Antimicrobials for anaerobic infections

- **Aerobic**: Grow in 18% O₂ 10% CO₂
- **Facultative anaerobes**: Can grow in “room air” or under anaerobic conditions
- **Moderate anaerobes**: Grow in 2-8% O₂
- **Strict (obligate) anaerobes**: Only grow in <0.5% O₂

- 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
- Frequently polymicrobial can involve mixtures of anaerobes and aerobes

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

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Spore forming?</th>
<th>Toxins</th>
<th>Location</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gm+ cocci</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>no</td>
<td></td>
<td>mouth, gut</td>
<td>oropharyngeal infections, brain abscess</td>
</tr>
<tr>
<td>Gm- cocci</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veillonella</td>
<td>no</td>
<td></td>
<td>mouth, gut</td>
<td>opportunistic; bite</td>
</tr>
</tbody>
</table>

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
Nitroimidazole compound
In clinical use for >45 years
Given as PO, IV, or topical
Anti-anaerobic activity
  - E.g. *C. difficile*, *B. fragilis*,
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**

- 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

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**Spectrum of activity: Protozoa**

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

- *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

- *Giardia lamblia*
  - Giardiasis: infection of the small intestine
  - Diarrhea
**Spectrum of activity: Anaerobic bacteria**

- *Clostridium difficile*
  - Frequent cause of antibiotic-associated diarrhea
  - Pseudomembranous colitis
  - Resistance observed: alternative is vancomycin (oral)

- Bacterial vaginosis
  - Bacterial overgrowth, often involving *Gardnerella vaginalis*, other anaerobes

- *Helicobacter pylorii*
  - Peptic ulcers, potentially leading to stomach cancer
  - Combine with PPI, bismuth, and another antibiotic (e.g. tetracycline)

**Uses**

- Intra-abdominal infections
  - Polymicrobial, but often involving *B. fragilis* (gm- anaerobe)
  - Pseudomembranous colitis
  - Resistance observed: alternative is vancomycin (oral)

- Bacterial vaginosis
  - Intra-vaginal gel: some 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

- Metallic taste: lasts the duration of therapy
- Disulfiram-like reaction
  - Avoid alcohol for at least 3 days after last dose
- Rare peripheral neuropathy
- Seizures
- Urine darkens
- Drug interactions: in the liver, inhibits metabolism of phenytoin, warfarin, carbamazepine, numerous 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 chromosomally and plasmid-encoded resistance
  - Appears to require multiple changes, hence acquisition of resistance not simple
- Less reductase activity, reduces amount of activated drug and reduces uptake
- Increased DNA repair
- Drug inactivation via chromosomally or plasmid-encoded reductase enzyme ($nim$) that converts MTZ to non-toxic forms instead of to reactive radical

- 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
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

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Clindamycin properties

- Mainly used for anaerobic infections
- Well-absorbed: 90% bioavailable after 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. related 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

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
Adverse reactions

- 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
• Competitive inhibitor for para-aminobenzoic acid (PABA) in the biosynthesis of folic acid

• Depleting folic acid hinders the eventual production of DNA so bacteria are unable to reproduce

• Often given with trimethoprim (e.g., SMX/TMP), synergistic
  • Alone, each is bacteriostatic, together bactericidal

• Mammalian cells do not synthesize folate, they actively import dietary folate

• Bacteria do not take up folate, they make it
Spectrum of activity

- Not very effective against anaerobes, some oral anaerobes
- Urinary tract infections (UTI)
  - *E. coli* (in some communities, resistance is >20%)
  - *Proteus mirabilis*
- CA-MRSA: in out-patient setting, an alternative to vancomycin
- *H. influenzae*
- *Salmonella*
- *Toxoplasma gondii*: toxoplasmosis
- *Pneumocystis jiroveci*

Products

- **Trimethoprim/Sulfamethoxazole** (1:5 ratio TMP:SMX, “trim-sulfa”, co-trimoxazole)
  - CA-MRSA
- **Sulfadiazine or Sulfadoxine-pyrimethamine**
  - *Plasmodium falciparum* (malaria) if choloquine resistant
- **Sulfadiazine-pyrimethamine**
  - *Toxiplasma gondii*
- **Dapsone**
  - *Mycobacterium leprae* (leprosy)
Metabolism and toxicity

- "Slow acetylators" have a higher risk of developing toxicity, lower clearance
- Patients deficient in enzyme G6PD higher risk of developing hemolytic anemia due to reduced ability to regenerate glutathione