Intra-abdominal Infections

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Objectives

- Describe pathogenesis & clinical characteristics of intra-abdominal infections
- Identify most likely etiologic organism(s)
- Review appropriate drug therapy

Intra-abdominal Infections

Infections contained within the peritoneum or retroperitoneal space.

- Peritoneal cavity contains:
  - Stomach
  - Jejunum, Ileum
  - Appendix
  - Large intestine (colon)
  - Liver, gallbladder and spleen
- Retroperitoneal space:
  - Duodenum
  - Pancreas
  - Kidneys

Intra-abdominal Infections

- Appendicitis
- Peritonitis
- Intra-abdominal Abscess
- Diverticulitis
- Antibiotic-Associated Diarrhea
  - (Clostridium difficile)
- Food Poisoning/Traveler's Diarrhea
- Helicobacter pylori
- Pelvic Inflammatory Disease
- Viral
- Parasitic

Anatomy of the GI Tract

- GI microflora depends on the anatomic site!

Normal GI Microflora

- Stomach:
  - Total bacterial count 0-10^8 log organisms/g
    - Helicobacter pylori
    - Streptococci
    - Lactobacilli
- Upper Small Intestine:
  - Total bacterial count 0-10^9 log organisms/g
  - Aerobes
    - Enterococci
    - Staphylococci
    - Lactobacilli
    - E. coli, Klebsiella
  - Anaerobes
    - Bacteroides
**Normal GI Microflora**

- **Ileum**
  - Total bacterial count $10^{9}$ log organisms/g
  - **Aerobes:**
    - Streptococci
    - Staphylococci
    - Escherichia coli, Klebsiella
  - **Anaerobes:**
    - Bacteroides
    - Clostridium

- **Large Intestine (Colon)**
  - Total bacterial count $10^{10}$ log organisms/g
  - **Aerobes:**
    - Escherichia coli, Klebsiella
    - Enterobacter
    - Enterococci
    - Staphylococci
  - **Anaerobes:**
    - Bacteroides
    - Peptostreptococci
    - Clostridium
    - Bifidobacteria

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**Peritonitis**

**Inflammation of the serous lining of the peritoneal cavity due to:**
- Microorganisms
- Chemicals
- Irradiation
- Foreign body injury

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**Peritonitis**

- **Primary Peritonitis**
  - No focus of disease is evident
  - Bacteria transported from blood stream to peritoneal cavity (Cirrhosis, CAPD)
- **Secondary Peritonitis**
  - Acute perforation of the GI tract (gastric, diverticular (diverticulitis), appendix (appendicitis), gallbladder, tumor perforations) [66%]
  - Post-operative peritonitis [24%]
  - Post-traumatic peritonitis [10%]


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**Clinical Symptoms**

- Abdominal pain
- Anorexia (N/V)
- Fever (100 to 102 °F)
- Abdominal distention and tenderness
- Hypoactive or faint bowl sounds
- Leukocytosis

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**Peritonitis**

- Normally: 20 to 50 mL transudate
- Peritoneal membrane measures approx. 1.7 m²
- WBC < 300 cells/mm³
- Protein: <3 g/dL

- Bacterial peritonitis: 300 to 500mL inflow/hr resulting in hypovolemia.
  - WBC > 300 cells/mm³
  - Gram stain + for bacteria

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**Peritonitis**

<table>
<thead>
<tr>
<th>Microbiology</th>
<th>Primary Peritonitis</th>
<th>Secondary Peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae (60%)</td>
<td>Enteroabacteriaceae (&lt;1%)</td>
<td>Enteroabacteriaceae</td>
</tr>
<tr>
<td>S. pneumonia (15%)</td>
<td>Enterococci (6-10%)</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>S. marces/PSA (CAPD)</td>
<td>anaerobes (&lt;1%)</td>
<td>Enterococci</td>
</tr>
<tr>
<td>S. aureus/MRSA (CAPD)</td>
<td>P. aeruginosa</td>
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**Treatment**

- Cefotaxime, pip/tazo, ampic/sulb, carbenem, tigecycline, moxifloxacin, (amp + cipro/levo/AG + metronidazole)
Primary Peritonitis

- Relatively infrequent
- 25% of patients with alcoholic cirrhosis
- 60% of all patients on chronic ambulatory peritoneal dialysis (CAPD) will have at least one episode in 1st year.
- Average incidence in CAPD patients is 1.3 to 1.4 episodes/yr.
- Catheter connecting abdominal cavity to exterior body is a major risk factor.

Peritonitis in CAPD

- Antibiotics may be given intraperitoneal via the dialysate: (exchanges every 4 to 6 hrs)
  - Gentamicin and tobramycin: 8mg/L
  - Clindamycin: 1 to 3 mg/L
  - Cephalosporins: 125 mg/L
  - Ampicillin: 50 mg/L
  - Vancomycin: 30 mg/L
  - Amphotericin B: 3 mg/L
- Reasonable empiric therapy
  - Gentamicin or tobramycin PLUS vancomycin
  - Cefazolin PLUS vancomycin
- Duration: 2 to 3 weeks

Clinical Question

“Recommend dosing for intraperitoneal administration of an antibiotic for a CAPD patient with a Staphylococcus peritonitis”

Appendicitis Case

- LF, an 18 yr female, was admitted to the hospital with diffuse abdominal pain, diarrhea, and nausea. Her pain was localized to the right side of the abdomen.
- Cefazolin was initiated and LF was taken to surgery for a ruptured appendix to be removed.

What are the considerations in a ruptured appendix?
- Microbial
- Therapeutics

Appendicitis Case, cont.

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What are the considerations in a ruptured appendix?
- Microbial
  - Staphylococcus? NOT most important
  - E. coli? Yes
  - Anaerobes? Yes
- Therapeutics
  - Cefazolin alone? No
  - Unasyn yes - why?

Appendicitis

- Highest incidence 10-19y/o, male>female
- Pathophysiology: Relationship to onset of sx
  - 0-24h after sx onset: obstruction within appendix → inflammation & occlusion of vascular & lymphatic flow → bacterial overgrowth → necrosis
  - >24h after sx onset: perforation (60%)→ abscess/peritonitis
- Early sx: dull, non-localized RLQ pain, indigestion, bowel irregularity, flatulence
- Later sx: pain/tenderness more localized, N/V
  - Fever >103F, leukocytes >15000: perforation likely
Appendicitis

- Acute, non-perforated appendicitis
  - Cefazolin + metronidazole
- Perforated appendicitis
  - Cover enteric gram – rods and anaerobes
  - (2nd/3rd generation cep or FQ) + metronidazole
  - Cefoxitin, piperacillin/tazobactam, ampicillin/sulbactam, imipenem
  - Antibiotics are started before surgery, continued for 7-10 days
  - Switch to PO based on patient status

Sample Exam Question:

- For initial treatment in a pt with a ruptured appendix and no other contributing factors, which of the following is an incorrect choice?
  - Amoxicillin/sublactam (Unasyn) +/- Aminoglycoside
  - Piperacillin/tazobactam (Zosyn) +/- Aminoglycoside
  - Tigecycline (Tigecil) +/- Aminoglycoside
  - Clindamycin + Ampicillin + Aminoglycoside
  - Clindamycin + Metronidazole
  - Moxifloxacin + Metronidazole

Appendicitis Case, cont.

- LF improved post-operatively & completed 7d course of PO cephalexin. 4d after completing antibiotics she felt diffuse pain over the appendectomy site. Abdominal CT scan revealed a peritoneal abscess. Abscess was drained & fluid sent to the lab.
  - What organism(s) are most likely to be responsible for the abscess?
    - Likely MRSA, not covered by cephalexin
    - Gram negative bacteria not covered by 1st generation cephalosporins
    - Anaerobic bacteria not covered by cephalexin
  - Was the cephalexin an appropriate choice of abx for LF?
    - No, LF should have remained in the hospital for 7-10 days with IV tx
    - No, there was not appropriate coverage with a 1st generation cep: not adequate coverage of gram –’s and anaerobes
  - Yes, but metronidazole should have been added for anaerobic coverage: an agent with anaerobic coverage should be added, but also need gram - coverage

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  - Clindamycin + Ampicillin + Aminoglycoside
  - Clindamycin + Metronidazole
  - Moxifloxacin + Metronidazole

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Intra-abdominal Abscess

Figure 49
Diversititis. Multiple sigmoid diverticula (arrow), one of which has perforated to produce large abscess (large arrow).
Intra-abdominal Abscess

- Abscess: purulent collection of fluid, necrotic debris, bacteria, inflammatory cells that is walled off/encapsulated by adjacent healthy cells in an attempt to keep pus from infecting neighboring structures.
- Encapsulation can prevent immune cells/abs from attacking contained bacteria, low O2 in capsule → anaerobes thrive here!
- Result of chronic inflammation, develop over days–yrs
- Located within peritoneal cavity or visceral organs
- May range from a few milliliters to a liter in volume

Microbiology

- Usually mixed infection: aerobes & anaerobes within the same abscess
- E. coli
- Klebsiella
- Enterococci
- B. fragilis
- Clostridium

Management of Intra-Abdominal Infections

- Combination of modalities:
  - Surgical
    - Prompt drainage of abscess (secondary peritonitis) and/or debridement
    - Resection of perforated colon, small intestine, ulcers
    - Repair of trauma
  - Support of Vital functions:
    - Blood pressure/fluid replacement
    - Monitor heart rate
    - Monitor urine output (0.5 ml/kg/hr)
    - Appropriate antimicrobial therapy

Empiric Antibiotic Therapy

- MUST include aerobic/anaerobic coverage

  Agents with Aerobic and Anaerobic activity:
  - Ampicillin/sulbactam (Unasyn) (intemecillin)
  - Piperacillin/tazobactam (Zosyn) (intemecillin)
  - Imipenem/cilastatin (Primaxin)
  - Meropenem (Merrem)
  - Etrapenem (Invanz)
  - Aminoglycoside + clindamycin or metronidazole
  - Tigecycline (Tigacil)
  - Moxifloxacin (Avloxo) (active against 83% of Bacteroides strains)

- (+ metronidazole: per IDSA guidelines CID 2003;37 997)

Antimicrobial therapy:

- Chloramphenicol: also includes aerobic Gram +/–
- Clindamycin (also includes aerobic Gram +)
- Metronidazole (anaerobic coverage only)

- Aerobic activity:
  - Aminoglycosides
  - Gentamicin, tobramycin (Gram negatives only)
  - Beta-lactams:
    - Cefotaxime (Claforan)
    - Ceftriaxone (Rocephin)
  - Aztreonam (Azactam) (Gram negative only)

- Quinolones:
  - Ciprofloxacin (Cipro) (Mostly Gram negative)
  - Levofoxacin (Levaquin) (Gram +/– and some anaerobic coverage)
  - Moxifloxacin (Avelox) (Gram +/– and anaerobic)
  - Vancomycin/Lincosamide/Linezolid (Enterococci, MRSA)
Antibiotic Therapy

- Factors involved in selection:
  - Severity of infection, suspected infecting organism(s) and resistance patterns, efficacy, toxicity (renal dysfunction), allergies
  - Evaluating response:
    - Improvement in 2 to 3 days
    - Switch to oral antibiotic therapy
  - Failure to improve:
    - Resistant organisms
    - Recurrent surgical infections
    - Other infections: (urinary tract infections, pneumonia)

Antibiotics and GI flora

- Broad spectrum antibiotics can change the normal GI flora
  - Increases in *Candida* or Gram-negative bacteria
  - Proliferation of antibiotic-resistant organisms
  - Pseudomembranous colitis from over proliferation of toxin-producing anaerobe, *Clostridium difficile*.

Antibiotic Associated Diarrhea

Antibiotic therapy (broad spectrum agents: clindamycin, ampicillin, 3rd generation cephalosporins are most common)

- Disruption of normal colonic flora
- *C. difficile* colonization (gram +, spore forming anaerobe)
- Release of toxins A (enterotoxin), B (cytotoxin), & binary toxin CDT (associated w/ recent outbreaks)
- Damage to colonic mucosa (pseudomembranous plaques), inflammation, intestinal fluid secretion

Pseudomembranous Colitis

“Antibiotic Associated Diarrhea”

*Clostridium difficile*:

- Toxin mediated disease
  - Toxin A (major)
    - Overproduction in outbreak strains of *C. difficile* due to deletion in tcdC gene.
  - Toxin B (minor)
  - Binary toxin CDT
    - Associated with recent outbreaks (NEJM 2005; 353: 2433)
    - *C. difficile* strains with binary toxin are often resistant to quinolones
- Toxins cause inflammation, necrosis, loss of fluid electrolytes
Antibiotic Associated Diarrhea

- Spectrum of disease
  - Colitis w/o pseudomembrane formation
  - Severe abdominal pain, fever, water diarrhea, nausea, low fever
- Pseudomembranous colitis
  - Stool culture of C. diff, presence of stool culture of C. diff, presence of toxin A or B, endoscopy
- Symptom onset can occur shortly after start of abx or several weeks after tx stopped
- C. diff risk if abx use in past 2 months
- Diagnosis: stool culture of C. diff, presence of toxin A or B, endoscopy

Pseudomembranous colitis

**FIRST LINE:**
- Metronidazole (Treatment of Choice)
  - 250mg PO QID or 500mg PO/IV TID x 10-14 days

**ALTERNATIVE:** (if not responding to metronidazole or recurrences)
- Vancomycin
  - 125mg PO QID x 10-14 days +/- rifampin 600mg PO BID
- Always stop the drug responsible for causing the infection as soon as possible!

**RECURRANCES:**
- 1st: Retreat with either metronidazole or vancomycin, dosed as above, x 10-14d
- ≥2nd: Vancomycin taper/pulse therapy
  - 125mg PO QID x 7d, then 125mg PO BID x 7d, then 125mg PO QD x 7d, then 125mg PO every 3 days x 14d
- Can add 3 week course of probiotics (Saccharomyces boulardii 500mg PO BID) starting during final week of taper and continued for 2 weeks after vanco taper
- Counteract disturbances & reduce risk of colonization by pathogenic bacteria

(Per IDSA treatment guidelines)

Pseudomembranous colitis

**FIRST LINE:**
- Metronidazole vs. vancomycin
  - Similar in non-severe cases with time to resolution of diarrhea, side effects, and relapse rates
  - 20-25% recurrence, not related to tx choice, dose or duration
- Metronidazole: cheaper, preferred due to concern of VRE
- Vancomycin: okay if pt is pregnant, <10yo, or if severe case with sx of systemic toxicity (potential for better cure rate than metronidazole)
- MUST give PO – concentrations in gut aren’t high enough with IV

**ALTERNATIVE:**
- Tolevamer
- IVIG
- Nitazoxanide vs. metronidazole (non-inferior)
  - Musher et al. CID 2006:43:421-7
  - Musher et al. CID 2007:44:846-8
  - Anion binding resins: bind toxins
  - Cholestyramine and colestipol
  - Oral treatment for the treatment of C. diff infection as soon as possible!
- Vancomycin: okay if pt is pregnant, <10yo, or if severe case with sx of systemic toxicity (potential for better cure rate than metronidazole)
- Must give PO – concentrations in gut aren’t high enough with IV

**Clinical Question**

- What is the best antibiotic treatment for this patient?
- What is the likely organism responsible?
- What other info do you need about the patient?
What is the likely organism responsible?
- E. coli
- *Clostridium difficile
- Shigella

What other info do you need about the patient?
- Ht and wt to calculate IBW for accurate dosing
- Is this the first or recurrent episode, severity of sx, pregnancy status, allergies, etc.
- Both of the above

This is the pts first episode; what is the best antibiotic treatment?
- Metronidazole 500mg PO Q 8h x14d (yes!)
- Vancomycin 125mg PO or IV Q 6h x14d (IV vanco not effective!)
- Vancomycin pulse/taper with probiotic overlap (not indicated for first episode)

References
- Goldstein EJC, Snydman DR. Intraabdominal infections: review of the bacteriology, antimicrobial susceptibility and role of antibiotics in their therapy. JAC. 2004; 53(S2):ii29-36.