Anaerobic infections

PART 3: Infection with Gram-negative obligate anaerobes (*Bacteroides* spp. and other abscess-forming bacteria)

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What are these lectures about?

- **Clostridium spp.**
  - Gas gangrene/myonecrosis
  - Tetanus
  - Botulism
  - Antibiotic-associated colitis
  - C. perfringens, C. septicum, C. histolyticum, C. novyi, etc.
  - C. tetani
  - C. botulinum
  - C. difficile

- **Bacteroides spp.**
  - Abscesses
  - B. fragilis, B. distasonis, B. thetaiotamicron

- **Other obligate anaerobes**
  - Fusobacterium, Prevotella, Porphyromonas spp.
### Bacterial species in the colon present in >90% of fecal specimens

<table>
<thead>
<tr>
<th>Bacterial Category</th>
<th>Log organisms/gm (dry weight)</th>
<th>Range of log organisms/gm (dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides</td>
<td>11.3</td>
<td>9.3 – 13.8</td>
</tr>
<tr>
<td>Eubacterium</td>
<td>10.8</td>
<td>5.1 – 13.6</td>
</tr>
<tr>
<td>Anaerobic cocci</td>
<td>10.7</td>
<td>4.0 – 13.6</td>
</tr>
<tr>
<td>Clostridium</td>
<td>9.9</td>
<td>4.0 – 13.2</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>8.9</td>
<td>3.9 – 12.8</td>
</tr>
<tr>
<td>Gram-negative facultative</td>
<td>8.7</td>
<td>4.0 – 12.5</td>
</tr>
<tr>
<td>Other facultative organisms</td>
<td>6.8</td>
<td>1.0 – 12.5</td>
</tr>
</tbody>
</table>

Data Source: Mandell et al. Principles & Practice of infectious Diseases
**Composition of Feces**

- **Bacteria**
  - Undigested debris
  - Gram- obligate anaerobes
  - Gram+ obligate anaerobes
  - All facultative bacteria (Gram + and Gram -)
Gram Stain of Feces

Gram-negative obligate anaerobes

Gram-positive obligate anaerobes

Gram-negative facultative bacteria

Gram-positive facultative bacteria
Case: appendicitis

• An 18-year-old college freshman comes to the hospital with diffuse abdominal pain, diarrhea, and nausea without vomiting. Pain is localized to the right side of the abdomen.
• P.E.: tenderness with rebound tenderness over the right lower quadrant.
• She is treated with a 1st generation cephalosporin
• She is taken to surgery where a perforated appendix is removed. The surrounding peritoneum is irrigated.
• Cultures of the peritoneum grow a mixture of bacteria, typical of those found in stool.
• On post-op day #2, her temp spikes to 38.6°C.
• Blood cultures obtained preoperatively grow *E. coli*.
• She completes a 7-day course of cefazolin and improves. Since she has no further symptoms and follow-up blood cultures are negative, the antibiotic is stopped.
• 36 hours later, her temperature is 38.8°C and she feels diffuse pain over the site of the appendectomy.
• A CT scan of her abdomen reveals a retroperitoneal abscess.
CT scan: Ruptured Appendix

Case (continued)

- The abscess is drained, and cultures of pus from the drainage grow *Bacteroides fragilis*.
- She is treated with ampicillin-sulbactam for 14 more days. Her drain is pulled after 7 days, and she has an uneventful recovery.
Gram stain of drainage
B. fragilis in pure culture
Questions to consider

• How did the two episodes of her disease differ with regard to pathogenesis and to the kind of bacteria involved?
• Why did *B. fragilis* survive the first course of antibiotic treatment?
• Was she treated properly? What could have been done to lessen the likelihood of abscess formation?
• How does *B. fragilis* facilitate intra-abdominal abscess formation?
Gorbach’s experiment

RX GIVEN

None

Clindamicin

Gentamicin

Clindamycin & gentamicin

E. coli & B. fragilis injected i.p.
**Bacteroides spp.**

- Obligate anaerobes
- 25% of all colonic bacteria
- Usually involved in infections resulting from perforation of an abdominal viscus
  - ruptured appendix
  - diverticulitis
  - post-op after bowel surgery and/or dehiscence of a surgical anastamosis
- Any *Bacteroides* spp. may be involved in a polymicrobial infection, but most abscesses contain *B. fragilis*
Survival features of *Bacteroides*

- Bacterial enzymes digest complex polysaccharides
  - Nutritional advantage
  - May improve human nutrition by digesting complex plant polysaccharides in food (symbiosis with the host)
  - Can digest and consume human glycans, (e.g., mucin, hyaluronate, chondroitin $SO_4$)
  - Neuraminidase: exposes sialylated polysaccharides to enzyme digestion (required for abscess formation)

- *Bacteroides* spp. are relatively aerotolerant
  - Human peritoneum and tissues are less anaerobic than the colon
What’s special about *B. fragilis*?

1. More aerotolerant than other species and more resistant to reactive oxygen species
   - Possesses a superoxide dismutase (SOD)
   - Possesses catalase (CAT)

\[
\begin{align*}
    \text{O}_2 + 2\text{H}_2\text{O} & \xrightarrow{\text{SOD}} 2\text{H}_2\text{O}_2 \\
    2\text{H}_2\text{O}_2 & \xrightarrow{\text{CAT}} 2\text{H}_2\text{O} + \text{O}_2
\end{align*}
\]
What’s special about *B. fragilis*?

2. The outer membrane LPS (lipid A) is modified to be less toxic than that of *E. coli*
   - Allows for host tolerance of large numbers of organisms without toxicity
What’s special about *B. fragilis*?

3. It has a complex capsular polysaccharide that is essential for abscess formation
   - Composed of at least 8 polysaccharides
   - Each is capable of transcriptional phase variation (synthesis genes preceded by an invertable region containing a promotor)
   - Polysaccharide A is essential for abscesses in animal models and is zwitterionic
Special features of *B. fragilis* CPC

- Phase variation of CPC synthesis genes
- Polysaccharide A
- Activation of CD4⁺ T-lymphocytes
- Abscess formation
Antibiotic resistance in *Bacteroides*

- Most carry a beta-lactamase gene (resistant to penicillin, ampicillin, 1\(^{st}\) gen. ceph.)
- Harbors conjugative transposons
  - Can exchange genes with other *Bacteroides* and with other species
  - ex. clindamycin resistance (only ~60% sensitive now)
Abscess formation

- Infectious inoculum is high
- Spillage of intestinal contents into the peritoneum → most are killed by the immediate inflammatory response
- Containment by the omentum
- Facultative bacteria establish first
- Aerotolerant anaerobes survive
- Microbial synergy is usually required
Microbial synergy in abscess formation

↑ *E. coli* and other facultative bacteria

Carbohydrate digestion = more free sugars

↑ *Bacteroides* spp.

Consumption of O$_2$ + decreased blood flow = more anaerobiasis
Response to bacteria in the peritoneum

- Role of the omentum
- Inflammatory mediators increase vascular permeability → plasma and fibrin influx
  - fibrous collagenous capsule forms around site
  - central area features acidic pH, live and dead PMNs, and mixed bacterial flora
  - may include other *Bacteroides*, *Clostridia*, or *Peptostreptococcus* spp.)
Treatment of peritonitis and peritoneal abscesses

• Abscesses must be drained surgically or by percutaneous catheters (+ repair any leak)

• Antibiotic therapy effective against colonic flora, including facultative and obligate anaerobic organisms
  – β-lactams or cephalosporins + metronidazole
  – β-lactam-β-lactamase inhibitor combinations
  – Carbepenems
  – Clindamycin is becoming less useful
Questions to consider

• How did the two episodes of her disease differ with regard to pathogenesis and to the kind of bacteria involved?
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• Was she treated properly? What could have been done to lessen the likelihood of abscess formation?
• How does *B. fragilis* facilitate intra-abdominal abscess formation?
Other *Bacteroides*-associated diseases and other obligate anaerobes of interest
Case: Fever, cough, chest pain, and really bad breath

• A 53 year old man comes to the ED for fever and chest pain. He is coughing spasmodically with minimal sputum production.

• The patient is a heavy alcohol user and has had “blackouts” and seizures

• P.E. T=38.4. Carious teeth noted, many fractured. Crackles over the left lung noted.
Case (continued)

- He is admitted and started on ceftriaxone for probably pneumonia
- Later the same night, the patient starts coughing copious amounts of grayish, putrid sputum that can be detected on the next ward.
- A chest xray is taken, and treatment with metronidazole is added.
Lung abscess
Aspiration pneumonia
Gram stain of mixed oral flora
Oral, Gram-negative anaerobes

- Common pathogens in dental infections, chronic sinusitis, aspiration pneumonia, lung abscesses
  - *Porphyromonas asaccharolytica, gingivalis, forsythus*
  - *Prevotella melaninogenicus* (named for brown pigment production)
- These species are usually (not always) sensitive to clindamycin. PCN+metronidazole usually works well.
- Infections are polymicrobial and usually include oral (viridans) streptococci, anaerobic strep, and other oral bacteria.
Case: pelvic inflammatory disease

• A 24 year old woman presents with pelvic pain and vaginal discharge.
• She has been treated for gonorrhea in the past and has had two prior episodes of the current illness in the past year.
• P.E. Temp=38C. There is lower abdominal tenderness in the RLQ and exquisite tenderness of the cervix and enlargement of the right Fallopian tube on pelvic exam.
Case (continued)

- A pregnancy test is negative
- Because she has been unable to eat without vomiting, she is admitted and treated with IV ceftriaxone, oral doxycycline, and oral metronidazole
- No cultures are obtained; an HIV test is negative
- Why is metronidazole used?
PID microbiology

• Primary pathogens: gonococcus, chlamydia
• Secondary pathogens:
  – Facultative enteric organisms (e.g., *E. coli*)
  – GI and vaginal anaerobes
    • *Prevotella bivius* and *Prevotella disiens*
    • *Peptostreptococcus* spp.
  – *Haemophilus*
Case: neck and chest pain

• A 22 year old male who recently had an prolonged episode of pharyngitis now presents with high fever, and exquisite pain, tenderness and swelling of his left neck for 2 days.
• This morning, he developed sharp pain in the left lower chest with deep breathing
• A blood culture is positive for an anaerobe
Fusobacterium

Source undetermined
Lemierre’s syndrome

• Or “post-anginal sepsis” (very rare)
• Occurs after prolonged or severe pharyngitis
• Septic thrombophlebitis with *Fusobacterium necrophorum* (probably from the mouth) associated with septic pulmonary emboli to the lungs
What have you learned about Gram-negative, obligate anaerobes

- *Bacteroides* participate in intra-abdominal abscesses when intestinal contents spill into the peritoneum
- Formation of abscesses is a synergistic process involving anaerobes & facultative bacteria
- *B. fragilis* has special capacity to tolerate oxygen and to induce abscess formation via its CPC
- Other *Bacteroides*-like anaerobes are involved in polymicrobial dental, lung, or pelvic infections

Slide 12: Source undetermined


Slide 32: Source undetermined

Slide 33: Source undetermined


Slide 41: Source undetermined