Antimicrobials: Drugs that Weaken the Cell Wall

Cell Wall Weakeners

- Beta Lactams
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Aztreonam
- Vancomycin
- Teicoplanin

Bacterial Cell Wall

- Bacterial cytoplasm is hypertonic
  - Tendency to swell and lyse
  - Cell wall is a rigid layer outside the membrane that prevents swelling
- Basic structure:
  - Peptidoglycan polymer chains
  - Crossbridges hold chains together
  - Transpeptidases: bacterial enzymes needed for cell wall synthesis
  - Autolysins: enzymes that break down the cell wall

Penicillin: Basic Method of Action

- Penicillin Binding Proteins (PBPs): Penicillin targets: located on **membrane**
- Inhibits transpeptidases: weakened, abnormal cell wall
- Prevents inhibition of autolysins: destruction of cell wall
- To work, PCNs must
  - Penetrate cell wall
  - Bind to PBP

Bacterial Resistance to PCNs

- Inability of PCN to reach PBP (i.e. inability to penetrate the cell wall, esp gram neg)
- Inactivation of PCN by enzymes (penicillinases and beta-lactamases)
  - Genes for pencillinases are located on both chromosomes and plasmids
- Less common mechanism of resistance to PCN: alteration of PBP structure

PCN Classification

- Most common classification is by spectrum
  - Narrow spectrum
    - Penicillinase vulnerable
    - Penicillinase resistant (anti-staphylococcal)
  - Broad spectrum
  - Extended spectrum

Prototypical PCN

- Pencillin G: first discovered
  - Bacteriocidal to gram + and some gram –
  - Narrow spectrum
  - Penicillinase senstitive (vulnerable)
- Uses:
  - Pneumonia and meningitis (strep pneumo)
  - Strep pyogenes (strep throat, scarlet fever, endocarditis, flesh eating bacteria)
  - Syphillis (Treponema pallidium)

PCN G: Pharmacokinetics

- Availability as salts: potassium, procaine, benzathine
- Absorption
  - PO: no can do; inactivated by gastric acid
  - IM: potassium salt is rapidly absorbed; procaine and benzathine last up to a month but cause low blood levels
  - IV: only potassium salt can be given IV

PCN G: Pharmacokinetics

- Distribution
  - Most tissues
  - Crosses joints, eys, and BBB only with inflammation, e.g. meningitis
- Elimination
  - Through kidneys
  - Adjust dose in renal insufficiency or failure

Side effects and Toxicity

- Least toxic of all antibiotics
  - Most side effects are caused by salt
    - Potassium may cause dysrhythmias
    - Procaine may cause bizarre behavior
- Allergic reaction is the major concern
  - 1% – 10% of population is allergic
  - Mild to life threatening reactions
  - Prior exposure is needed; *occurs naturally
  - Medic alert bracelet

PCN Allergy

- 5% - 10% of PCN allergy is cross-reactive
- Allergy is not to PCN itself, but to breakdown products
- Types
  - Immediate: 2 – 30 minutes
  - Accelerated: 1 – 72 hours
  - Late: days to weeks
- Anaphylaxis is possible (0.02%)

Treatment of Patients with PCN Allergy

- Verify reaction
- Avoid PCN
- Mild reactions: cephalosporins may be tried (5% - 10% cross reactivity)
- Severe reactions: use vancomycin or macrolide
- If no other alternative, desensitization may be tried. Administer with anthistamines; epinephrine on hand PRN

PCN Interactions

- Aminoglycosides: inactivates if mixed in same IV solution with PCN
- Probenecid causes PCN retention in kidneys
- Bacteriostatic antibiotics decrease efficacy of PCN

Other narrow Spectrum PCN

- Penicillin V (aka VK)
  - Same as Penicillin G, but can be given orally
  - May be taken with meals

Narrow Spectrum Penicillinase Resistant PCNs

- Used for staphylococcus
- 90% of staph produces penicillinase
- MRSA: resistance by altering PBPs
- Agents
  - Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin
  - Methicillin (no longer available in U.S.)

Broad spectrum Penicillins (aka Aminopenicillins)

- Same action as Penicillin G plus increased activity against gram-negative bacilli
  - H. influenzae, E. coli, Salmonella, Shigella
  - Penetrate cell wall better
  - Vulnerable to Penicillinase
- Agents
  - Ampicillin
  - Amoxicillin (most popular penicillin)
  - Bacampacillin

Extended Spectrum PCNs

- Activity includes Aminopenicillins plus:
  - Pseudomonus, Enterobacter, Proteus, Klebsiella
  - Vulnerable to penicillinase
  - Primarily used for Pseudomas aeruginosa, often in combo with aminoglycosides (don't mix!)
- Agents
  - Ticarcillin, Carbenicillin indanyl, Mezlocillin, Piperacillin

PCN/beta-lactamse inhibitor Combos

- Enhances action of PCN against penicillinase producing bacteria

- Unasyn: Ampicllin + sulbactam
- Augmentin: Amoxicillin + clavulanic acid
- Timentin: Ticarcillin + clavulanic acid
- Zosyn: Piperacillin + tazobactam

Cephalosporins

- Beta-lactam antibiotics
  - Similar in action to PCN
  - More resistant to Beta-lactamases
  - Broad spectrum
  - Low toxicity
- Mechanism of action
  - Same as penicillin
- Resistance: usually beta-lactamase

Cephalosporin Classifications

- Four Generations: as progress:
  - Increased gram negative activity
  - Decrease gram positive activity
  - Increased resistance to beta-lactamases
  - Increased ability to cross BBB
- See table 81-2 on page 899
- Only one drug currently in fourth generation

Cephalosporin Pharmacokinetics

- 24 Cephalosporins in U.S.
  - 12 can be given PO
  - 2 can be given PO as well as IM/IV
  - Some can be given PO, and some IM/IV
- Distribution: high to most areas; CSF is not reached with generations 1 and 2.
- Elimination: kidney; renal dosing in failure
  - Exception: Ceftriaxone and cefoperazone hepatic elimination

Adverse Effects

- Allergic reactions: maculopapular rash after 2 – 3 days is most common; severe immediate reaction is rare
- Cross reactivity with PCN
- Bleeding: cefmetazole, cefoperazone, cefotetan can interfere with Vit K metabolism
- Thromboplebitis: dilute and infuse slowly to avoid

Cephalosporins: Interactions

- Probenecid: delays renal excretion
- Alcohol: three drugs that interfere with Vit K metabolism may induce ETOH intolerance
- Anti-coagulants

Cephalosporins: Uses

- 1st and 2nd Generation are usually used prophylactically in hospital, not for active infections
- 3rd Generation used for a variety of infections
  - Meningitis, Pneumonia, Nosocomial infections
  - Ceftriaxone especially popular in ER because it can be given one dose IM
- 4th Generation is still being established

Cephalosporin use

- 24 to choose from; how do you choose?
  - Cost, dosing schedule, patient setting
- Recognize:
  - Cephalexin
  - Cefazolin
  - Cefuroxime
  - Cefaclor
  - Ceftriaxone
  - Ceftazidime
  - Cefepime

Carbapenems

- Beta-lactam antibiotics with broadest spectrum; IV or IM only
- Used for mixed infections with anarobes, staph, and gram-negative bacilli
- Agents
  - Imipenem (given with cilastin to prolong effects)
  - Meropenem
  - Ertapenem

Monobactam (a class of one)

- Aztreonam
  - Beta-lactam antibiotic
  - Narrow spectrum: only gram negative bacilli
  - Highly resistant to beta-lactamase

Vancomycin (A drug without class)

- Does not contain beta-lactam
- Used for:
  - MRSA
  - Pseudomembranous colitis (c. diff)
- Poor PO absorption: used for c. diff
- Usually given IV. Low therapeutic range
  - Potentially toxic: ototoxic, thrombophlebitis, nephrotoxicic
  - Must monitor levels
  - Infuse over 60 minutes to avoid histamine reaction

Teicoplanin

- Investigational drug
- A better vancomycin?
  - Active against MRSA
  - Fewer side effects
  - IM injection possible
- Therapeutic niche has not yet been established