Know Your Antibiotics I

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Disclosures

- None

Outline

- Bacterial targets
- Different classes of antibiotics
- Spectrum of bacterial coverage
- Side effects
- Resistance mechanisms

Case 1

- A 12 yr old previously healthy female arrives at the emergency department with complaints of high fever, malaise, painful urination and severe flank pain. Lab tests indicate the presence of white blood cells and E.coli in her urine. A diagnosis of kidney infection (pyelonephritis) is made, and the decision is made to use a beta-lactam antibiotic that has both an appropriate antibacterial spectrum of activity, and good tissue penetration, yet is more resistant to beta-lactamases than narrow spectrum penicillins. The drug that best fits these characteristics is:
- ceftriaxone
- daptomycin
- fosfomycin
- nitrofurantoin
- vancomycin

Case 2

- A 14 year-old boy develops a bad case of otitis media a few days after swimming in a lake. His previous medical history is unremarkable except for having had a minor skin rash two years ago after being treated with amoxicillin for a sore throat. Which of the following shares a common mechanism, but would be very unlikely to produce a similar allergic reaction (e.g. ~1-2% or lower chance)?
- ampicillin
- cefaclor
- clarithromycin
- clindamycin
- gentamicin

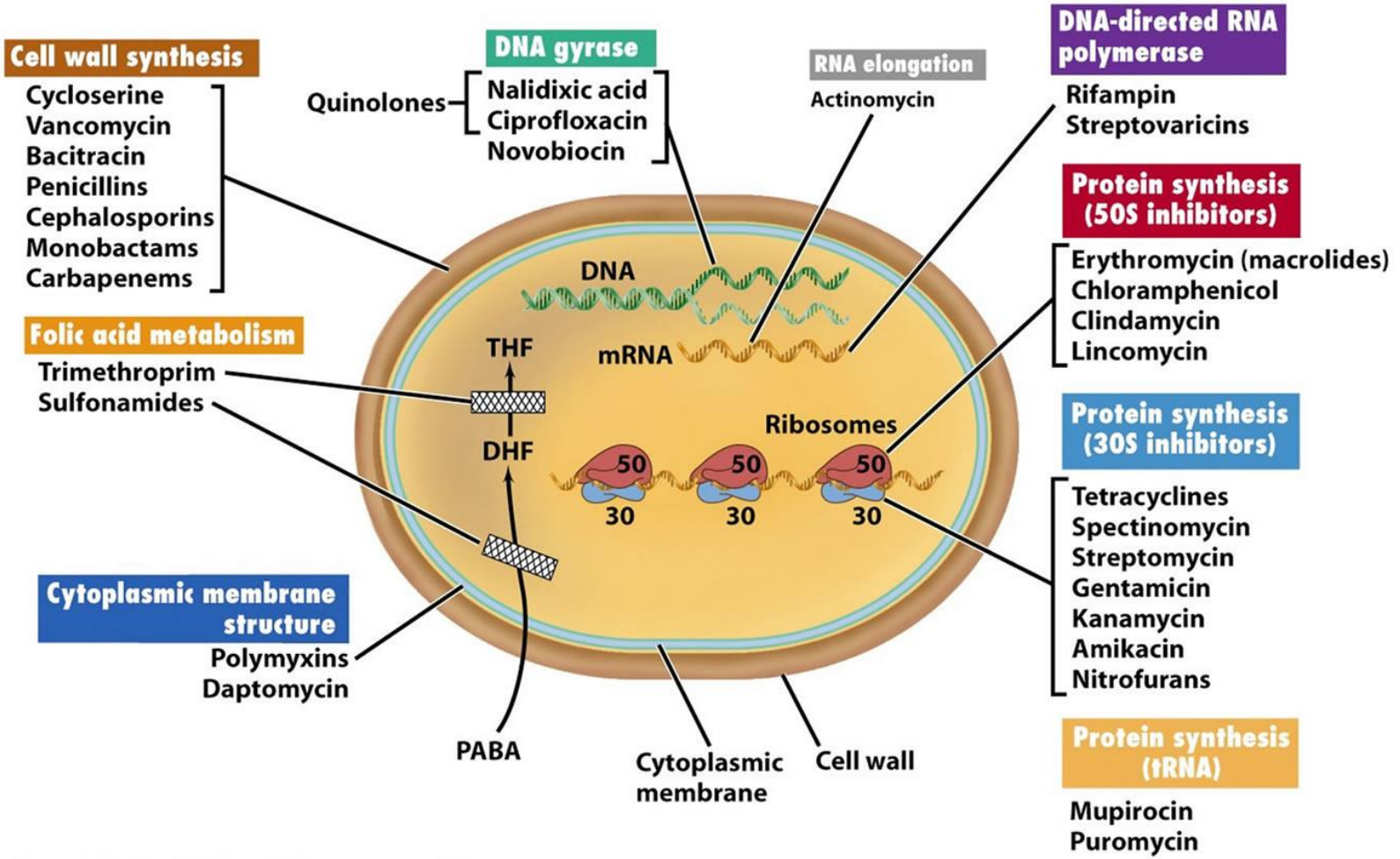

Figure 20-14 Brock Biology of Microorganisms 11/e

Cell Wall Inhibitors

- The β-lactams: penicllins, cephalosporins, carbapenems, monobactams

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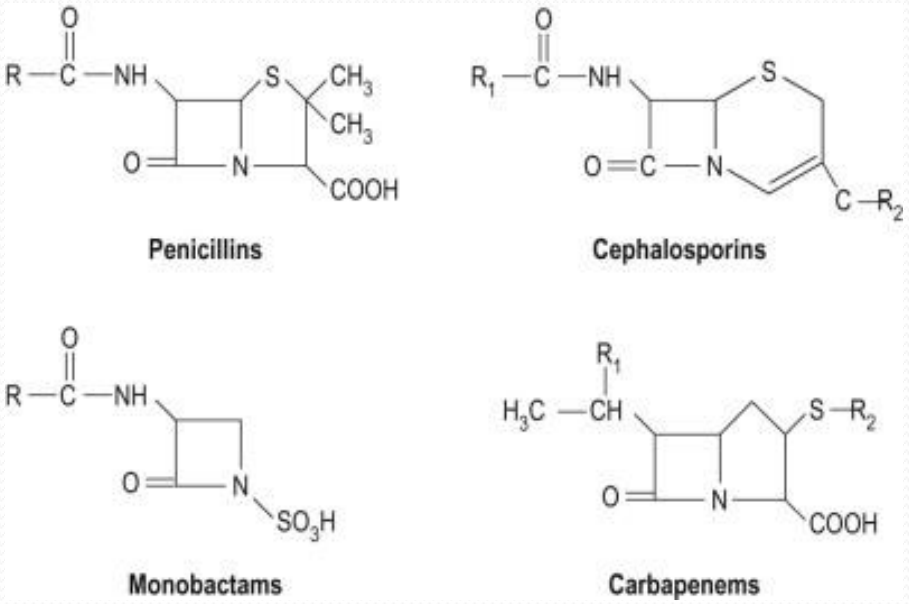
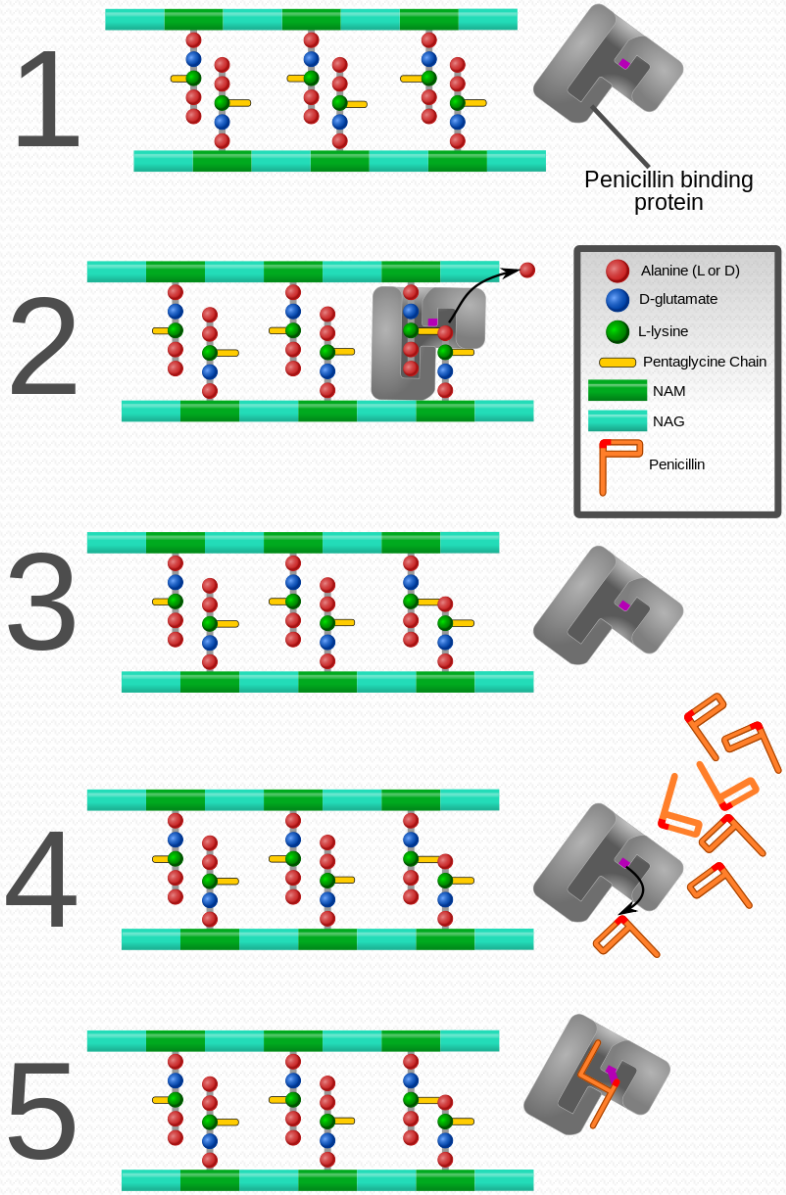
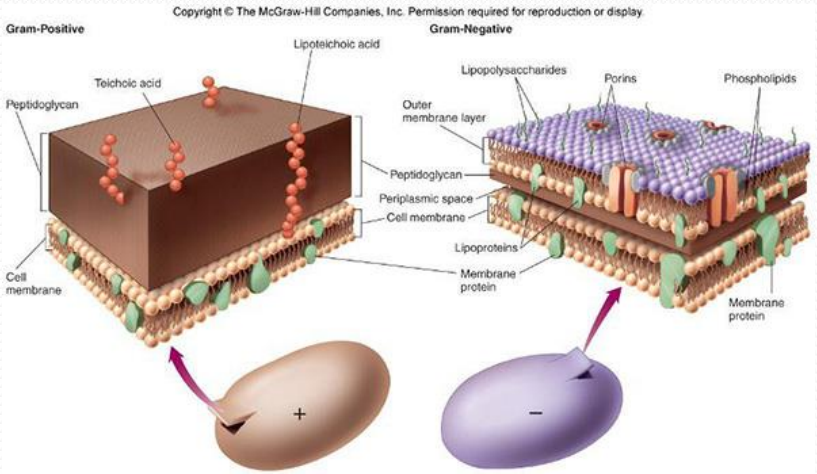


Mechanism of action





Penicillins

- Natural penicillins: Pen G and Pen V (most active against strep)
- Amino penicillins: Ampicillin, amoxicillin (1st group of penicillins to have activity against Gram negatives, most active against Listeria and enterococci)
- Penicillinase-resistant penicillin: Methicillin, Nafcillin, Oxacillin (active against *S. aureus* and strep)
- Extended-spectrum penicillins: Ticarcillin, pipercillin (derivatives of aminopenicllins, better activity against Gram neg, stronger binding to the PBPs and greater penetration through outer membrane)
- Beta-lactamase inhibitor combination: Amox-clav, Amp-sulbactam (also active against beta-lactamse producing strains of Hemophilus, Moraxella, and enterobacteriaceae, not active against pen R S. pneumoniae) Pipercillin-tazobactam (covers MSSA, some enterobacteriaceae, Pseudomonas, anaerobes)

Adverse effects

- Little dose-related toxicity

Type of reaction	Freq (%)	Most common offender
Diarrhea	5	Amp
BM suppression	1-4	Naf, Ox, Pip, Pen G
Hepatitis	1-4	Ox, Naf
Interstitial nephritis	1-2	Meth
Delayed Hypersensitivity	4-8	Amp
IgE-mediated	0.004-0.4	Pen G

Cephalosporins

- 1st generation: Cephalexin, Cefazolin – active against GPC, including MSSA, variable activity against GNRs, minimal activity against *H. flu* and *M. catarrhalis*
- 2nd generation: Cefuroxime, Cefoxitin – equal to slightly less activity against GPCs, better activity against H. flu and M. catarrhalis. Cefoxitin has anaerobic activity, also a potent inducer of AmpC
- 3rd generation: Cefixime, Cefdinir, Ceftriaxone, Cefotaxime, Ceftazidime – Excellent activity against GNRs, GAS and *S. pneumoniae*, but variable against Staph. High CSF penetration
- 4th generation: Cefepime – rapidly penetrates OM in GNRs, increased affinity to PBPs, enhanced stability to ESBLs. Has anti-pseudomonal activity.

- 5th generation: Ceftaroline - approved for treatment of SSTI, pneumonia, active against MSSA, MRSA including those strains with increased MIC against Vancomycin, not active against ESBL producing GNRs

Adverse effects

- Like penicillin, almost no dose-related toxicity
- 4% of those with documented Pen have cross-reactivity with Cephalosporins, avoid using if history of Pen anaphylaxis
- Frequent cause of drug fever
- Particularly associated with C. diff colitis
- Ceftriaxone can cause biliary sludging
- Ceftriaxone is contraindicated in neonates because it displaces bilirubin from albumin binding sites, resulting in a higher free bilirubin serum concentration

Carbapenems

- Imipenem, Meropenem, Ertapenem
- Have the broadest activity among all β-lactams
- Including MSSA and Amp S Enterococci
- Most strains of Pseudomonas
- Stable against most ESBLs
- Ertapenem can be given as a daily dose, but does not get into CSF readily

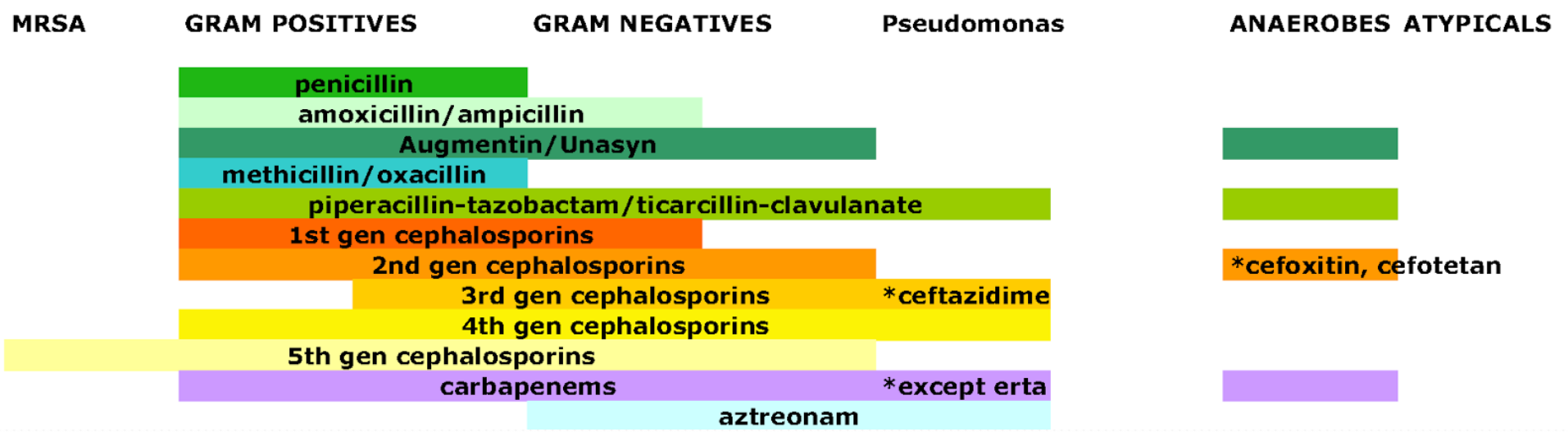
Adverse effects

- Imipenem: in pts with CNS infection, increased risk of seizures due to competitive inhibition of GABA (may be true for Ertapenem as well)
- Other main side effects: diarrhea, rash, vomitting
- Rates of hypersensitivity cross-reaction in pts with Pen allergy is <1%

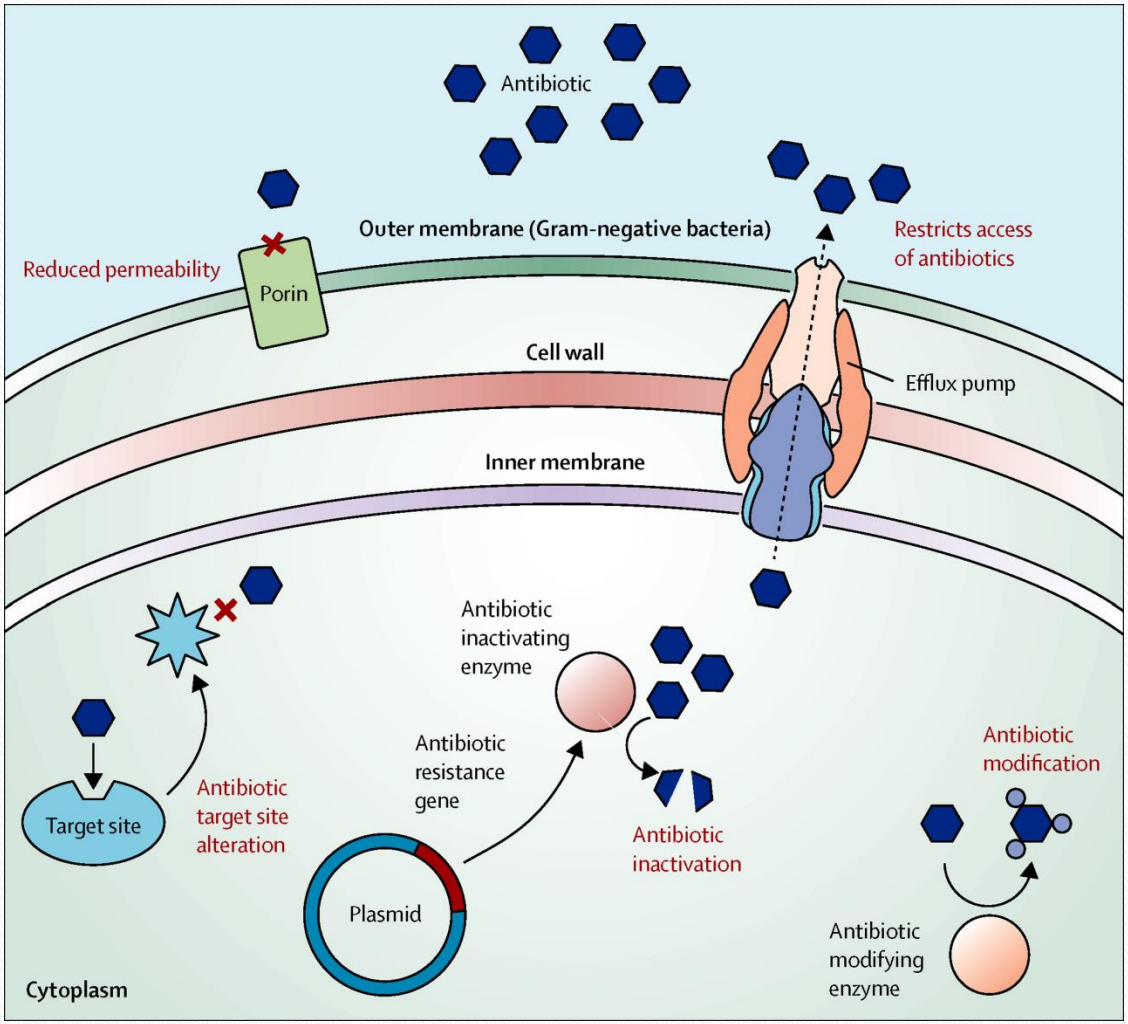
Others

- Vancomycin: forms complexes with the peptide precursors and prevents cross-linking of the peptidoglycan layers, no cross-resistance with β-lactams, active against aerobic and anaerobic Gram positive
- Monobactams: Aztreonam; active against aerobic, GNRs similar to Ceftazidime, is weekly immunogenic and can be used in patients with Pen allergy. If Ceftaz allergy, greater chance of cross-reaction because of similar side chain.

Summary of spectrum



Resistance Mechanisms



Lancet. 2014 Aug 23;384(9944):703-13.

Case 3

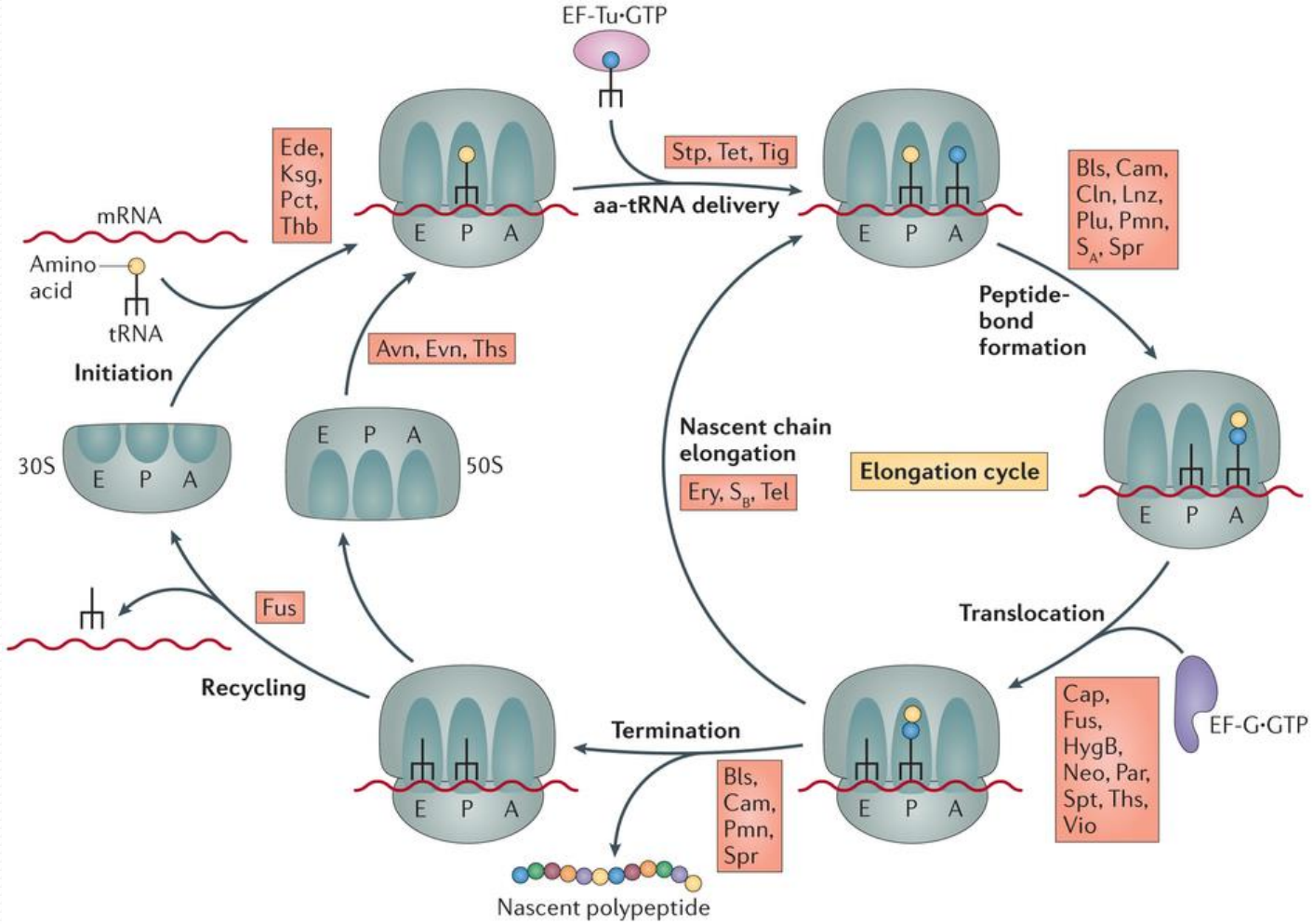
- You are seeing a 7 month old infant in clinic who was born at 30 weeks. His NICU stay was complicated by E. coli meningitis for which he received a prolonged coarse of cefotaxime and gentamicin. At discharge, at 3 months of age, he had a normal hearing test, was feeding well and was at the 10% percentile for his weight. Mom reports that she has not yet started to babble. Which of the following evaluations should be considered at this time?
- A complete blood count
- Head US
- Hearing evaluation
- Ophthalmology exam

Case 4

- Amongst those antibiotics that act by inhibiting protein synthesis, several members this drug class are known to produce side effects related to both drug interactions caused by inhibition of P-450 and cardiac effects (QT prolongation/Torsade de pointes). Which drug class is this?
- Aminoglycosides
- Fluoroquinolones
- Macrolides
- Rifamycins
- Tetracyclines

Protein synthesis inhibitors

- Inhibit protein synthesis at the ribosomal level



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Aminoglycosides

- Bind irreversibly to the 30s subunit, disrupts elongation of the peptide chain by impairing proof-reading
- Co-treatment with β-lactams increases intracellular access of AGs
- Transport to the ribosome is dependent on a proton gradient that is inhibited by low pH and O_2

Anti-bacterial spectrum

- Wide range of aerobic GNRs, MSSA, some enterococci, some mycobacteria
- Gentamicin and Tobramycin have similar spectrum, except Tobra has better activity against Acinetobacter and Pseudomonas
- Amikacin is most resistant to enzymatic breakdown, active against MAC, rapid growing Mycobacteria and Nocardia
- Streptomycin is not commonly used because of limited activity against common GNRs and GPCs, but active against *F. tularensis, Y. pestis* and *M. tuberculosis*

Side effects

- Effect proximal renal tubules, cochlea, vestibular apparatus
- Nephrotoxicity reduced with once daily dose, increased with prolong use, volume depletion, use of loop diuretics
- Cochlear damage manifests tinnitus or high-frequency hearing loss → easy to miss, may be delayed
- Hypomagnesemia, low birth weight and prolong use increases risk of ototoxicity

Resistance

- Mutations in 30s ribosome not that common, multiple binding sites – low-level resistance
- In Staph reduced permeability develops quickly if used as monotherapy
- Plasmid mediated production of AG-modifying enzymes is the most common mechanism of resistance – high-level resistance

Macrolides

- Erythromycin, clarithromycin, azithromycin
- Reversibly bind to the 50s subunit, causes disassociation of peptidyl-tRNA
- Erythromycin: active against Bacteroides, *B. pertussis*, mycoplasma, spirochetes, MSSA, *S. pneumoniae*, Neisseria spp. Legionella.
- Clarithromycin: greater activity against upper resp GNs, *N. gonorrhea*, Chlamydia spp. *S. pneumoniae* resistant rates mirror those of Pen
- Azithromycin: Better activity against *S. pneumoniae*, and GNs such and *V. cholerae*, Shigella.

Adverse effects

- Usually well tolerated
- Most common adverse effect is GI disturbance, most common with erythromycin, a motilin receptor agonist. This is dose dependent.
- Erythromycin use was linked to a seven-fold increase in pyloric stenosis
- Are metabolized by P450 pathway so many drug interactions and potential toxicities
- Case reports suggest an increase in the risk of torsades de pointes; studies have shown prolongation of the QT interval and blockade of the potassium channel important for cardiac repolarization.

Resistance mechanisms

- Many Gram negative inherently resistant due to impermeable outer membrane
- High level resistance can be caused by 1) chromosomal mutation in domain V of the 50S ribosome, 2) plasmid mediated altered methylation of 23S rRNA component of 50S – confers resistance to macrolide and clindamycin
- Efflux pumps – MefA and MsrA (plasmid)

Tetracycline

- Doxycycline, minocycline, tigecycline
- Passively diffuse through the OM and transported actively within the cytoplasm
- Bind reversibly to the 30S ribosome
- Excellent activity against Chlamydia, Mycoplasma and rickettsiae, MSSA, *B. burgdorferi*
- Tigecycline: Broad spectrum – MRSA, VRE, ESBL producers (not pseudomonas)

Adverse effects

- GI side effects most common – most sever esophageal ulceration
- Contraindicated in children <8 yrs – chelates calcium and can deposit in bones and teeth, dose-related effect
- Associated with pseudotumor cerebri – reversible
- Increased sun sensitivity
- Affects absorption of OCPs and iron

Resistance mechanism

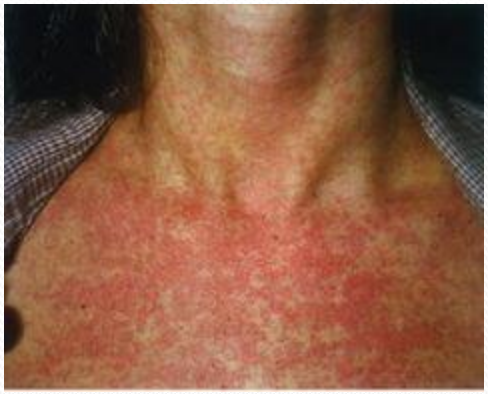
- Efflux pumps
- Target alteration in the ribosome
- Enzymatic inactivation

Lincosamide

- Clindamycin
- Binds 50S ribosome – similar to macrolides (esp erythromycin) therefore potential antagonism
- Active against many Gram positives, not enterococci
- 30-40% of MRSA at Duke is Clinda R
- Anaerobes such as Bacteroides, Fusobacterium, Prevotella, Clostridium (except C. diff),

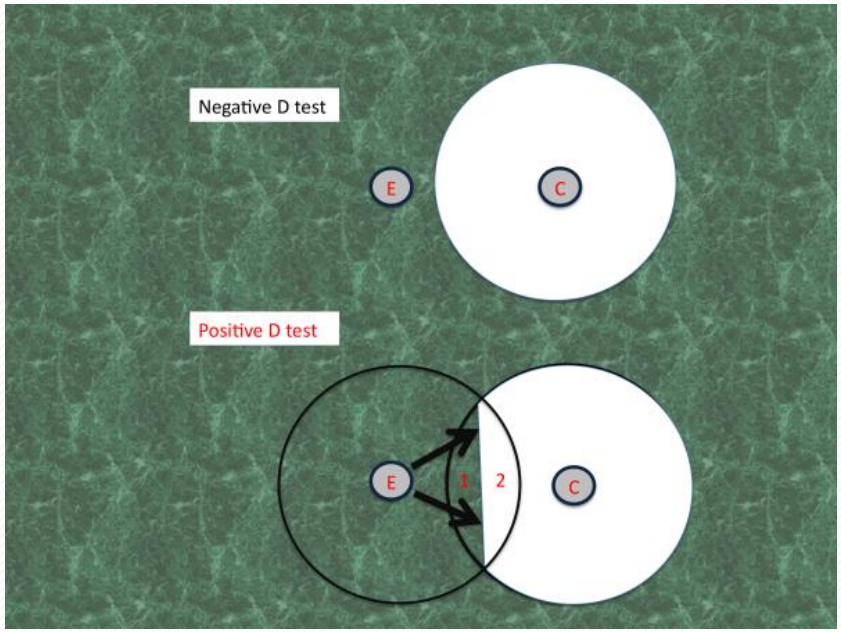
Adverse effects

- Up to 10% of patients can have a generalized morbilliform-like rash
- 20% have self-limited diarrhea – increases risk of C. diff and pseudomembranous colitis
- Colitis is unrelated to dose of drug or route of administration, can occur from 4 days after start or therapy to 2-10 weeks after discontinuation
- In neonates – cases of fatal gasping syndrome associated with preservative Benzyl alcohol



Resistance mechanism

- Alteration of 50S ribosome
- Plasmid mediated resistance similar to macrolide
- Staph isolates that are resistant to macrolides but sensitive to Clindamycin should under go a D-test



Linezolid

- A synthetic compound: new class of oxazolidinone
- Binds 50S ribosome and prevents its binding to the 30S ribosome
- Active against MRSA, CONS, VRE
- Broad activity against Nocardia and non-TB mycobacteria
- No gram negative activity

Adverse effects

- Most common: GI symptoms, rash and headache
- Dose and duration dependent BM suppression – anemia, thrombocytopenia, less commonly neutropenia
- Weekly monitor CBCD if on therapy longer than 2 weeks
- Peripheral and optic neuropathy, lactic acidosis and serotonin syndrome in pts on SSRI

Resistance mechanism

- Target mutations – though cross-resistance with other classes is rare because of novel mechanism
- Resistance in up to 4% of clinical isolated of enterococci esp. *E. faecium*

Case 5

An 18 yr old female presents to clinic with a history of recurrent UTIs. She complains of bilateral flank pain, dysuria and increased urinary frequency. Her last 2 Ucx grew Amp R E. coli. Which of the following antibiotics would NOT be suitable for empiric therapy.

- Levofloxacin
- Moxifloxacin
- Ciprofloxacin
- Amoxicillin-clavulanate
- TMP-SMX

Fluoroquinolones

- Ciprofloxacin, levofloxacin, moxifloxacin
- Derivatives of Nalidixic acid
- Only class to inhibit DNA synthesis – binds DNA gyrase and topoisomerase
- Levo and moxi have greater potency than cipro against GPCs.
- Moxi has activity against anaerobic bacteria, and does not reach adequate concentration in the urine
- Cipro is the most potent against GNRs, active against Pseudomonas and Serratia
- Also active against atypical pathogens and some TB and non-TB mycobacterial strains

Adverse effects

- Most common: GI, headaches, dizziness, rash
- Rare: prolonged QT syndrome, hallucinations, reversible tendonitis, or tendon rupture concern in adolescents, but reported more in >60 yrs

Resistance mechanism

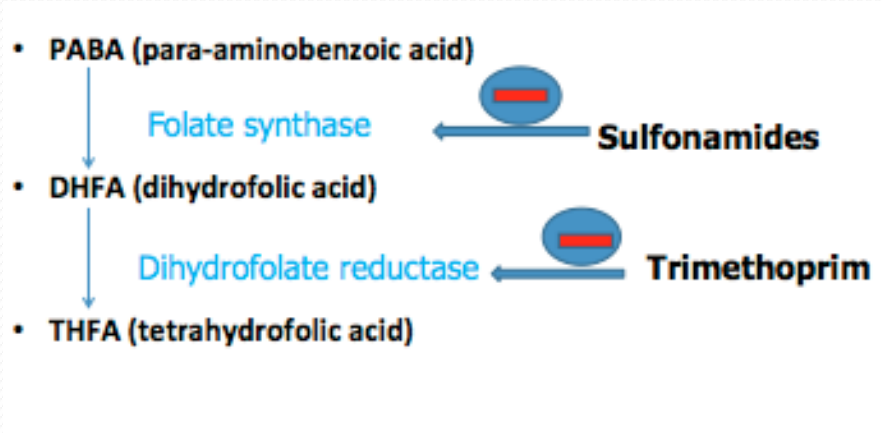
- Chromosomal mediated alteration of targets
- Plasmid mediated resistance among enterobacteriaceae: 1) Qnr protein that protects gyrase, 2) enzyme that inactivates drug
- In some parts of the world resistance among enterobacteriaceae >50%

Sulfonamides

- Structural analogs of p-aminobenzoic acid (PABA) and compete with it in nucleotide synthesis
- SMX combined with TMP is most common member
- SMX competitively inhibits folate synthetase and reduces the amount of dihydrofolic acid
- TMP binds and inhibits dihydrofolate reductase
- Reduced folic acid – essential co-factor in nucleotide synthesis
- Broad activity against

  Gram positives and

  Gram negatives



Adverse effects

- Most common: GI and hypersensitivity in 1-4%– SMX related
- Hypersensitivity icludes erythema nodosum, SJS, anaphylaxis
- CNS: aseptic meningitis
- Interstitial nephritis, hemolytic anemia (G6PD), prolong use → megaloblastic anemia (impaired folate use)
- In neonates causes hyper bili

Resistance mechanisms

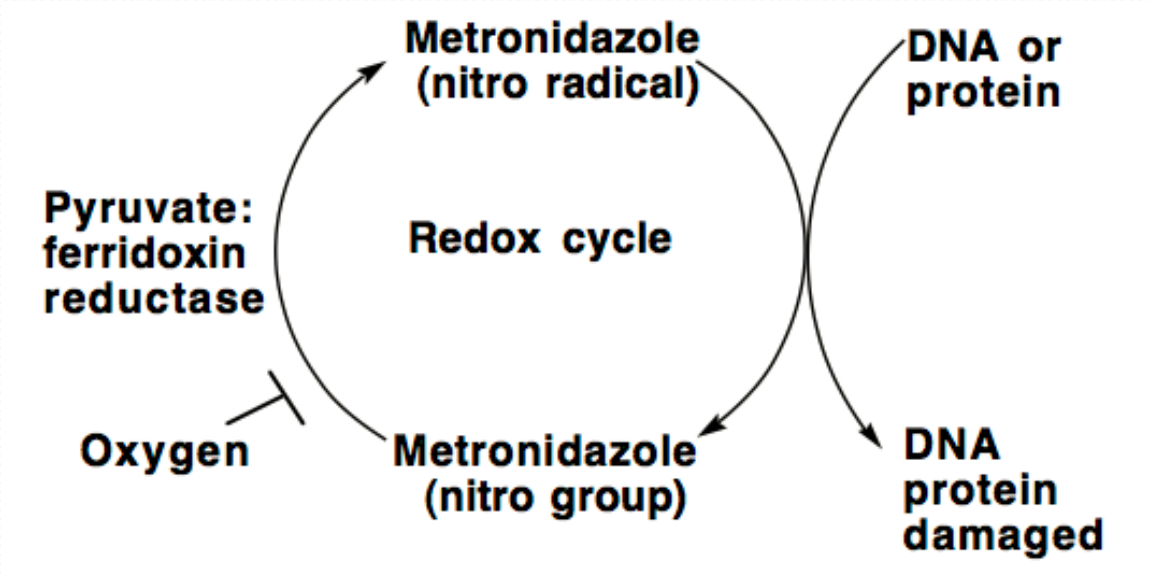
- Hyperproduction of PABA (Neisseria and staph)
- Altered enzyme targets (E. coli, Neisseria, strep)
- Decreased cell wall permeability

Case 6

A 21-year-old female college student is treated with metronidazole after presenting to student health services with itching, discharge, and pain in her vagina. At a party shortly afterward she experiences facial flushing, nausea, tachycardia, dyspnea, headache, and abdominal cramps after consuming alcohol. Serum levels of which of the following are likely elevated in this patient following alcohol consumption:

- Acetaldehyde
- Uric acid
- Cytochrome P-450 enzymes
- Triglycerides
- Amylase

Metronidazole



- Metronidazole is active against a broad array of anaerobes, protozoa, and microaerophilic bacteria.
- Bactericidal activity against *Bacteroides* spp, *Clostridium* spp, *Prevotella* spp, *Fusobacterium* spp.
- Among gram-positive anaerobic bacilli, limited activity against *Actinomyces* spp, *Propionibacterium* spp, and *Lactobacillus* species are resistant to metronidazole.
- Facultative anaerobes such as *Gardnerella vaginalis*
- Metronidazole is also active against anaerobic protozoa such as *T. vaginalis, E. histolytica, Giardia lamblia, Blastocystis hominis,* and *Balantidium coli*.

Adverse effects

- GI: most common, unpleasant metallic taste
- Neurologic: Seizures, peripheral neuropathy, dizziness, vertigo, ataxia, confusion, encephalopathy, irritability, weakness, insomnia, headache, and tremors have been reported among patients receiving metronidazole, particularly among those receiving high doses of the drug
- Disulfaram like reaction

Resistance

- More than 95% of anaerobes remain sensitive to Metronidazole
- C. diff: Of 282, 134 (47.5%) patients resistant to imidazole, 17 (6.1%) resistant to vancomycin, and 9 (3.2%) resistant to imidazole and vancomycin, by PCR testing
- Mechanism of resistance not well understood

Thanks!