pneumoniae*.
3. Endocarditis (*MRSA*, enterococci, or penicillin-allergic patients).
4. *C. difficile* pseudomembranous colitis (oral vancomycin).

Adverse Effects

1. **Hypersensitivity Reactions**: Skin rash, anaphylaxis.
2. **Red Man Syndrome**: Rapid IV infusion leads to flushing, hypotension, tachycardia (vancomycin-specific).
3. **Nephrotoxicity**: Risk increases with serum concentrations >20 µg/mL.
4. **Ototoxicity**: Can occur, especially at high doses or with prolonged use

Topical Cell Wall Inhibitors

1. **Bacitracin**: Topical use for ophthalmic and dermatological infection with gram-positive infections.used ti irrigate the meninges intraoperatively.
2. **Mupirocin**: It is used topically for treatment of dermatological infections, like traumatic skin lesions and impetigo caused by Staph. aureus and Strept. pyogenes.
3. **Fosfomycin**: Oral use for uncomplicated cystitis caused by *E. coli* or *Enterococcus faecalis*.

   Side effect : diarrhea, nausea, headache , vaginal yeast infection, anaphylaxis, clostridioides difficile associated diarrhea.

Miscellaneous Cell Wall Inhibitors

1. **Cycloserine**: Used in tuberculosis treatment.
2. **Tunicamycin :** it has antifungal activity and it induces endoplasmic reticulum stress and arrest of cell cycle in different cancers including breast carcinoma**.**
3. **Ramoplanin**: Effective against multiple antibiotic-resistant C*. difficile*, used orally.
4. **Lantibiotics**: Natural compounds with activity against gram-positive bacteria, useful in food preservation and infection prevention.

Membrane-Disrupting Antibiotics

1. **Polymyxins**: Effective against multidrug-resistant gram-negative bacteria (*Pseudomonas*, carbapenemase producers).given IV or inhalation. Limited use due to neurotoxicity and nephrotoxicity.
2. **Daptomycin**: Treats vancomycin-resistant gram-positive infections, given IV .It binds to bacterial membranes resulting in depolarization, loss of membrane potential and cell death. Side effect: myopathy

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