Anaerobic Infections

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Goals

• To understand the metabolic features of anaerobes and relate them to the pathogenesis of anaerobic infections.

• To determine what host factors predispose to the evolution of serious anaerobic infections, such as diabetes, soft tissue injury, compromise of mucosal barriers and wound contamination with soil anaerobes.

• To be able to recognize an anaerobic infection and plan interventions based upon those factors that will inhibit the progression of such infections, including appropriate choice of antibiotics to cover them.
Medically Important Bacteria

Normal (pyogenic) Bacteria: Grow easily in routine culture

Aerobic and facultative

Weirdo Bacteria: Often require special procedures

Anaerobes: Above and below the diaphragm
Anaerobes: Above and below the diaphragm

Gram-positive

Cocci

Rods: Clostridium, Propionibacterium, Lactobacillus

Gram-negative

Cocci

Rods: Bacteroides, Prevotella, Fusobacterium
What is an “Anaerobe”

• Strict anaerobes (obligate anaerobes) grow in the absence of oxygen (they cannot tolerate 0.5% $O_2$).

• Some anaerobes are aerotolerant (they can live in the presence of small amounts of oxygen).

• Most clinically important anaerobes (*Bacteroides fragilis*, *Prevotella* spp. and *Fusobacterium* spp.) are moderate anaerobes (they can tolerate 2% to 8% $O_2$).

• Other bacteria are considered to be facultative anaerobes, they can live with or without the presence of $O_2$ (i.e. grow aerobically or anaerobically).
Diverse microbiota along the GI tract
## Normal Flora of Humans

<table>
<thead>
<tr>
<th>Anatomical Site</th>
<th>Bacterial Concentrations (per ml or per gram)</th>
<th>Anaerobes : Aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Airway-Saliva</td>
<td>$10^8 - 10^9$</td>
<td>1 : 1</td>
</tr>
<tr>
<td>Gingival crevices</td>
<td>$10^{11} - 10^{12}$</td>
<td>1000 : 1</td>
</tr>
<tr>
<td>GI Tract - Ileum</td>
<td>$10^4 - 10^7$</td>
<td>1 : 1</td>
</tr>
<tr>
<td>Colon</td>
<td>$10^{11} - 10^{12}$</td>
<td>1000 : 1</td>
</tr>
<tr>
<td>Female Genital Tract</td>
<td>$10^8 - 10^9$</td>
<td>3 - 5 : 1</td>
</tr>
<tr>
<td>Endocervix and Vagina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin surface</td>
<td>$10^4 - 10^6$</td>
<td>100 : 1</td>
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<tr>
<td>and Intrafollicular</td>
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</table>
# Selected Predominant Anaerobes of the Normal Flora of Humans

<table>
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<th>Predominant Anaerobes</th>
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<tr>
<td>Gingival crevices</td>
<td><em>Bacteroides</em></td>
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<tr>
<td></td>
<td><em>Prevotella</em></td>
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<td></td>
<td><em>Fusobacterium</em></td>
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<td></td>
<td><em>Actinomyces</em></td>
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<td></td>
<td><em>Anaerobic cocci</em></td>
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<tr>
<td>Colon</td>
<td><em>Bacteroides</em></td>
</tr>
<tr>
<td></td>
<td><em>Prevotella</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium</em></td>
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<tr>
<td>Female Genital Tract</td>
<td><em>Lactobacillus</em></td>
</tr>
<tr>
<td></td>
<td><em>Bacteroides</em></td>
</tr>
<tr>
<td></td>
<td><em>Prevotella</em></td>
</tr>
<tr>
<td>Skin</td>
<td><em>Propionibacterium acnes</em></td>
</tr>
</tbody>
</table>
General Properties of Anaerobes

- Anaerobes are fastidious and difficult to isolate.
- Require special collection, transport and culture.
- Anaerobes grow slowly in the laboratory.
- Anaerobic infections are likely to be polymicrobial rather than a single organism.
Typical mixed anaerobic infections

- Most anaerobic infections are mixed flora and not caused by a single organism.

- Note the presence of rods and cocci which are both Gram positive and negative.
Infections tend to occur from normal flora spread from a breach in a contiguous location.

Some infections occur in the setting of mucosal barrier defects (Colon cancer, micro-perforation of diverticuli, aspiration in setting of impaired mental status due to alcohol).

Other infections/syndromes may be introduced from exogenous sources (Tetanus, Botulism and C. difficile).
Anaerobic Oral Flora

- Mouth flora is predominately anaerobic.
- Anaerobic infections caused by oral flora are generally mixed infections, not associated with a single organism.
Anaerobic Pulmonary Infection
Lung Abscess and Empyema

Empyema
Air-fluid level within a lung abscess
Diagnosis of Anaerobic Infections (1)

- A closed space infection, often adjacent to a mucosal surface.
- Often subacute presentation.
- Foul smelling discharge and fetid odor.
- Necrotic gangrenous tissue and abscess formation.
- Gas formation within tissues (N.B. Enterobacterales can also produce gas).
- Mixed flora seen on Gram staining of tissues.
- Bacteremia without growth of organisms in aerobic blood culture bottles.
Gas Production by Anaerobes

- Physical finding: Crepitus on palpation of the neck area.
- Gram stain of aspirated material will show mixed flora.
- Culture will show several species of anaerobic bacteria.
Diagnosis of Anaerobic Infection (2)

- Infections occurring on antibiotics that are not active against anaerobic flora.
- Infections related to tumor / destructive lesion.
- Septic thrombophlebitis: Eg. septic abortion with pulmonary emboli.
- Bite wound infections, often human bites.
- Myositis or fasciitis from a crush injury.
• Associated with adjacent oral flora:
  – *Bacteroides* spp., *Prevotella* spp., *Fusobacterium* spp. and *Streptococcus* spp.

• Central nervous system: Brain and epidural abscesses

• Pleural and pulmonary infections
  – Pneumonia
  – Empyema: weight loss, anemia, subacute presentation

• Upper airways: Gingivitis, dental abscesses and perimandibular space infections.
  – Lemierre’s syndrome: pharyngitis complicated by jugular venous septic thrombosis, septic pulmonary emboli, with *Fusobacterium necrophorum* bacteremia
  – Ludwig’s angina: sublingual and submandibular space infection leading to tongue protrusion and potential asphyxia
Adjacent normal flora:
- Colon (*Bacteroides* spp., *Prevotella* spp., *Clostridium* spp.)
- Pelvic (*Lactobacillus* spp., *Bacteroides* spp. and *Prevotella* spp.)

Intra-abdominal infections
- Peritonitis
- Abscess (*Bacteroides fragilis* most common, however may be mixed other GI microbiome organisms)
Anaerobic Infections; Female Genital Tract

• Adjacent normal flora:
  – Colon (*Bacteroides* spp., *Prevotella* spp., *Clostridium* spp.)
  – Pelvic (*Lactobacillus* spp., *Bacteroides* spp. and *Prevotella* spp.)

• Tubo-ovarian abscess, Septic thrombophlebitis of pelvic veins, Amnionitis, Endometritis

• Toxic shock-like syndrome
  – Associated with *Clostridium sordellii* after abortion (spontaneous or induced), childbirth or other gynecologic procedure
  – Patients present with edema, effusions, leukemoid reaction, hemoconcentration, followed by shock. Fever tends to be present.
Anaerobic Infections; SSTI

• Exogenous introduction or predominant adjacent flora:
  – Human bites/clenched fist-mouth injuries: (oral anaerobes)
  – Diabetic foot abscess: (Mixed; GI microbiome esp. *B. fragilis*)
  – Clostridial cellulitis-(e.g. *C. perfringens*) post trauma or surgery-gas found in skin.
  – Necrotizing fasciitis
    • Mixed aerobic/anaerobic infection. May occur post trauma/surgery in diabetics, peripheral vascular disease or immunocompromised patients.
    • Fournier’s gangrene: abrupt, severe pain in the perineal area, with infection rapidly spreading to gluteal muscles and abdominal wall or penis/scrotum in males if unchecked
    • Monomicrobial - Group A streptococcus - most common
Conditions for Diagnosis

- Requires agar stored under anaerobic conditions
- Culture and characterization of organisms in an anaerobic environment, usually under nitrogen atmosphere.
• Some anaerobic infections may require surgical debridement/drainage in addition to antibiotics (eg. Brain and epidural abscesses, Empyema, Intra-abdominal abscess, Necrotizing fasciitis, Clostridial cellulitis, Diabetic foot infections)

• Antibiotics: **MICU Team**
  – Metronidazole
  – Imipenem (Meropenem, Doripenem, Ertapenem)
  – Clindamycin, Chloramphenicol [and Cefotetan]
  – Unasyn (Ampicillin-sulbactam), Zosyn (Piperacillin-tazobactam)
  – Tigecycline
Case 1

• A 19 y/o girl presents to her pcp with c/o of a sore throat. Her boyfriend is not ill and a monospot is negative. Subsequently within less than 2 weeks she presents to the YNHH ED with fevers, hypoxia and hypotension, requiring intubation and vasopressors.

• CT of her neck and chest reveals multiple pulmonary cavitary lesions and a thrombosed left internal jugular vein. Her anaerobic blood cultures are growing a Gram negative rod.
You suspect Lemierre’s syndrome. The most likely organism is?

– *Clostridium difficile*
– *Bacteroides fragilis*
– *Fusobacterium necrophorum*
– *Peptostreptococcus spp.*
Case 2

• An afebrile 10 month old child presents to the ED with recent constipation and generalized weakness. His parents noted poor head control, poor suck, and weak cry.

• While under your care in the ED you note new onset of cranial nerve palsies, his extremities become markedly more floppy and he develops hypoxia requiring intubation.

• The family reports that they recently changed to a non-lactose formula and began adding honey to sweeten the soy-based milk
Case 2

• You suspect?
  – Clostridium tetani
  – Clostridium difficile
  – Clostridium botulinum
  – Clostridium perfringens
The likely culprit
C. *botulinum*

- **Microbiology**
  - Anaerobic gram-positive rod. Spores are highly heat resistant and found in soil and marine environments
  - Home canned foods are the most common source

- **Disease Types**
  - Food borne botulism (25%)
    - Usually associated with home canning
  - Wound botulism
  - Infant botulism (72%) (avoid honey)
C. botulinum

• Pathogenesis
  – Botulinum neurotoxin can be ingested or produced in intestine or wound
  – Toxin enters the blood stream and is transported to peripheral nerve endings where it interferes with release of Ach

• Food Borne Botulism
  – Wide spectrum of illness
  – Incubation 18-36 hours
  – Cranial nerve involvement occurs early
    • Diplopia, ptosis, dysarthria, dysphagia
  – Symmetric, descending paralysis
  – Respiratory failure and death is possible
C. botulinum

• Food borne Botulism
  – Patients are afebrile and may c/o:
    • Nausea, vomiting, abdominal pain
    • Dizziness, blurred vision, dry mouth, very dry/sore throat, constipation and urinary retention

• Wound Botulism
  – Long incubation period
    • ~10 days
    • No GI symptoms. Wound may appear benign
  – Symmetric descending paralysis noted
  – Risks include heroin use, C-section, trauma with soil contamination
**C. botulinum**

- **Treatment**
  - Close monitoring and supportive care
  - Antitoxin (available from CDC)
    - Only inactivates unbound toxin
    - Needs to be given within 72 hours of symptom onset
Case 3

• A 72 y/o F with h/o dementia presents from an ECF with fever, diarrhea and abdominal cramping. She was recently placed on cefazolin x 6 weeks for osteomyelitis and subsequently was noted by staff to have decreased PO intake, voluminous diarrhea with c/o of abdominal pain. Her stools did not remit with addition of ciprofloxacin, she is sent to the ED with report of a markedly increased WBC count.
Case 3

- You suspect pseudomembranous enterocolitis. Your main concern is infection with which organism?
  - *Clostridioides difficile*
  - *Bacteroides fragilis*
  - *Fusobacterium necrophorum*
  - *Peptostreptococcus spp.*
Antibiotic Associated Colitis

- Colitis due to overgrowth of toxin-producing *C. difficile*.
- Pseudomembranous colitis is shown above.
- Arrows on CT scan show thickened bowel wall.
C. difficile

• Microbiology
  – Spore forming Gram positive rod
  – Normal bowel flora or acquired-recent hospital or nursing facility
  – Organism produces two toxins (A and B)

• Pathophysiology
  – An altered intestinal flora usually results from antibiotic exposure
  – Toxin production and disease occurs due to rapid growth of toxin producing strains in the setting of decrease in competing flora
Clinical Manifestations
- Diarrhea preceded by recent exposure to antibiotics
- Abdominal cramping, fever, leukocytosis and increased stool WBC

Complications
- May include: dehydration, hypotension, toxic megacolon, colonic perforation
C. difficile

• Diagnosis
  – Multiple approaches available:
    • PCR: Too sensitive?
    • 2 Step: Bug +/- → Toxin +/-
    • Combo: Bug & Toxin +/-

• Treatment (Change in 2018 Guidelines)
  – First Line: vancomycin (oral) or fidaxomicin
    • Fidaxomicin:
      – Novel, narrow spectrum macrocyclic antibiotic
      – Expensive and not better than vancomycin for most cases
      – Its use is usually reserved for relapsed / refractory cases

  – If first line is limiting: metronidazole
Case 5

• A 44 y/o male is admitted to your service on your call night.

• On review of his last discharge summary you note that he was recently hospitalized for an episode of diverticulitis.

• He now presents with c/o recurrence of abdominal pain and fevers. LLQ tenderness is noted on exam.
Case 5

- CT of his abdomen and pelvis reveals an intra-abdominal abscess.
- You initiate antibiotics with pipercillin-tazobactam + vancomycin
- Despite therapy on hospital day 2, one out of four of his blood culture bottles return positive with an anaerobic gram negative rod
Case 5

- You suspect the most likely organism is?
  - *Clostridium difficile*
  - *Bacteroides fragilis*
  - *Fusobacterium necrophorum*
  - *Peptostreptococcus spp.*
Bacteroides fragilis

- Anaerobic gram negative rod
- Members of the phylum Bacteroidetes comprise a significant proportion of the anaerobes in the colon
- *B. fragilis* is only a small percentage of this phylum, but is one of the most common anaerobes isolated from intra-abdominal abscesses
- Can make a $\beta$-lactamase
- A “marker” organism for other anaerobes; more aerotolerant
Case 6

• While rotating through the ED you are asked to evaluate a 65 year old homeless male who presented with trismus (lockjaw) and difficulty swallowing.

• After talking with the patient you note that he is febrile and is sweating profusely. You also gather that his symptoms began after cutting his hand on a piece of metal he found on the New Haven green.
Case 6

• The most likely diagnosis is?
  – Botulism
  – Syphilis
  – Tetanus
  – Ehrlichiosis
C. tetani

• Microbiology
  – Gram positive anaerobic rod
  – Spores are found in soil, feces of many animal species, human skin and contaminated heroin

• Epidemiology
  – Occurs worldwide. Infection occurs through contamination of wounds.
  – May follow elective surgery, burns, puncture wounds, crush wounds, otitis media, dental infections, animal bites, abortion and pregnancy
  – May be a complication of IVDA (especially heroin), piercing, tattoos
C. tetani

• Pathogenesis
  – Usually enters through a wound. Under anaerobic conditions, the spores germinate. Local toxin production
  – Dissemination of toxin via blood and lymphatics. Toxin interferes with neurotransmitter release
  – Unopposed muscle contraction

• Clinical Features
  – Incubation period 3-21 days. Trismus often first sign
  – Neck stiffness, difficulty swallowing and rigidity of abdominal muscles may be seen. Fever may be present
  – Sweating. HTN and tachycardia, Muscle spasms
  – Tetanic seizure: sudden burst of tonic contraction of muscle groups (flexion and adduction of arms, clenched fists, lower extremity extension)
C. tetani

- Clinical diagnosis
  - No confirmatory laboratory test. Recovered from wound in only ~30%

- Antitoxin levels can be measured, but “protective” levels never rule out disease

- Management
  - Clean wounds. Supportive care
  - Tetanus immune globulin-only removes unbound tetanus toxin. IVIG can be used if TIG unavailable
Anaerobic organisms are present throughout the human body (esp. at mucosal sites).

Most infections involving anaerobes are mixed and often occur adjacent to mucosal sites.

*B. fragilis* is a *marker* of anaerobe involvement at sites of infection.

Some commonly used antibiotics cover most anaerobes, and body-site specific treatment guidelines often incorporate anaerobic coverage.

There are important clinical syndromes involving specific anaerobes that you must know.