the ANTIBIOTICS lecture

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Nothing to disclose …

Agenda

1. Beta Lactams:
    1. Pencillins
    2. Cephalosporins
    3. Carbapenems
    4. Monobactam-Aztreonam
2. Sulfonamide

3. Protein Synthesis Inhibitors
    1. Aminoglycosides
    2. Macrolides
    3. Tetracyclines

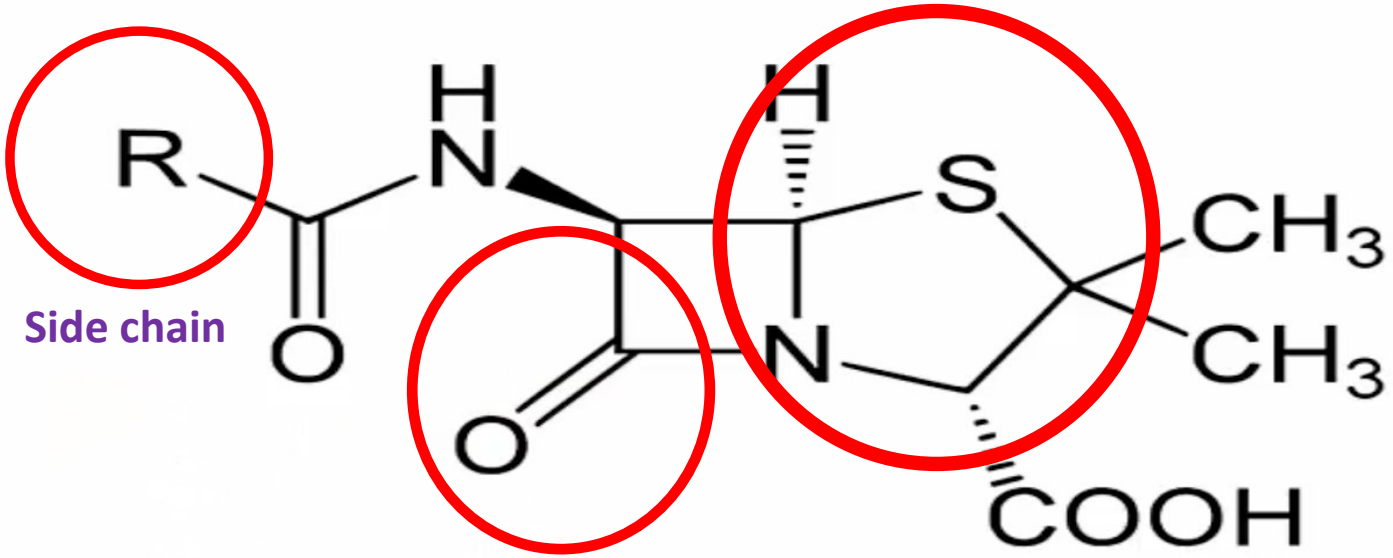
Beta Lactam Antibiotics

1. Penicillins,
2. Cephalosporins,
3. Carbapenems,
4. Aztreonam

PENICILLINS

Penicillins

Thaizolidine Ring:
Penicillin



Side chain

Beta lactam Ring:
Penicillin
Cephalosporins
Carbapenems
Monobactam - Aztreonam

Image courtesy of Wikipedia/Public Domain

Types of PENICILLINS

- Natural
  - Pen G, Pen VK
- Aminopenicillins
  - Amoxicillin, Ampicillin
- Anti Staphylococcus
  - Oxacillin, Nafcillin, Dicloxacillin
- Anti Pseudomonal
  - Piperacillin, Ticarcillin

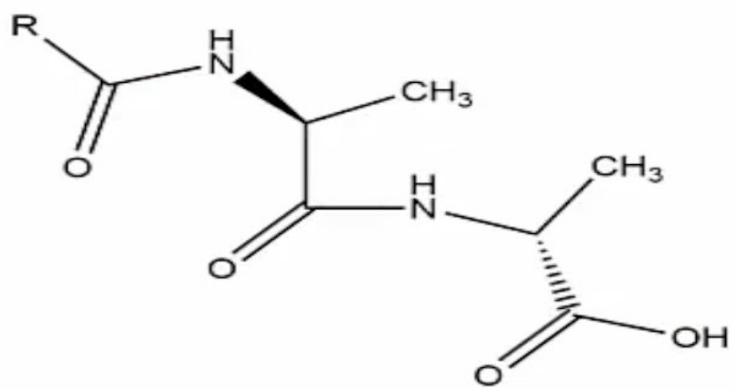
Mechanism of action

- ***Penicillin binding proteins*** >> Inactivates enzymes (D-ala-D-ala)
- Wall breakdown >> Autolysis >> cell death (Bactericidal)

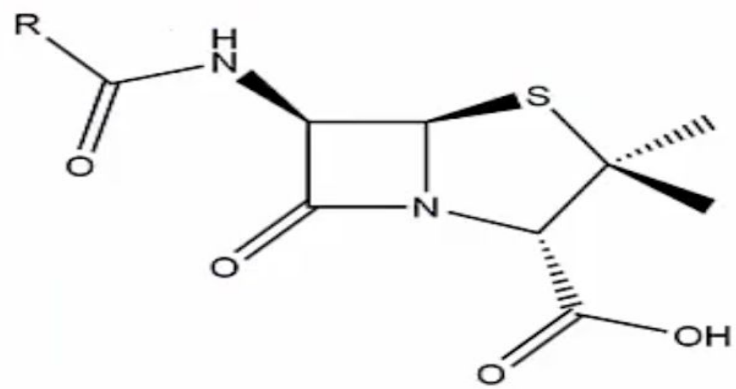
- The same mechanism for all beta lactam antibiotics ☺️

Penicillin

Mechanism of Action



D-Ala-D-Ala Terminus



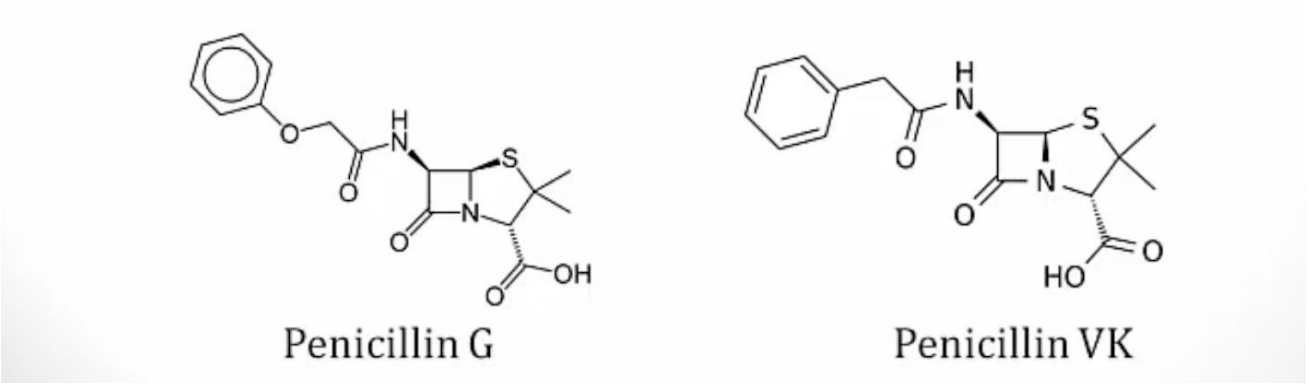
Penicillin

Omargs10/Wikipedia

Natural Penicillins

Fungal !!

- Penicillin G (IM and IV)
- Penicillin VK (oral)
  - Probenecid (Gout drug) >> Inhibits renal secretion PCN >> Boosts PCN levels → co-administered in special circumstances



Penicillin G and VK

Clinical Uses

- *Narrow spectrum* >> few specific modern uses
- Gram positives
  - Strep pyogenes (strep throat)
  - Actinomyces
- Treponema Pallidum (syphilis)
- *Rare* uses (**only in susceptible isolates**)
  - Neisseria meningitides
  - Strep. pneumonia

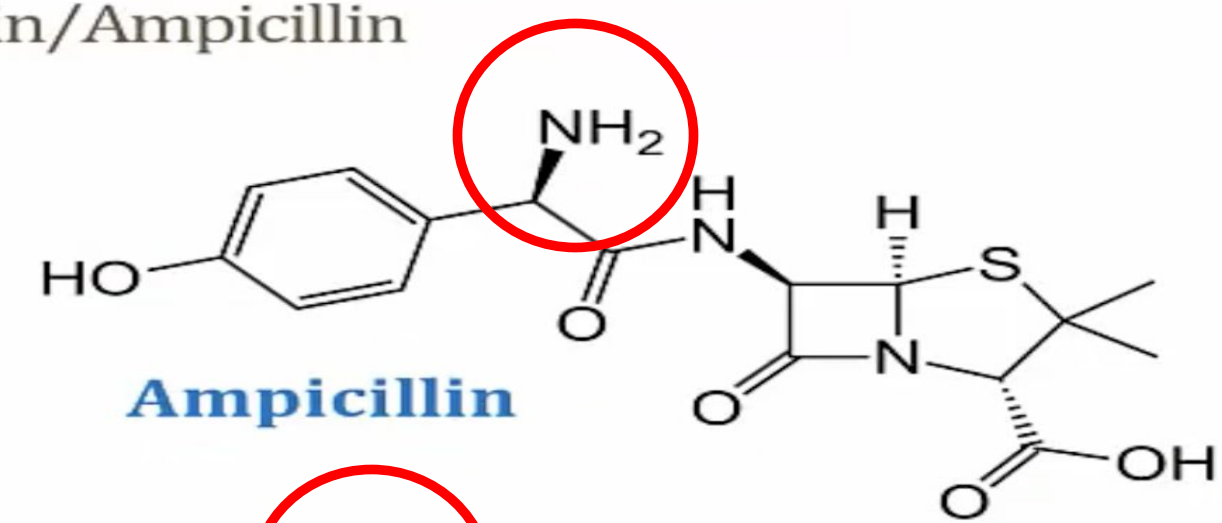
Aminopenicillins

Amoxicillin, Ampicillin

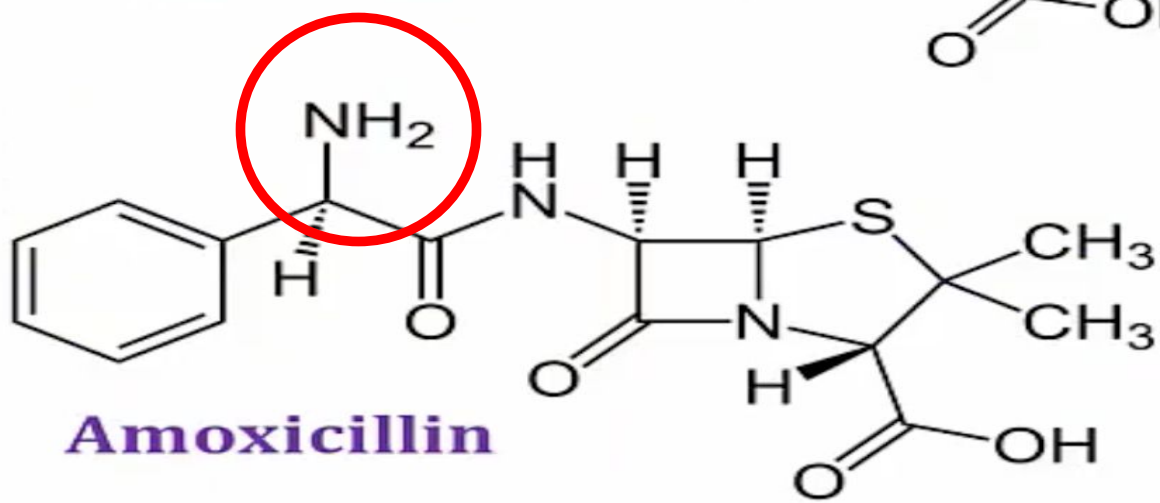
- Amoxicillin (oral)
- Ampicillin (IV) >> Poor bioavailability when given orally
- Penetrate porin channel of gram-negative bacteria
- Sensitive to beta lactamase enzymes
- Covers penicillin bacteria plus some gram negatives

Aminopenicillins

Amoxicillin/Ampicillin



Ampicillin



Amoxicillin

Aminopenicillins

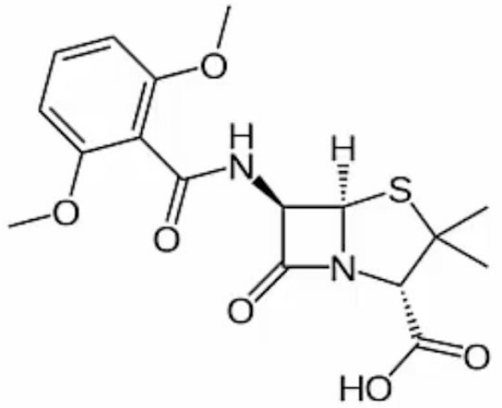
Amoxicillin, Ampicillin

- Bacterial
  - H. Influenza, E. Coli, Proteus, Salmonella, Shigella
  - ***Listeria*** (gram +)
- Main Clinical Uses
  - Otitis Media, Bacterial sinusitis
  - Meningitis
    - Newborns, elderly
    - Listeria coverage

Anti-Staphylococcal Penicillins

Oxacillin, nafcillin, dicloxacillin

- High frequency of adverse effects (interstitial nephritis)
- Covers ***Staph Aureus*** (non-MRSA) and most ***strep***
- Side chain protects B-lactam from staph penicillinase
  - Prototype: Methicillin >> No longer used



Methicillin

Anti-Staphylococcal Penicillins

Oxacillin, nafcillin, dicloxacillin

- Common uses
  - Community acquired cellulitis
  - Impetigo
- ***Staph endocarditis based on culture data***
- Side effects similar to penicillin

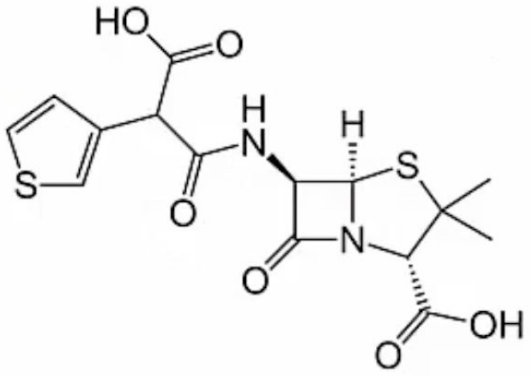
Åsa Thörn

Ujb 98

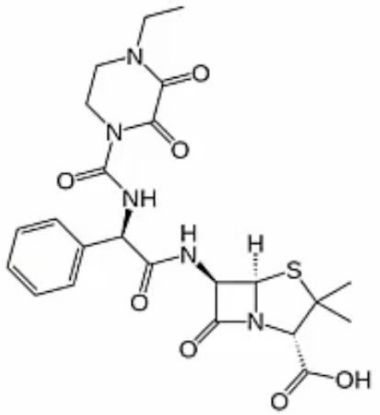
Anti-Pseudomonal Penicillins

Ticarcillin, Piperacillin

- Greater porin channel penetration
- Effective against ***Pseudomonas aeruginosa***
- Susceptible to B-lactamases!!!
  - Given with B-lactamase inhibitor
- Broad-spectrum antibiotics
  - Most gram-positive (not MRSA)
  - More gram-negative (pseudomonas)
  - Most anaerobic bacteria
- Hospitalized patients with sepsis/PNA



Ticarcillin
(Carboxypenicillin)



Piperacillin
(Piperazine penicillin)

Penicillins

Resistance

- Mo
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- Re
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- Be
  -
    - Some other penicillins
    - Some cephalosporins
  - Many gram negative bacteria and Staphylococcus aureus

B-Lactamase Inhibitors

- Clavulanic Acid, Sulbactam, Tazobactam
- Inhibit bacterial B-lactamase
- Added to some penicillins to expand coverage
  - Aminopenicillins
  - Antistaphylococcal penicillins
- ***Little/no effect used alone***

ds

B-Lactamase Inhibitors

Clavulanic Acid, Sulbactam, Tazobactam

- Used with aminopenicillins
  - Amoxicillin / Clavulanicacid (Augmentin)
  - Ampicillin / Sulbactam
  - Increases activity against ***S. Aureus, H. flu***
  - Also increases activity against anaerobes (B. fragilis)
- Used with Anti-Pseudomonal penicillins
  - Ticarcillin-clavulanate
  - Piperacillin-tazobactam (Zosyn)
- Common uses:
  - Otitis media/sinusitis (Broad-spectrum)
  - Bite wounds (Polymicrobial with anaerobes)
  - Hospitalized patients with sepsis / PNA

Penicillin Adverse Effects

Hypersensitivity (allergic) reactions

- Commonly leads to hypersensitivity (allergic reaction)
  - 1st exposure: Sensitization
  - 2nd exposure: Hypersensitivity reaction
- ***Symptoms resolve on stopping drug***

Penicillin Adverse Effects

- Hypersensitivity (allergic) reactions
- **Acute "*immediate*"**
  - Type I, IgE-mediated
  - Usually within 1 hour of taking drug
    - Histamine release
    - Itching, urticaria
    - Bronchospasm
    - Anaphylaxis

James Heilman, MD

Penicillin Adverse Effects

Maculopap

- Type-IV
- Days or
- Most cc
- Itchy or
- **Absenc**
- Commc
  pharyng

Wikipedia/Public Domain

ven for

Romano A et al. Diagnosis of nonimmediate reactions to β-lactam antibiotics. Allergy 2004

Penicillin Adverse Effects

Skin R

- Stev
  - R
  - S
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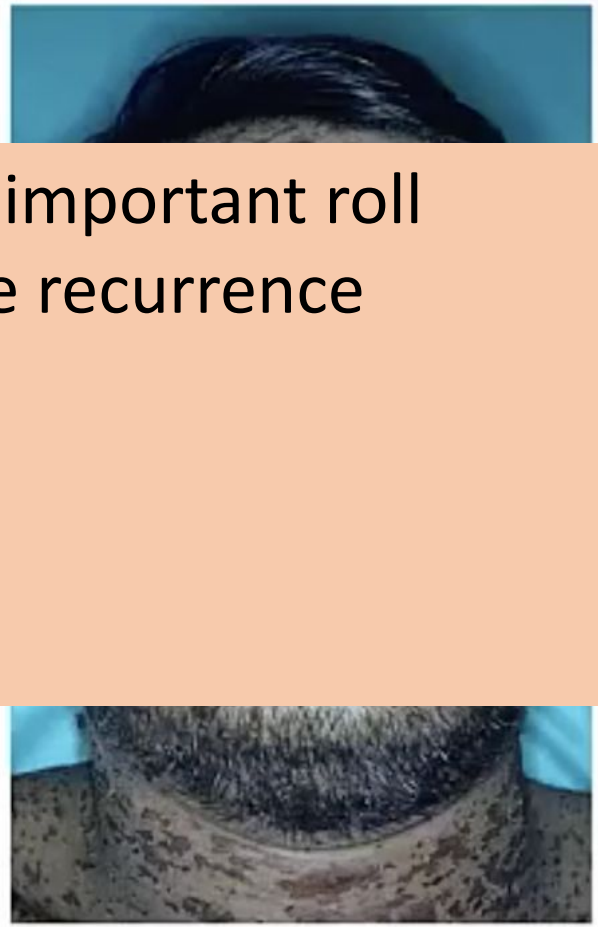
  - V
- Toxic epidermal necrolysis
  - Severe form SJS (>30% skin)
- Mortality: ***SJS*** 1-5%; ***TEN*** 25-35%

- ***Immune mediated***, CD8 T-cells play important roll
  - Re-challenge with drug can cause recurrence
- **Antibiotic associations**:
  - Sulfonamides (TMP-SMX)
  - ***Aminopenicillins***
  - Cephalosporins



Dr. Thomas Habif/Wikipedia

Penicillin Adverse Effects

Interstitial Nephritis

- Considered a Type IV hypersensitivity reaction. (T cells & Mast cells)
- Classic presentation
  - Fever
  - Oliguria, Increased BUN/Cr
  - Eosinophils in urine OR White cells and WBC casts "***sterile pyuria***"

Penicillin Adverse Effects

Hemolytic Anemia

- Type II hypersensitivity
- High doses can lead to extrinsic hemolytic anemia
  - PCN binds to surface RBCS >> Elicits immune response >> Antibodies against PCN bound to RBCS >> Direct Coombs test: ***positive***

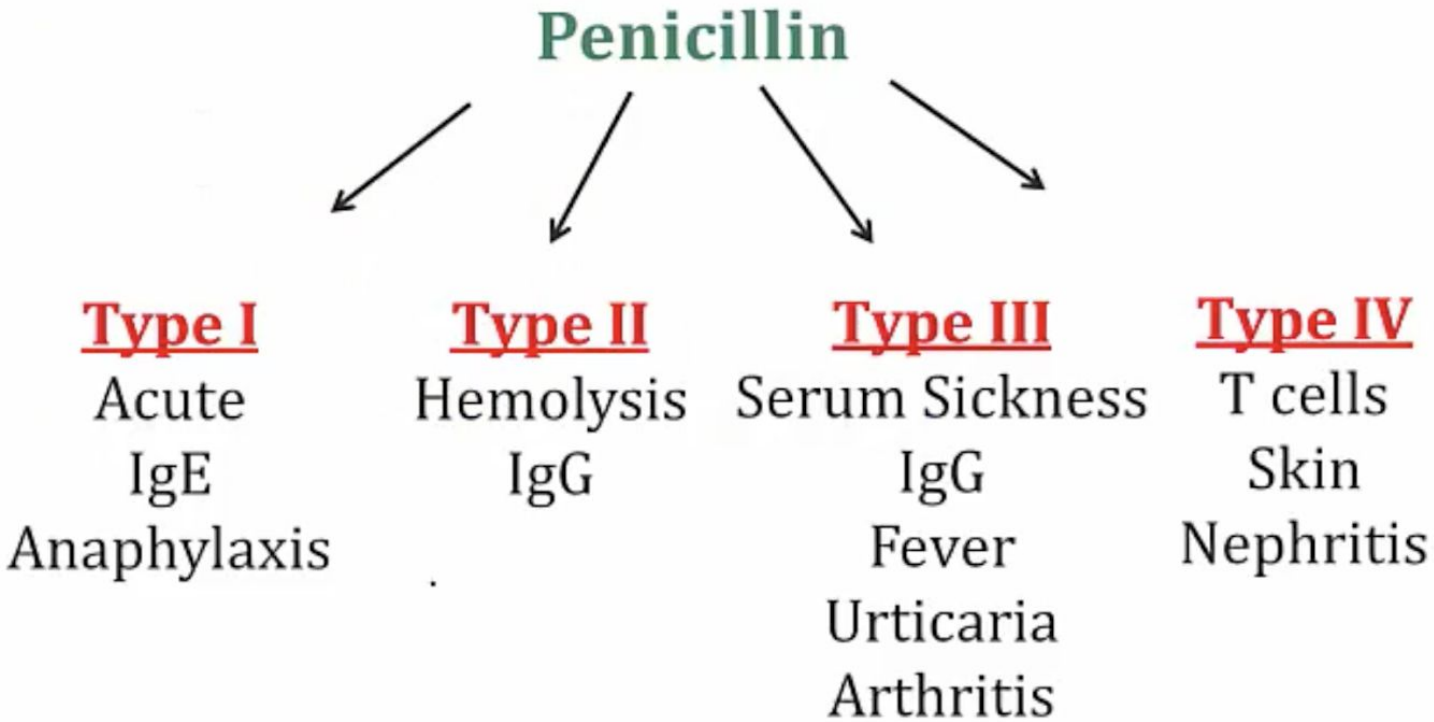
Penicillin Adverse Effects

Hypersensitivity (allergic) reactions

- Serum Sickness
  - Type III hypersensitivity reaction
  - Days/weeks after exposure
  - Immune complex disorder (IgG)
  - Complement activation
- Urticaria, fever, arthritis, lymphadenopathy

Tatum A et al. Severe serum sickness-like reaction to oral penicillin drugs: three case reports. Ann Allergy Asthma Ummunol 2001

Penicillin Immunology



Penicillin Adverse Effects

C. Difficile Infection

- Diarrhea following antibiotic therapy >> Antibiotic depletes normal intestinal flora >> C. Difficile growth → pseudomembranous colitis
- May occur with any antibiotic, Frequent associations:
  - Clindamycin
  - Fluoroquinolones
  - Cephalosporins
  - Penicillins

Penicillin Adverse Effects

Jarisch-Herxheimer Reaction

- Occurs with PCN therapy for ***spirochete*** infections, Classically occurs in syphilis
  - Febrile syndrome
  - Fever, chills, flushing, hyperventilation
  - Usually 2 hrs after starting therapy
  - Due to bacterial cell death → immune response

Other Beta Lactam Antibiotics

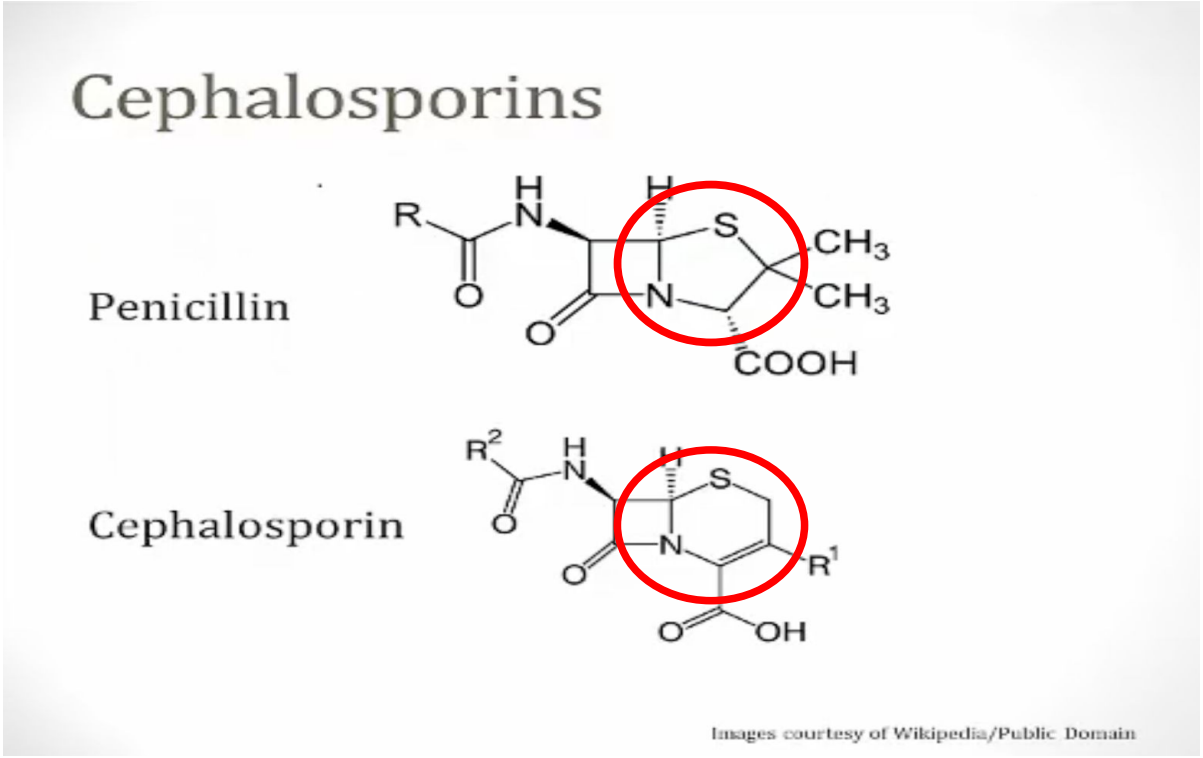
Cephalosporins, Carbapenems, Aztreonam

- ***Similar mechanism to penicillin***
  - Bind transpeptidases (penicillin-binding proteins/PBPS)
  - Prevent peptidoglycan crosslinking
  - Autolysis >> Usually bactericidal
- ***Potentially susceptible to beta lactamase***
- *Hyper sensitivity* and *adverse reactions* are similar to Penicillins

CEPHALOSPORINS

Cephalosporins

- Divided into 1st through 5th generation
  - 1st generation: Mostly gram positive coverage >> Successive generations: increased gram (-) coverage



Cephalosporins

1st Generation Cephalosporins

Cefazolin, cephalexin

- Developed to treat S. Aureus resistance to penicillin
- Covers many gram (+) including S. Aureus (not MRSA)
  - ***Stable against S. Aureus beta lactamase***
  - Does not cover enterococcus or listeria
  - Susceptible to gram negative beta lactamases
- Main uses:
  - Surgical wound (skin) infections
  - Cefazolin given pre-op for prevention

Cephalosporins

2nd Generation Cephalosporins

Cefuroxime, Cefoxitin, Cefotetan

- Developed to treat amoxicillin-resistant infections
- Increased affinity for gram (-) PBPS
- ***More resistant to beta lactamase***
- Increased gram (-)
  - H. influenza, Enterobacter, Proteus
  - E. coli, Klebsiella, Serratia, N. gonorrheae
- Increased anaerobic coverage (B. fragilis)

Cephalosporins

- Cefuroxime (oral):
  - Otitis media (S. pneumonia, H. flu)
  - UTI in children (E. coli; no fluoroquinolones)
- Cefoxitin/cefotetan (IV):
  - PID (covers Neisseria; also give doxycycline for Chlamydia)
  - Pre-op in children with appendicitis
    - E. coli, Covers gram negatives and some anaerobes
    - Usually given with metronidazole

Cephalosporins

3rd Generation Cephalosporins

Ceftriaxone, Cefotaxime, Ceftazidime

- Broad gram (-) coverage
  - More resistance to beta lactamase enzymes
  - More gram (-) PBP affinity
- Ceftriaxone, Cefotaxime: Poor coverage pseudomonas
- **Ceftazidime: Covers pseudomonas**
- *Most achieve good CSF penetration (meningitis)*

Cephalosporins

Ceftriaxone

- Commonly used for
  - N. gonorrhea
  - Commonly used in meningitis
  - Active against S. pneumonia, N. meningitidis
  - *Good CSF penetration*
- ***Ceftazidime***
- Used in hospitalized patients with
  - Gram negative infections
  - Sepsis/pneumonia

Cephalosporins

4th Generation Cephalosporins

Cefepime

- Broad spectrum (>3rd generation drugs)
  - MSSA
  - Many gram (+)’s
  - Many gram (-)'s including pseudomonas
- *Resistant to some ESBL*
- Hospitalized patients with gram (-) infections

Cephalosporins

5th Generation Cephalosporins

Ceftaroline, Ceftobiprole

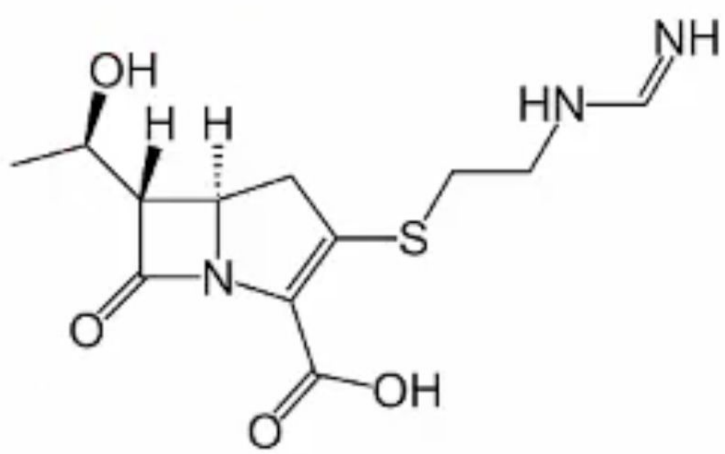
- *Active against MRSA*
  - Low affinity for most other beta-lactams
  - Covers MRSA and VRSA
  - Some gram negatives (not pseudomonas)
  - Studied in skin infections and pneumonia
- ***Ceftobiprole***
  - ***Covers pseudomonas as will !!***

CARBAPENEMS

Carbapenems

Imipenem, meropenem, ertapenem, doripenem

- B-lactams, ***<u>Resistant to cleavage by most B-lactamase</u>***



Imipenem

Carbapenems

- *Dru*
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- Us

ESBL

- Extended Spectrum Beta Lactamase
- Plasmid-mediated bacterial enzymes
- Confer resistance to most beta-lactam antibiotics
  - Penicillins, cephalosporins, aztreonam
- Found only in gram-negative bacteria:
  - Pseudomonas, Klebsiella, E. coli
  - Enterobacter, Salmonella, Serratia, Shigella

ns)

Carbapenems

Imipenem

- First
- Met toxic
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- *Ertapenem >> Once daily dosing*

Common side effects

Nausea, vomiting, diarrhea

Skin rash

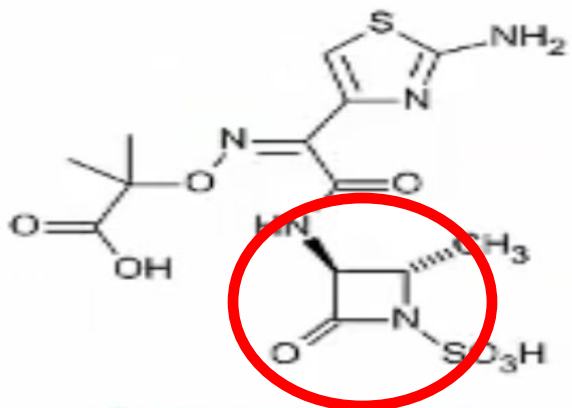
Neurotoxicity

Seizures >> Inhibition of GABA receptors >> Especially at high doses or with renal failure >> ***Lower risk with meropenem***

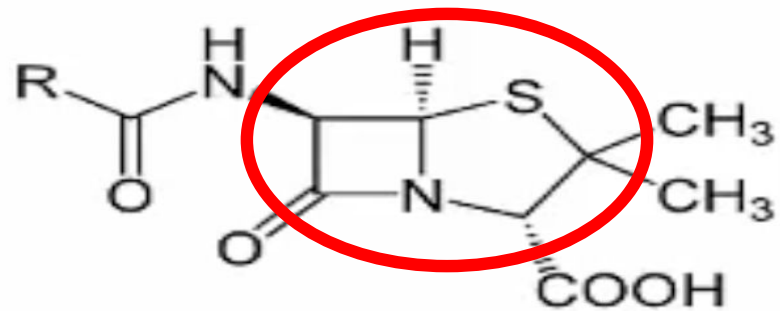
AZTREONAM
- monobactam -

Aztreonam

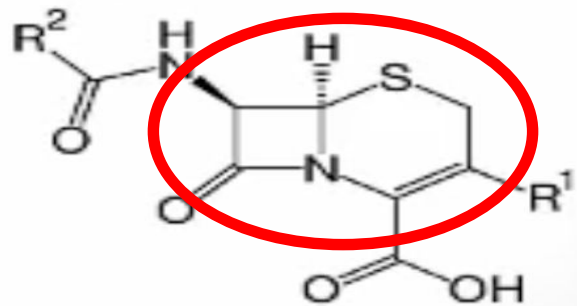
- Monobactam: β-lactam ring not fused to another ring



Aztreonam



Penicillins



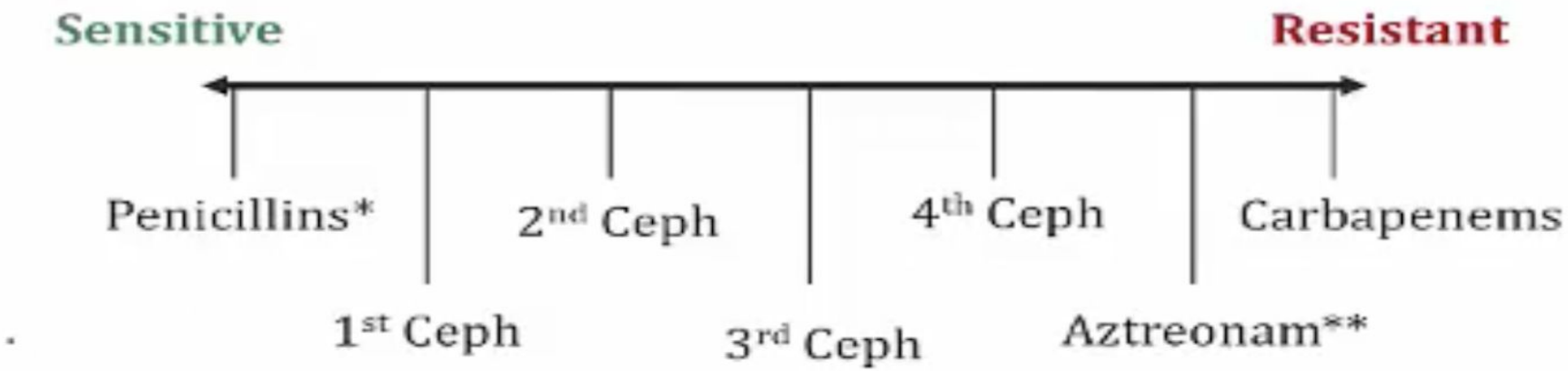
Cephalosporins

Aztreonam

- Binds penicillin-binding protein 3 (PBP-3)
  - Found in ***gram negative bacteria ONLY*** **>>** not active against G+ or anaerobes
  - Bactericidal
- Limited susceptibility to B-lactamase
  - Some resistance in ESBL bacteria
- *Active against pseudomonas*
- Given IV, and can Synergistic with aminoglycosides
- No cross reactivity in penicillin allergic patients >> main indication: **penicillin allergy**

β-lactamase Sensitivity

Based on side chain

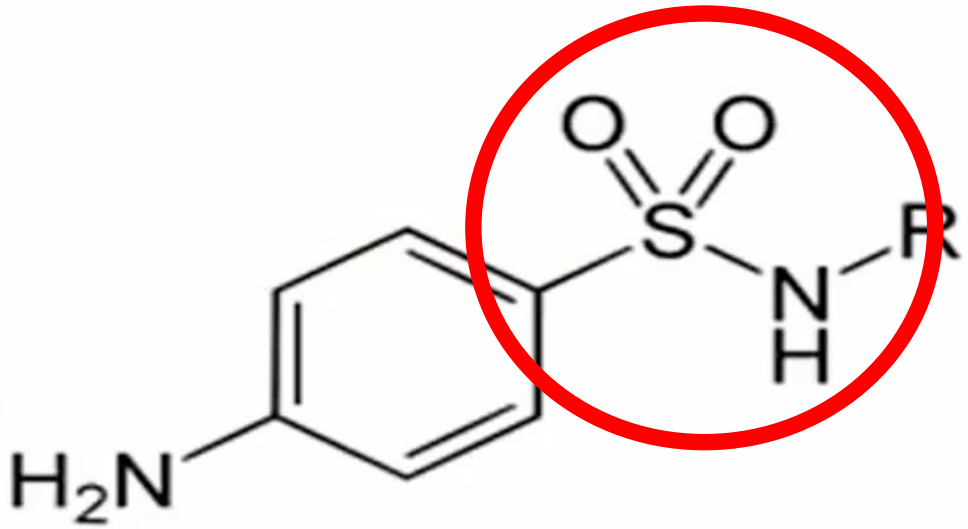


* Anti-staphylococcal penicillins resist staph penicillinase
** Gram negatives only

SULFONAMIDE

Sulfonamide Antibiotics

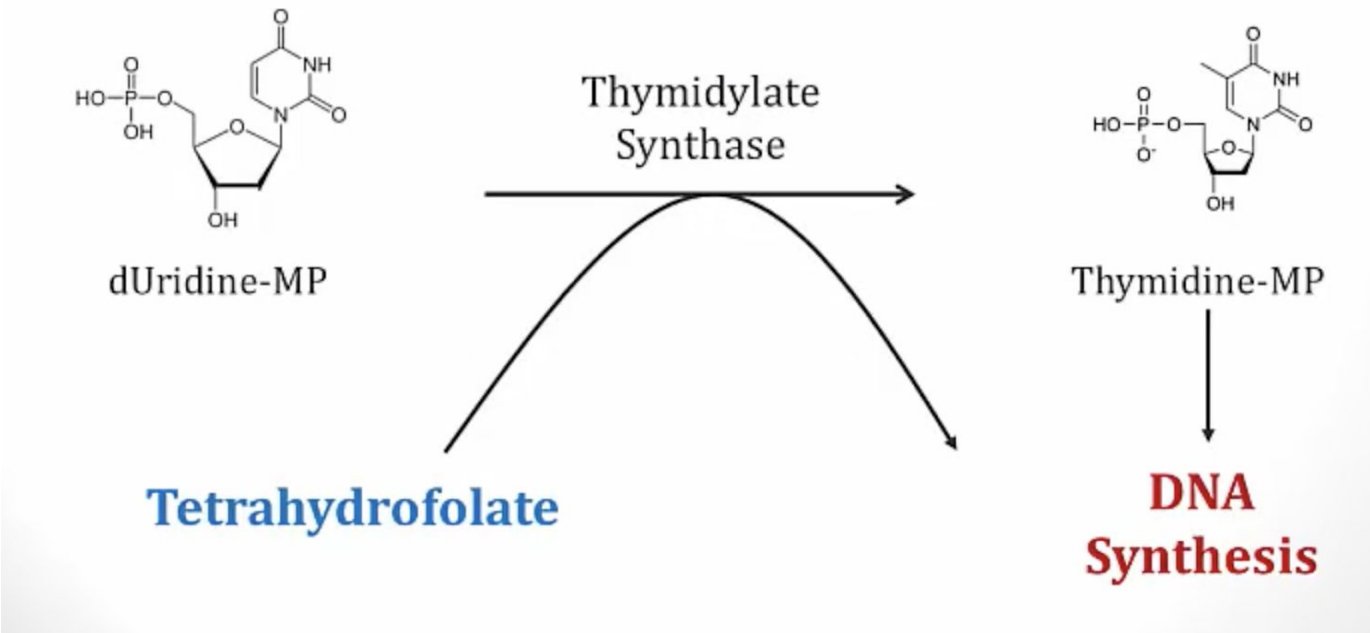
- Sulfonamide group = SO_2-N
- "Sulfa" drug = Contains sulfonamide group



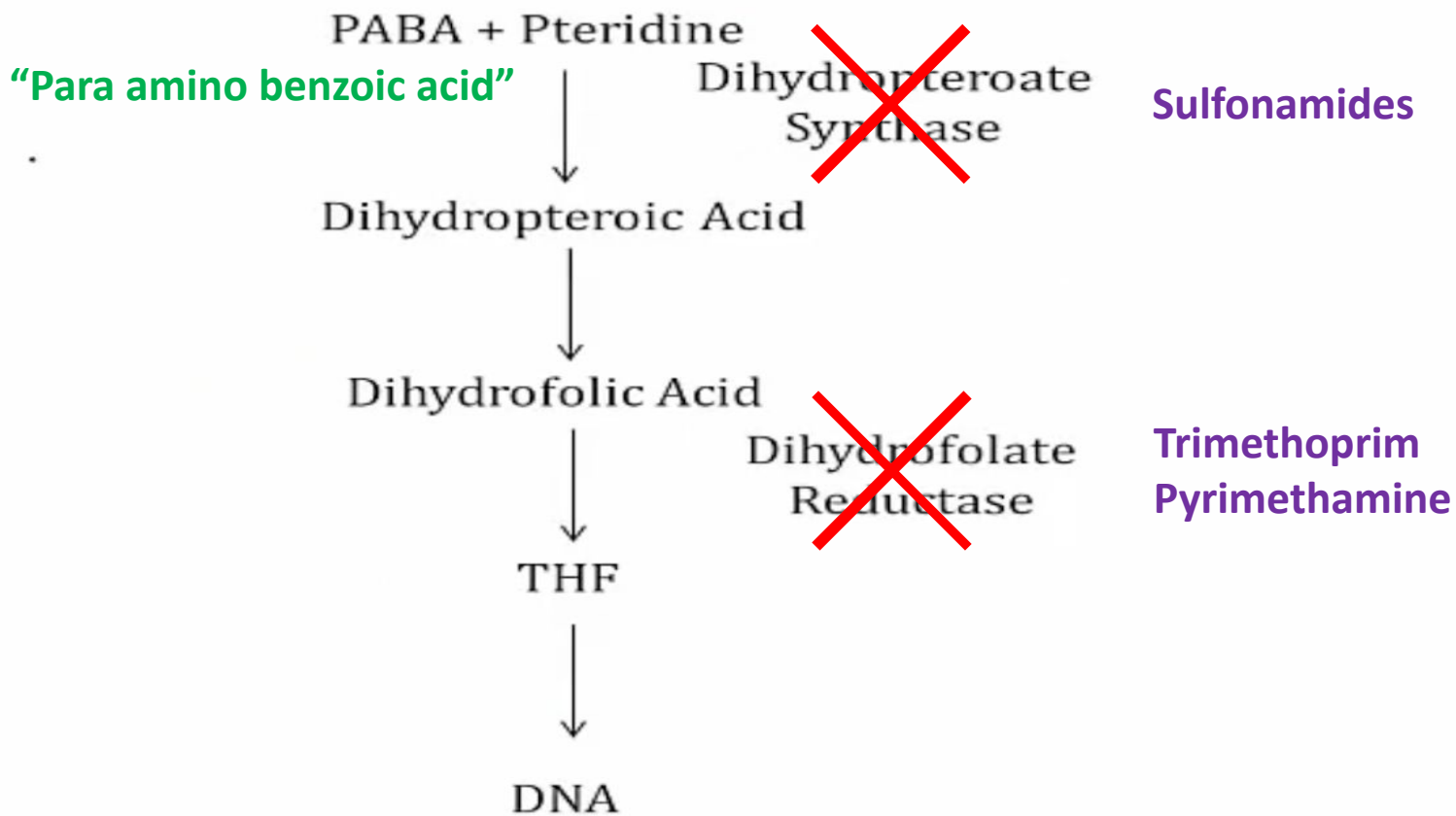
Sulfonamide

Bacterial Folate Synthesis

- Folate required for thymidine/DNA synthesis
- Mammalian cells: **use exogenous** folate (diet)
- Bacterial cells: no exogenous folate (must synthesize)



Bacterial Folate Synthesis



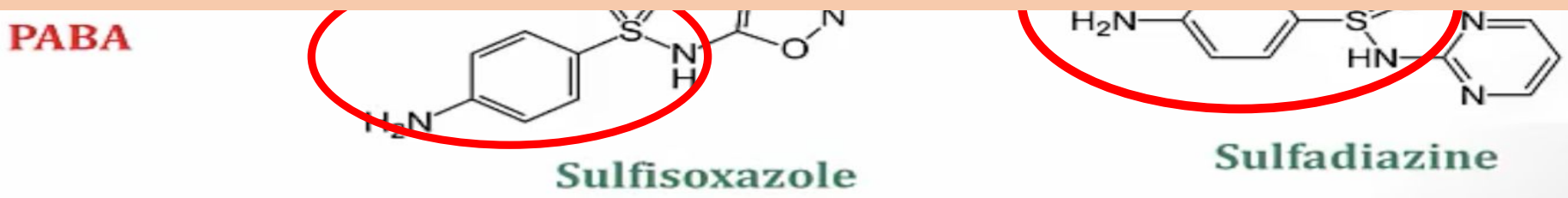
Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine

- Mimics of PABA
- Competitively inhibit dihydropteroate synthase

Sulfonamides Resistance

- Increased PABA
- Altered dihydropteroate synthase
- Decreased uptake



Sulfonamide

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine

- Usually given with trimethoprim
  - TMP-SMX (Bactrim)
  - Sequential block of THF synthesis
- Sulfadiazine
  - Silver-sulfadiazine (cream for burns)
- Sulfadiazine and pyrimethamine
  - Also sequential block of THF synthesis
  - Used in toxoplasmosis (HIV)

Sulfonamide Toxicity

- Hypersensitivity reactions ~3% of patients
- Sulfonamides Hypersensitivity (allergic) reactions >> Similar to penicillin allergic reactions: Anaphylaxis, Maculopapular rash, Serum sickness (fever, rash, arthritis), Interstitial nephritis
- *Stevens-Johnson Syndrome / Toxic epidermal necrolysis*

- Photosensitivity >> Drug interaction with UV light, Caused by many drugs, Common drugs: ***Tetracycline, Sulfonamides, Amiodarone***

Sulfonamide Toxicity

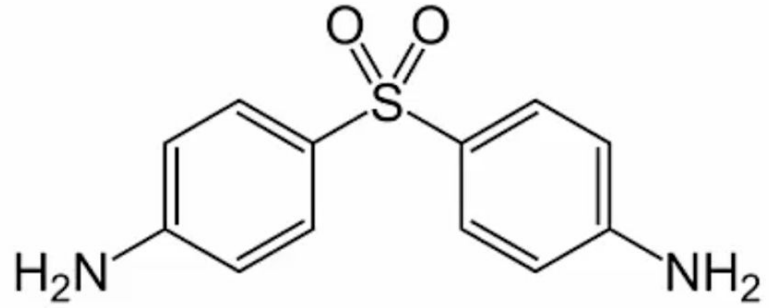
- **Hemolysis** in G6PD deficient >> *Sulfonamides are oxidants* >> trigger for hemolyisis. Other triggers >> *Dapsone*

- Kernicterus in infants
  - Sulfonamides → increased free bilirubin levels >> Unconjugated bilirubin is neurotoxic >> Basal ganglia, brainstem nuclei >> Permanent neurologic impairment >> Movement disorder (chorea, tremor), Hearing loss, Limited gaze

- Raise warfarin levels
  - Displaces warfarin from albumin >> INR level may rise in patients on warfarin therapy

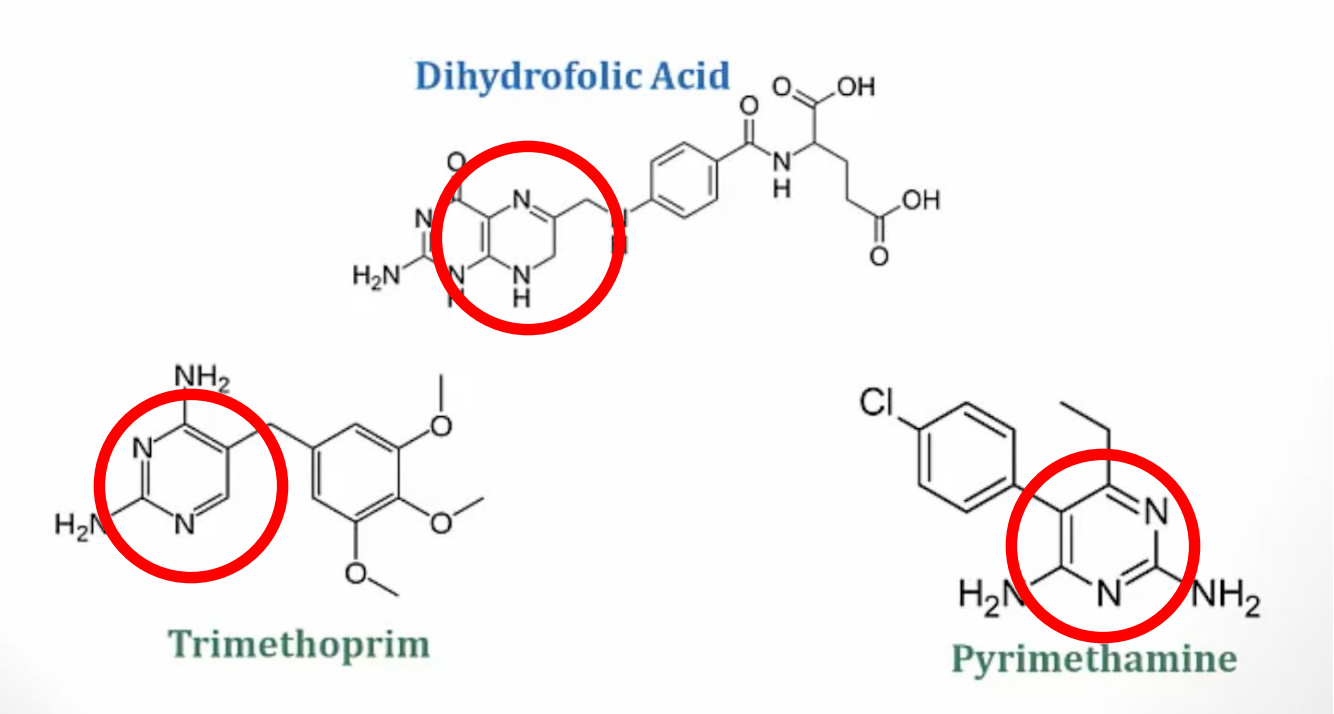
Dapsone

- Not a sulfonamide
  - Competes with PABA for dihydropteroate synthase
- Two main uses:
  - Mycobacterium leprae (leprosy)
  - Pneumocystis jiroveci



Trimethoprim / Pyrimethamine

- Mechanism of Action
  - Inhibit dihydrofolate reductase
  - Similar structure to dihydrofolate



TriMethoPrim - *SulfaMethoXazole*

Bactrim TMP-SMX

- Combination is ***bactericidal***
  - Covers many gram (+ & -)
  - *Does not cover pseudomonas or B. fragilis (anaerobes)*
  - Covers some fungi and parasites ☺️
- Common uses:
  - Urinary tract infections (covers E. Coli well)
  - Pneumocystis pneumonia in HIV (treatment/prophylaxis)
- TMP-SMX Pregnancy
  - Risk of kernicterus
  - Disrupts folic acid metabolism

Trimethoprim / Pyrimethamine Toxicity

- Bone marrow suppression
  - Pancytopenia: megaloblastic anemia, leukopenia, thrombocytopenia

- Can alleviate with leucovorin (folinic acid)
  - Converted to THF >> Does not require dihydrofolate reductase >> "***Leucovorin rescue***"

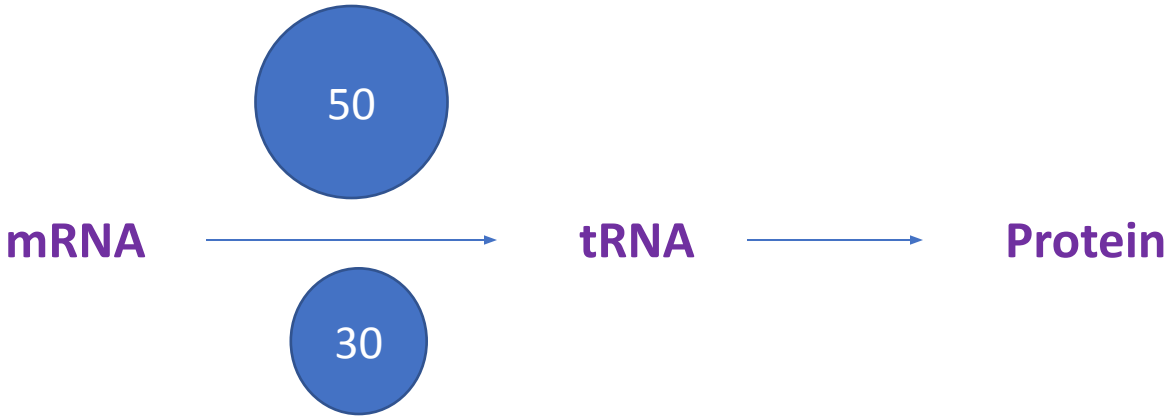
PROTEIN SYNTHESIS INHIBITORS

Protein Synthesis Inhibitors

- Aminoglycosides
- Macrolides
- Tetracyclines
- Chloramphenicol
- Clindamycin
- Linezolid
- Streptogramins

Protein Synthesis Inhibitors

- Bacterial Protein Synthesis
  - DNA ⟶ Transcription ⟶ RNA ⟶ Translation ⟶ Protein



1- Initiate process — Aminoglycosides / Linezolid

2- Add tRNA — Tetracycline

3- Add peptides translocate — Macrolides / Clindamycin

AMINOGLYCOSIDES

Aminoglycosides

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin

- Block initiation of protein synthesis
  - Primarily bind 30s >> Misreading of genetic code >> Bacteria cannot divide, produce cellular proteins >> Cell death (bactericidal)
- Require O_2 for transport into cells >> Not effective against anaerobes
- Not transferred into eukaryotic cells
  - Not effective intracellular organisms (Rickettsia/Chlamydia)
- Rarely Used alone to treat serious gram (-) infections
- What about: TB, ESBL, CRE, Abscess?

Aminoglycosides

- Streptomycin can be used for tuberculosis / Brucellosis
- N
- O
  - Ampicillin/gentamycin for newborn meningitis
  - Pip/Tazo + tobramycin for CF patients (pseudomonas)

- Resistance
  - "Aminoglycoside modifying enzymes"
  - Bacteria acquire enzymes that modify drug structure
  - Modified structure binds poorly to ribosomes
  - Phosphorylation (mediated by aminoglycoside kinases)
  - Adenylation/acetylation (mediated by transferases)

Aminoglycosides

Adverse Effects

- ***O***
- ***N***
- ***N***
  - Rare side effect >> Can block/limit release of ACh at neuromuscular junctions
- ***Pregnancy*** class D >> Reports of renal and ototoxicity in fetus

Aminoglycosides Monitoring

- Plasma levels need to be monitored
  - Trough level: Just before next dose
  - Peak level: Short time after dose
- High trough = risk of toxicity
- Low peak = less effective therapy

MACROLIDES

Macrolides

Azithromycin, Clarithromycin, Erythromycin

- 50S ribosomal subunit
- Covers many (G+) cocci, esp. strep and Some (G-) coverage
- Concentrated inside macrophages, other cells
- Effective against intracellular pathogens
  - Chlamydia (obligate),
  - Legionella (facultative)

Macrolides

- Community acquired pneumonia
  - Azithromycin covers Strep, H. flu, Atypical inf.
  - Good for penicillin allergic patients
- Chlamydia infection
  - Azithromycin (safe in pregnancy)
  - Often co-administered *with Ceftriaxone* (gonorrhea)
- ***Erythromycin***
  - Binds to motilin receptors in GI tract >> Can be used in GI motility disorders
- ***Clarithromycin*** >> Part of triple therapy for H. pylori

Macrolides Adverse Effects

- *Nausea, diarrhea, abdominal pain (motility)*
  - Erythromycin worst offender
- Prolonged QT on EKG
  - Erythromycin also worst offender
- Acute cholestatic hepatitis >> AST/ALT/Alk Phos/Bilirubin
- ***Rash*** >> Maculopapular allergic reaction
- P450 Enzyme Inhibitors >> Will raise serum levels of P450 metabolized drugs >> ***Theophylline, Warfarin***

TETRACYCLINES

Tetracyclines

Tetracycline, doxycycline, demeclocycline, minocycline

- Transported into bacterial cells
  - Binds 30S ribosome
  - Prevents attachment of tRNA
- Demeclocycline
  - *Not used as an antibiotic* >> ADH antagonist >> Given in SIADH >> Causes nephrogenic DI to reverse SIADH

Tetracyclines

Doxycycline

- Most commonly used member tetracycline family
- *Accumulates intracellularly*
- Covers many unusual/atypical bacteria
  - Most zoonoses
  - Chlamydia
- Used to treat acne vulgaris (also minocycline)
  - Covers propionibacterium acnes within follicles

Tigecycline … !!

Tetracyclines

Tetracycline, doxycycline, demeclocycline, minocycline

- Absorption impaired by minerals and antacids
  - Calcium, magnesium (antacids), Iron, Dairy including milk
  - These substances are cations that chelate the drug >> Cannot be taken with antacids or milk

Adverse Effects

- ***GI distress*** (common)
  - Epigastric pain, nausea, vomiting and anorexia
- ***Photosensitivity*** >> Red rash or blisters in sun exposed areas

Tetracyclines Adverse Effects

- ***Discoloration of teeth***
  - Brown-yellow discoloration of teeth
  - *Children under the age of eight* (does not occur in adults)
- ***Inhibition of bone growth*** in children
  - Deposit in bones >> Chelate with calcium
- Contraindicated in pregnancy
  - Cross placenta >> Can accumulate in fetal bone and teeth

CLINDAMYCIN

Clindamycin

- 50S ribosome
  - Prevents translocation, Same as macrolides
- Covers some ***gram (+)***
  - Staph, viridans strep, Strep pyogenes, and S. pneumoniae
- Covers many ***anaerobes***
  - Clostridium perfringens
  - Mouth anaerobes: Fusobacterium, Prevotella, Peptostreptococcus
- *Main use is to cover anaerobes "above the diaphragm"*
  - Aspiration pneumonia, Lung abscesses, Oral infections (mouth anaerobes)
- *Lots of resistance to clindamycin in B. fragilis* >> Anaerobic infections "below the diaphragm" >> ***Metronidazole***

Clindamycin Adverse Events

- ***Classic cause of C. difficile infection***
  - Up to 10% of patients >> Pseudomembranous colitis >> C. difficile overgrowth >> Massive, watery diarrhea

- ***Antibiotic-associated diarrhea***
  - Milder than C. diff infection >> Changes in GI flora >> Less absorption of solutes → osmotic diarrhea >> Stops when drug discontinued

LINEZOLID

Linezolid

- Binds to 50S Ribosome
  - Blocks initiation
- ***Main use:***
  - Vancomycin-resistant enterococcus (VRE) >> Epidemics in hospitals, Usually occurs in patients with prior antibiotic treatment
- *Weak monoamine oxidase (MAO) inhibitor*
  - Can cause *serotonin syndrome* >> High risk when given with SSRIS >> Fever, confusion, agitation, hyperreflexia
- Can cause ***Thrombocytopenia***!

Bacteriostatic vs. Bactericidal

Antibiotic Class	Action
Aminoglycosides	Bactericidal
Macrolides	Bacteriostatic
Tetracyclines	Bacteriostatic
Chloramphenicol	Bacteriostatic
Clindamycin	Bacteriostatic
Linezolid	Bacteriostatic (mostly)
Quinupristin/dalfopristin	Variable

Most protein synthesis inhibitors are bacteriostatic
Only aminoglycosides are bactericidal
Misread proteins travel to membrane and increase permeability

Source: Microbiol Rev. Sep 1987; 51(3): 341–350.

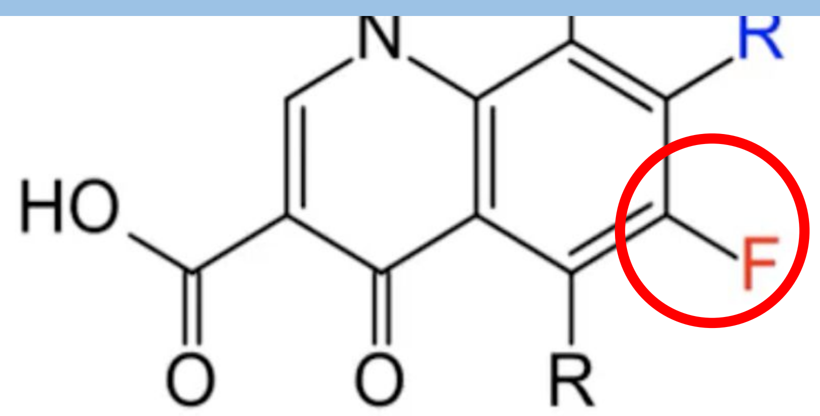
QUINOLONES

Quinolones

Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

Resistance Mechanisms

- Alterations of DNA gyrase and topoisomerase IV
- Alteration in cell permeability
- Efflux of drug



Quinolones

Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

- Many gram (+), gram (-), atypicals
- Common clinical uses (*adults only*)
  - UTIS (E. Coli, other enteric gram negatives)
  - Pneumonia (S. pneumo, H. flu, atypicals)
  - Abdominal infections (enteric gram negatives)

Quinolones

Ciprofloxacin

- Some gram positive coverage
  - Rarely used alone for gram positive coverage (resistance)
- Very good gram negative coverage
  - *Most reliable pseudomonas coverage*
- Used in UTIS, GI infections
- Cipro ear drops for otitis externa (swimmer's ear ? P. aeruginosa)

Quinolones

Levofloxacin

- *More gram positive/atypical* coverage than Cipro
  - Better strep pneumo coverage than Cipro
  - Covers most methicillin-susceptible Staph aureus
- *Less effective against pseudomonas* than Cipro
- Commonly used in pneumonia (strep, atypicals)

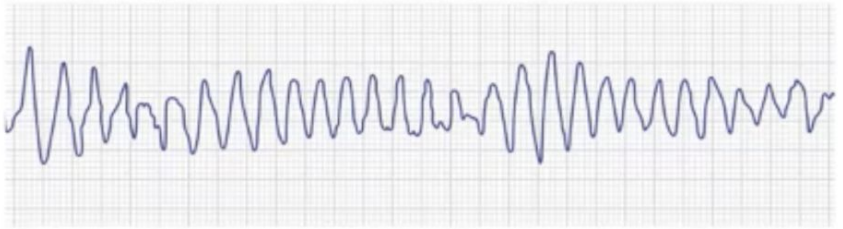
Quinolones

Moxifloxacin, Gatifloxacin, Sparfloxacin

- *Better gram (+)/atypical coverage* than Levofloxacin
- *Less effective for pseudomonas* than Levofloxacin
- Also used in pneumonia

Quinolones Adverse Reactions

- Gastrointestinal upset
  - Anorexia, nausea, vomiting, and abdominal discomfort
  - Up to 17% of patients
- Neurologic side effects
  - Headache, dizziness
  - 2 to 6% of patients
- QT prolongation on EKG
  - Caused by blockade of K+ channels
  - Can lead to torsade de pointes



Quinolones Adverse Reactions

- ***Tendon rupture***/tendonitis
  - Most commonly Achilles
  - More common older patients (>60), people on steroids
- Cannot use in *pregnancy/children*
  - Toxic to developing cartilage in animal studies
- *Antacids*
  - Disrupt absorption of many drugs, *Aluminum and magnesium* hydroxide, Sucralfate (contains aluminum)
- ***Key drugs*** that affected by this:
  - Tetracycline, *Fluoroquinolones*
  - Isoniazid, Iron supplements

Wikipedia/Public Domain

VANCOMYCIN

Vancomycin

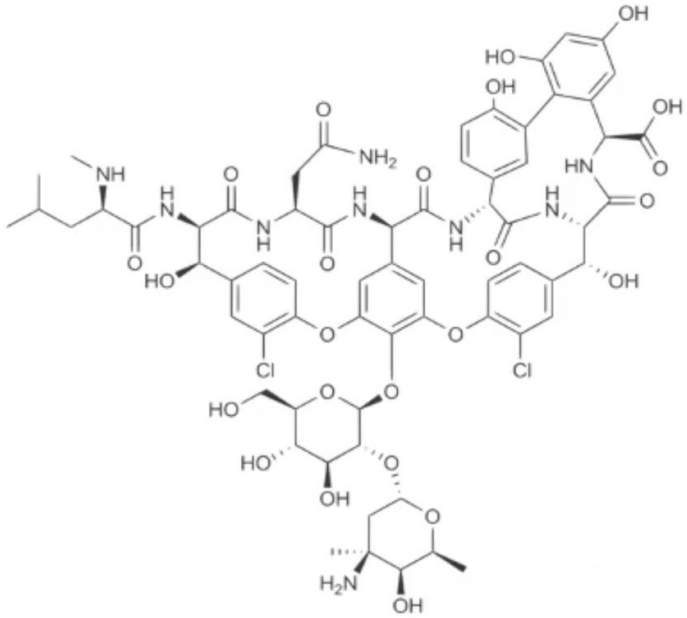
- Inhibits
  - Bind
    brea
- Same e
  - Beta
  - Vancomycin: block transpeptidase binding

Resistance

- Terminal amino acids change D-alanyl-D-alanine to >> **D-alanyl-D-lactate**
- VRSA emerges

Vancomycin

- Only effective in Gram + (huge!)
- *Two common uses*:
  - Methicillin resistant Staph Aureus (MRSA)
  - Oral therapy for C. difficile pseudomembranous colitis
- Often given empirically when MRSA is a concern
  - ***Endocarditis***
  - ***Severe pneumonia/sepsis***



Vancomycin Adverse Effects

- Generally well tolerated
- ***Nephrotoxicity "check Trough level"***
  - Less common with modern preparations
  - Increased risk if concomitant aminoglycoside therapy
- ***Ototoxicity*** >> Tinnitus, vertigo, and hearing loss reported (rare)
- Red man syndrome
  - Flushing, erythema, itching >> Usually affects upper body, neck, face more than lower body >> Occurs 10-20 minutes after start of infusion >> *Direct activation of mast cells* → histamine release "Pseudoallergic drug reaction"
  - May develop with first administration
  - *Infusion related* → slow infusion = no symptoms

METRONIDAZOLE

Metronidazole

- *Prodrug:* Must be reduced to activate
- Only ***anaerobic bacteria*** capable of reduction
- Reduced metronidazole → more drug uptake
- Activated form generates free radicals >> Interact with DNA >> DNA breakage/destabilization >> Cell death

Metronidazole Uses

- Good coverage of anaerobes "below the diaphragm"
  - ***Bacteroides fragilis***
  - ***Clostridium difficile***
- Peritonitis, abdominal abscesses, diverticulitis
- Often given *with quinolone* for anaerobic/GI gram(-)
  - Cipro/Flagyl often used for diverticulitis
- ***H. pylori*** (Triple therapy) and Gardnerella vaginalis
- Treatment of ***bacterial vaginitis***
- *Anaerobic protozoa* (lack mitochondria)
  - Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia

Metronidazole Adverse Reactions

- Unpleasant ***metallic taste***
- GI: Abdominal discomfort, nausea
- Neuro: Neuropathy, headache
- Disulfiram-like reaction >> Alcohol consumption with metronidazole >> *Warmth, flushing, sweating*. “Unclear mechanism”
- Metronidazole may not inhibit alcohol metabolism >> Patients should avoid alcohol

NITROFURANTOIN

Nitrofurantoin

- Rarely used antibiotic
  - Exact mechanism incompletely understood
- Bactericidal drug
- Only use is UTIs (concentrates in urine)
- Two things to know about this drug:
  - Used for ***UTIS in pregnancy*** (avoid TMP-SMX, quinolones)
  - Can trigger hemolysis in ***G6PD patients***


Mercé
Dankjewel
Hvala
Спасибо
Efharisto
Matondo
Спасибо
Toda
Mahalo
Rahmat
Xièxie
Grazie
Mauruuru
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