Anaerobic infections, metronidazole, clindamycin

MEDCH 561P

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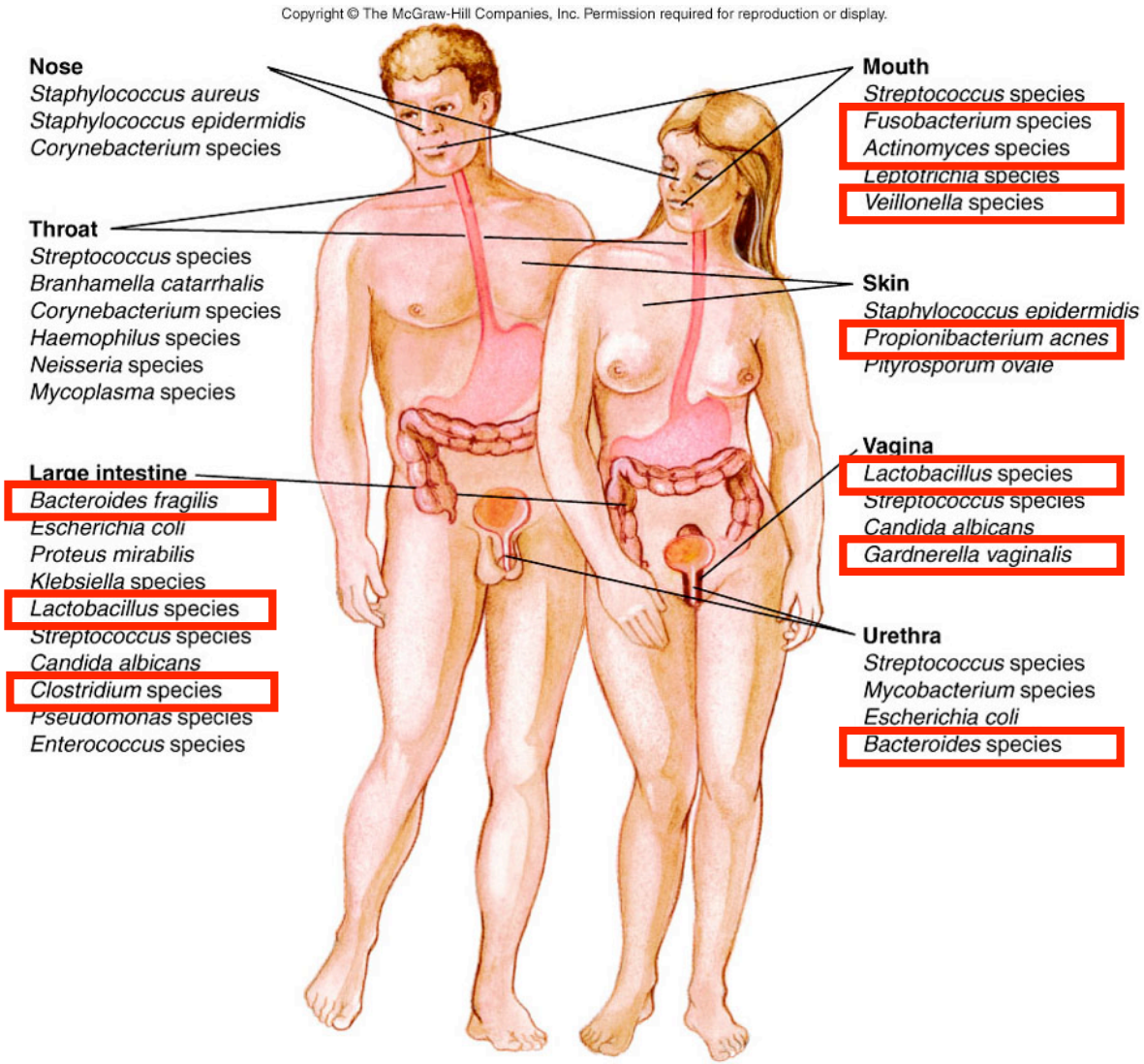
Antimicrobials for anaerobic infections

- Aerobic: Grow in 18% O_2 10% CO_2
- Facultative anaerobes: Can grow in "room air" or under anaerobic conditions
- Moderate anaerobes: Grow in 2-8% O_2
- Strict (obligate) anaerobes: Only grow in <0.5% O_2

- In polymicrobial infections, these different types of bacteria can coexist: e.g. facultative anaerobes can deplete the amount of oxygen present, producing an environment conducive for strict anaerobe growth
- "Fastidious": i.e. "difficult to please" bacteria require specialized environments for growth. As a result, they are hard to isolate, hard to culture, and hard to identify. Many anaerobes are in this category.

Antimicrobials for anaerobic infections

- Origin of infecting bacteria is typically from normal flora: skin, mucosa, gut
- Damage to host tissues allow bacteria to colonize: opportunistic
- Frequently polymicrobial can involve mixtures of anaerobes and aerobes



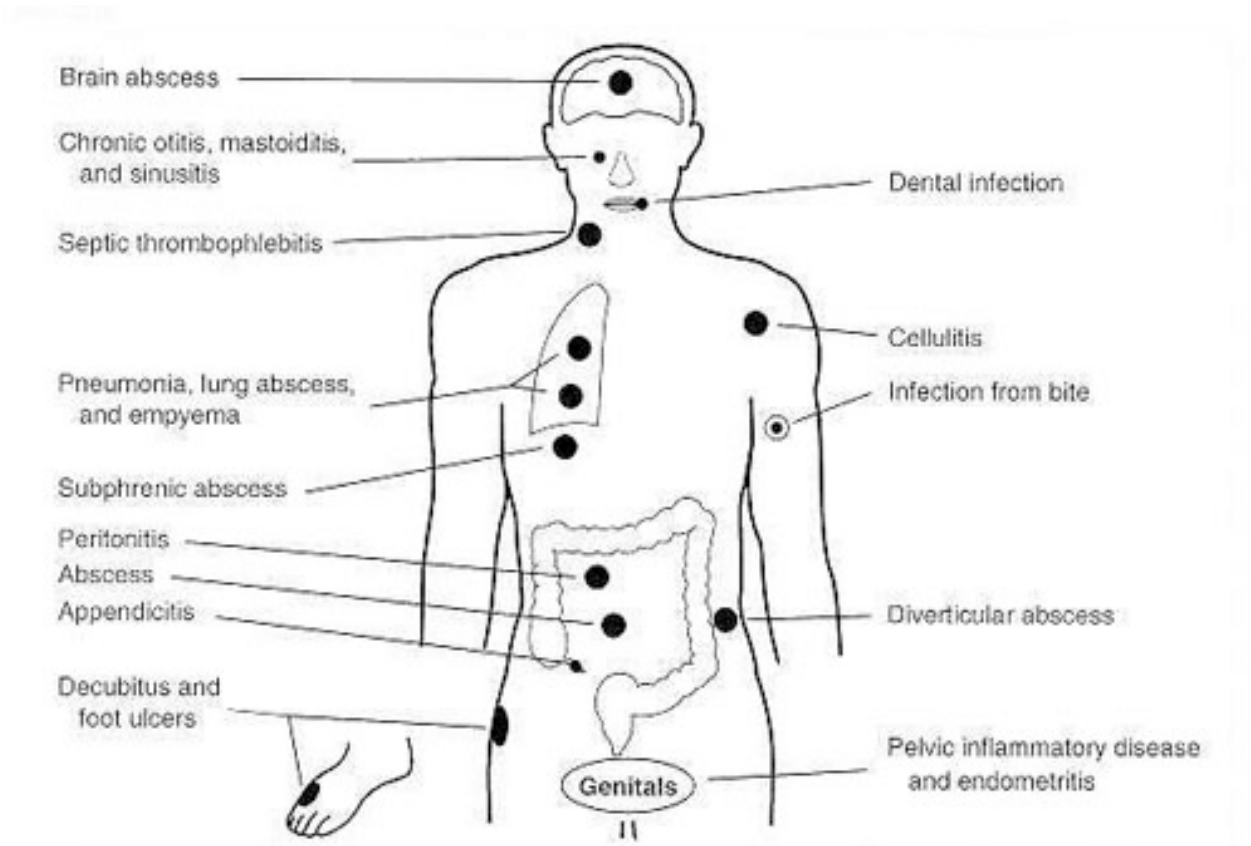
Common anaerobes and infections

Bacterium	Spore forming?	Toxins	Location	Pathology
Gm+ bacilli (rods)				
Actinomyces	no		URT, intestine	actinomycosis
Propionibacteria	no		skin	acne
Lactobacillus	no		mouth, gut, urogenital	bacteremia
Clostridium botulinum	yes	botulinum	exogenous (not flora)	botulism
Clostridium tetani	yes	tetanospasmin	exogenous (not flora)	tetanus
Clostridium perfringens	yes	alpha-toxin, theta-toxin, enterotoxin	gut, exogenous	gangrene (myonecrosis) enteritis, cellulitis
Clostridium difficile	yes	A enterotoxin, B cytotoxin	gut, exogenous	pseudomembranous colitis
Gm- bacilli (rods)				
Bacteriodes fragilis	capsule	enterotoxin	gut	diarrhea; abscess
Bacteriodes spp.	capsule		gut	abscess
Prevotella			mouth, urogenital	
Fusobacterium			mouth, gut	abscess
Porphyromonas			mouth, urogenital	

Common anaerobes and infections

Bacterium	Spore forming?	Toxins	Location	Pathology
Gm+ cocci				
Peptostreptococcus	no		mouth, gut	oropharyngeal infections, brain abscess
Gm- cocci				
Veillonella	no		mouth, gut	opportunist; bite

Traits of anaerobic infections

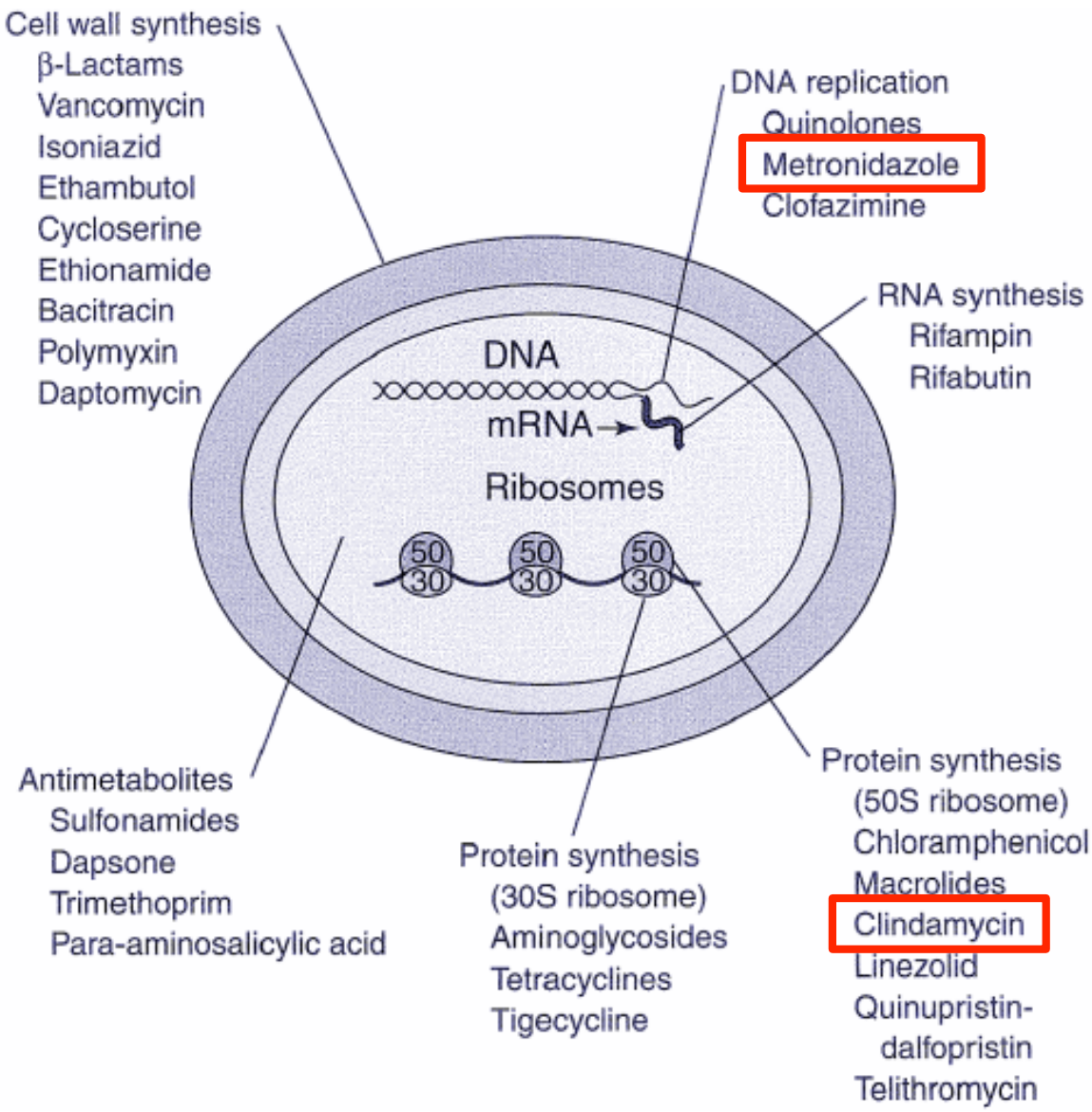


- Abscesses:
  - Limits penetration
  - Acidic pH, hypoxic, reducing environment
  - Debris: dead bacteria; targets in debris?
  - Can have high concentrations of beta-lactamases
  - Inoculum effect: not just the absolute drug concentration that matters for efficacy, but the amount of drug per bacterium or target

Common treatment for infections involving anaerobes

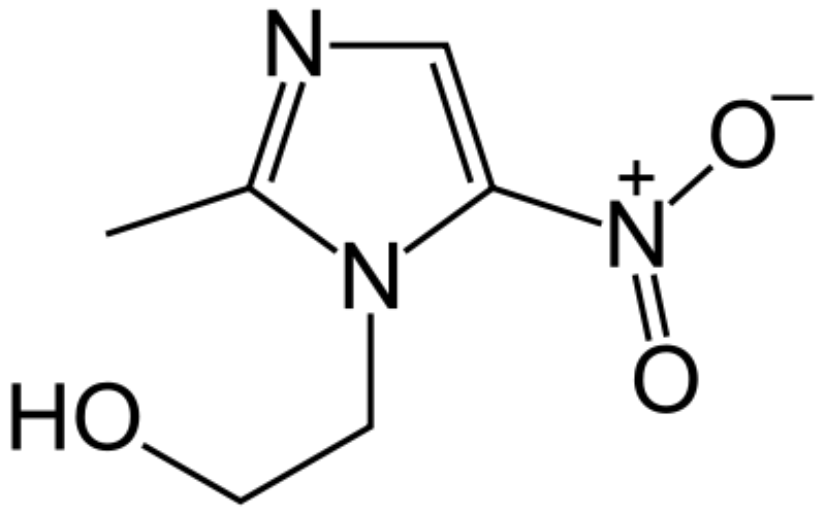
- In many cases draining and debridement is effective/essential
- Frequently used drugs (often in various combinations):
  - Clindamycin
  - Metronidazole
  - Penicillin G
  - Ampicillin/sulbactam
  - Piperacillin/tazobactam
  - Ticarcillin/clavulanate
  - Imipenem/cilastatin
  - Ertapenem
  - Meropenem
  - Doripenem
  - Vancomycin

Antimicrobial targets



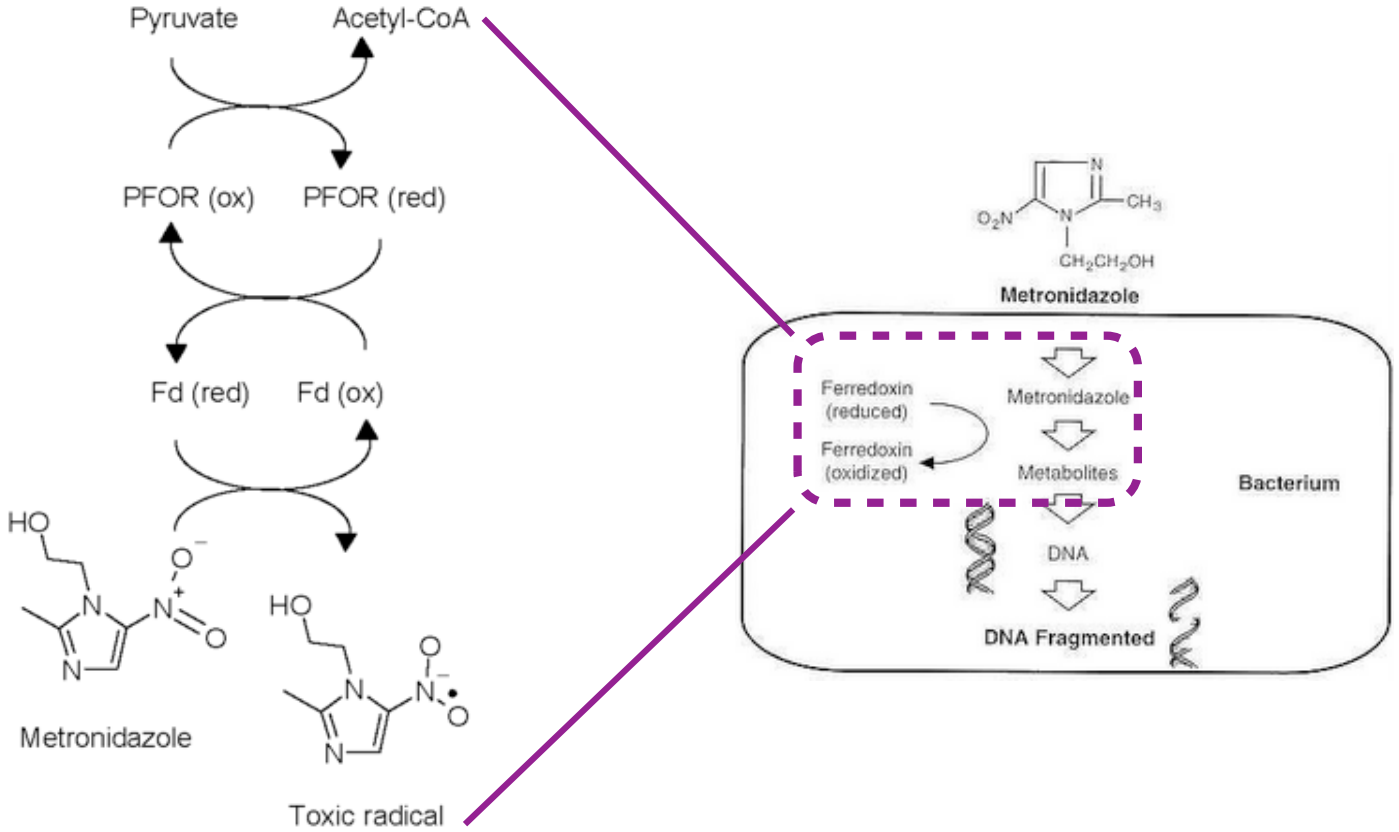
Metronidazole (MTZ)

- Nitroimidazole compound
- In clinical use for >45 years
- Given as PO, IV, or topical
- Anti-anaerobic activity
  - E.g. *C. difficile, B. fragilis,* etc.
- Anti-protozoal, anti-amoeba activity
  - Single celled eukaryotes: e.g. *Giardia, Trichomonas*



MTZ mechanism of action

- Bactericidal, cytotoxic to obligate anaerobes and some facultative anaerobes
- Concentration-dependent killing
- Diffuses across bacterial membranes
- Activated in anaerobic bacterial cytosol by pyruvate:ferrodoxin oxidoreductase system. Such redox pathways are present in anaerobic bacteria and protozoa, but not in aerobic bacteria or host cells.
- Activated radical reacts with numerous bacterial proteins, damaging them
- Radicals also modify the DNA causing it to fragment



MTZ in the body: distribution

- Essentially 100% bioavailable after oral administration
- Reaches very high serum concentrations
- Excellent tissue penetration
- Penetrates blood-brain barrier to CSF (~45%/100% for -/+ meningitis)
  - Good penetration into brain abscesses
- Metabolized in the liver
  - If there is liver impairment, serum concentrations remain high for extended time

MTZ Spectrum of activity: Anaerobic bacteria

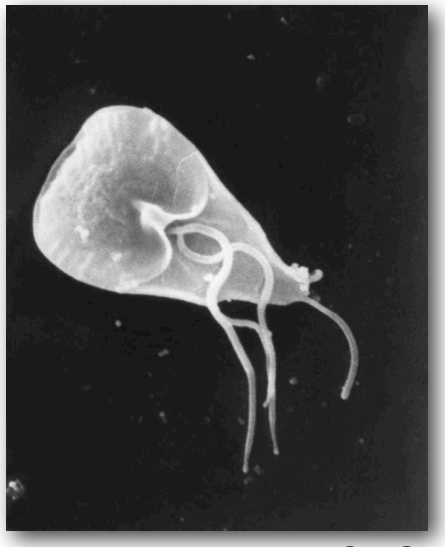
- *Clostridium difficile*
  - Frequent cause of antibiotic-associated diarrhea
  - Pseudomembranous colitis
  - Resistance observed: alternative is vancomycin (oral)
- *Bacteroides* species
- Bacterial vaginosis
  - Bacterial overgrowth, often involving *Gardnerella vaginalis*, other anaerobes
- *Helicobacter pylorii*
  - Peptic ulcers, potentially leading to stomach cancer
  - Combine with proton pump inhibitor (PPI), bismuth, and another antibiotic (e.g. tetracycline)

MTZ Spectrum of activity: Protozoa

- *Trichomonas vaginalis* (“Trich”)
  - Trichomoniasis, an STD; urogenital tract
  - Treat partner concurrently to prevent reinfection

CDC

- *Entamoeba histolytica*
  - Many people are asymptomatic carriers
  - Amoebiasis: gastrointestinal infection
  - Amoebic dysentery (inflammation of colon), colitis: invasion of intestinal lining
  - Can enter blood stream and traffic to liver: abscess



CDC

- *Giardia lamblia*
  - Giardiasis: infection of the small intestine
  - Diarrhea

Uses

- Moderate *C. difficile* infections
  - Vancomycin more effective in severe cases
- Intra-abdominal infections
  - Polymicrobial, but often involving *B. fragilis* (gm- anaerobe)
- Bacterial vaginosis
  - Intra-vaginal gel: low absorption (but serum levels lower than for PO)
- Topical cream
  - Acne (*Propionibacteria acnes*)
  - Not absorbed into system
- CNS infections
  - Administered with other antimicrobials to gain coverage of streptococci: e.g. Pen G, cefotaxime, ceftriaxone; vancomycin (pen allergic)

Adverse reactions

- Boxed warning: potential carcinogen
- Metallic taste: lasts the duration of therapy
- Disulfram-like reaction
  - Avoid alcohol for at least 3 days after last dose
- Rare peripheral neuropathy
- Seizures
- Urine darkens
- Moderate inhibitor of CYP3A4, weak inhibitor of CYP2C9: numerous drug interactions: in the liver, inhibits metabolism of phenytoin, warfarin, carbamazepine, many others
- Pregnancy Category B
  - Pass to fetus through placenta; passed through milk to infant
  - Lack of clear studies
  - Avoid during 1st trimester, only use if clearly needed

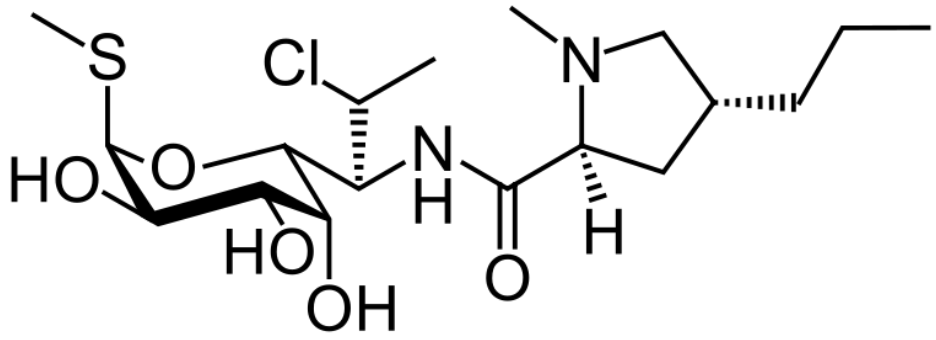
MTZ resistance

- Rare in the US; ~95% of anaerobes tested show sensitivity to metronidazole
- Some evidence of chromasomally and plasmid-encoded resistance
  - Appears to require multiple changes, acquisition of resistance not simple
  - Drug inactivation via chromosomally or plasmid-encoded reductase enzyme (*nim*) that converts MTZ to non-toxic forms instead of to reactive radical
- Less reductase activity, reduces amount of activated drug and reduces uptake
- Increased DNA repair
- Resistance in *Helicobacter pylori* 10-30%
  - Mechanism not well-understood; possibly reduced uptake
  - Efflux pump
- Resistance in *Trichomonas vaginalis* observed
  - Lower levels of reductase activity by reducing expression of enzyme

Metronidazole (MTZ) Summary

- Taken up by anaerobic bacteria, converted to a reactive radical that damages DNA and bacterial enzymes. Bactericidal
- Anti-anaerobic activity
  - *C. difficile*
- Anti-protozoal, anti-amoeba activity
- Given as PO, IV, or topical
  - Excellent oral bioavailability, tissue, abscess penetration
  - CNS
- Resistance is rare
- A number of adverse reactions: disulfram-like, drug-drug interactions

Clindamycin (a lincosamide)



- Binds 50s ribosomal subunit: inhibits protein synthesis
  - Bacteriostatic (can be bactericidal at high conc against some bugs)
  - Same binding site as macrolides, chloramphenicol
  - Strong PAE due to persistent binding to ribosome binding site
- Aerobic activity: *e.g. Staph.* (some MRSA), *S. pyogenes, S. pneumo*
- Anti-anaerobic activity: *B. fragilis, C. perfringens, Fusobacteria spp, Prevotella, Peptostreptococcus*
- Anti-plasmodia: Malaria: used as part of combination therapy

Clindamycin properties

- Mainly used for anaerobic infections
- Well-absorbed: 90% bioavailable afer oral administration
- Penetrates to bone
- Taken into leukocytes and macrophages; good abscess penetration
- Does not penetrate to CNS even during meningitis
- High gut levels even after IV administration
  - Excreted in bile: enterohepatic recycling
- Associated with propensity to cause *C. diff.* (boxed warning). Antibiotic associated diarrhea (AAD).

Spectrum of activity

- Aerobes
  - *Staph* including some coverage of CA-MRSA: by shutting down protein synthesis, Clindamycin also inhibits alpha cytotoxin expression for *S. aureus*
    - Other antimicrobials can induce alpha-toxin: e.g. beta-lactams, FQ
  - *Enterococci* are resistant
  - *H. flu*, *Neisseria meningitidis, Mycoplasma pneumoniae* resistant
  - Gm- aerobes generally resistant (poor Clindamycin permeability of outer memb)
- Anti-anaerobic activity: distinguishing attribute for Clindamycin
  - *B. fragilis*: increasing resistance has led to lower efficacy, (not recommended for intra-abdominal infections)
  - *C. perfringens*
  - *Propionibacteria*
  - *Fusobacteria spp*
  - *Prevotella*
  - *Peptostreptococcus*
  - *Actinomyces*
- Anti-plasmodia
  - Malaria: used as part of combination therapy

Clindamycin Uses

- Anaerobic infections
- Alternative drug for serious *Strep., Staph.* infections in penicillin allergic patients
  - But generally not first choice
- Alternative agent for:
  - STDs: BV, chlamydia
  - Parasites: *Toxoplasma gondii* (protozoa; cat feces, hazard to pregnant women), *pneumocystis jiroveci* (fungal pneumonia)
- For necrotizing fasciitis, can knock down *S. pyogenes* and reduce toxin production (pyogenic exotoxins, superantigen)
- Topical treatment for acne

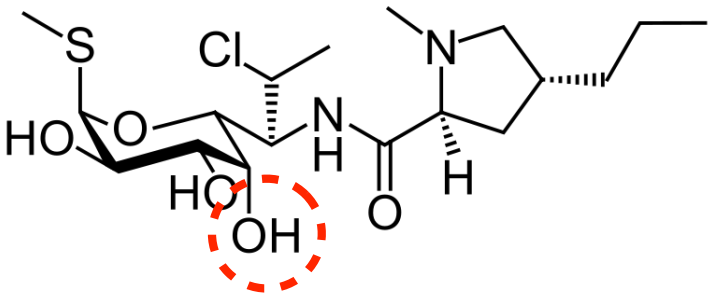
Clindamycin adverse reactions

- **Boxed warning:** Colitis due to fungal or bacterial overgrowth, *C. difficile.*
- Antibiotic associated diarrhea:
  - 2-20% of patients report
  - Some reports state PMC no more likely than with beta-lactam, others indicate several times more likely
  - Topical and vaginal preparations may also lead to AAD due to absorption
  - Can occur during therapy or weeks after therapy is done
- Skin rash: ~10% of cases
- Neuromuscular blocking properties: use with caution in patients receiving other blocking agents
- Reversible liver toxicity, jaundice (rare)
- Hematopoietic effects: neutropenia, leukopenia, etc. (rare)
- Pregnant women with BV:
  - Clindamycin PO associated with fewer miscarriages and pre-term birth
  - Intravaginal Clindamycin: greater risk of preterm birth (do not use)

Mechanisms of resistance

- Altered ribosomal binding site:
  - Methylation of an adenine in 23s RNA involved in binding (e.g. in *B. fragilis*)
  - Alteration of 50s ribosomal protein at binding site
  - These changes also give rise to macrolide resistance. Cross-resistance between macrolides and clindamycin. If resistant to one, likely resistant to the other too.

- Enzymatic modification of the drug:
  - Nucleotidylation of OH group on clindamycin



- In Gram-, poor penetration of outer membrane

Clindamycin Summary

- Inhibits bacterial protein synthesis; bacteriostatic
  - Cross-resistance with macrolides, chloramphenicol
- Anti-Staph, Strep activity
  - Also reduces toxin production
- Anti-anaerobic activity
- Anti-malarial activity
- Given as PO, IV, or topical
  - Excellent tissue, abscess penetration
  - not CNS
- Increased resistance, particularly with *B. fragilis*
- Associated with increased risk of AAD, *C. difficile* overgrowth