Intra-abdominal Infections

Marnie Peterson, Pharm.D., Ph.D., BCPS
College of Pharmacy
peter377@umn.edu

©2006 Marnie Peterson. This presentation is provided to facilitate the learning of participants within this course. It may not be modified, reproduced and/or circulated for other means without the permission of the author.

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

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

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

Anatomy of the GI Tract

GI microflora depends on the anatomic site!

Stomach:
- H. pylori
- Lactobacillus

Upper Intestine:
- Aerobes
- Enterococci
- Staphylococci
- Bacteroides
- Clostridium

Colon:
- Bacteroides
- Atibacter
- Clostridium
- Enterococci
- E. coli
- Klebsiella

Small Intestine:
- Aerobes
- Enterococci
- Staphylococci
- Lactobacilli

Normal GI Microflora

Stomach:
- Total bacterial count 0-10^8 log organisms/g
- H. pylori
- Strep
- Lactobacilli

Upper Small Intestine:
- Total bacterial count 0-10^7 log organisms/g
- Aerobes
- Enterococci
- Staphylococci
- Lactobacilli
- E. coli, Klebsiella
- Anaerobes
- Bacteroides
**Normal GI Microflora**

- **Ileum**
  - Total bacterial count $10^3-10^9$ log organisms/g
  - *Aerobes*:
    - Streptococci
    - Staphylococci
    - *Escherichia coli*, *Klebsiella*
    - Enterobacter
  - *Anaerobes*:
    - *Bacteroides*
    - *Clostridium*

- **Large Intestine (Colon)**
  - Total bacterial count $10^10-10^12$ log organisms/g
  - *Anaerobes*:
    - *Bacteroides*
    - *Peptostreptococci*
    - *Clostridium*
    - *Bifidobacteria*
  - *Aerobes*:
    - *Escherichia coli*, *Klebsiella*
    - Enterobacter
    - *Enterococci*
    - *Staphylococci*  

**Appendicitis**

- One of the most common causes of intra-abdominal infections.
- **Treatment**: Both Surgical and Antibiotics
  - Depends on presentation of appendix:
    - Normal, inflamed, gangrenous or perforated
    - Begin antibiotics before appendectomy is performed
      - Anti-anaerobic cephalosporin (e.g., *Cefoxitin*), Piperacillin/tazobactam, *Ampicillin/sulbactam*, Imipenem
      - Combination therapy:
        - Aminoglycoside +/- *Clindamycin* or *Metronidazole*.
        - *Moxifloxacin* +/- *Metronidazole*.
  - Continue antibiotics for 7 to 10 days if appendix is perforated or gangrenous (Switch to oral equivalents)

**Peritonitis**

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

**Clinical Symptoms**

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

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

**Peritonitis**

- Primary
  - No focus of disease is evident
  - Bacteria transported from blood stream to peritoneal cavity (Cirrhosis, CAPD)
- Secondary
  - Acute perforation of the GI tract (Gastric, Diverticular, Appendix, Gallbladder, Tumor perforations) [66%]
  - Post-operative peritonitis [24%]
  - Post-traumatic peritonitis [10%]

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

- Common Bacteria:
  - Escherichia coli
  - Enterococci
  - Klebsiella
  - Staphylococci (CAPD patients)
  - Methicillin resistant S. aureus
  - Pseudomonas aeruginosa
  - Bacteroides sp.

Clinical Questions

"Recommend dosing for intraperitoneal administration of an antibiotic for a CAPD patient with a Staphylococcus peritonitis?"

Peritonitis in CAPD

- Antibiotics may be given intraperitoneally via the dialysate: (exchanges every 4 to 6 hrs)
  - Gentamicin and tobramycin: 8mg/L
  - Clindamycin: 1 to 3 mg/L
  - Penicillin G: 50,000 units/L
  - Cephalexin: 125 mg/L
  - Ampicillin: 50 mg/L
  - Vancomycin: 30 mg/L
  - Amphotericin B: 3 mg/L
- Duration: 2 to 3 weeks

Case: ruptured appendix

- LF improved post-operatively and completed a 7 day course of oral cephalaxin. 4 days after completing antibiotics she felt diffuse pain over the site of the appendectomy. A CT scan of her abdomen revealed a peritoneal abscess. LF’s abscess was drained and fluid was sent to the laboratory.

- Was LF initially treated properly?
- What organism(s) are most likely to be responsible for the abscess?

Intra-abdominal Abscess

Figure 49: Divericulitis. Multiple sigmoid diverticula (arrows), one of which has perforated to produce (large arrow) a palpable abscess.
Intra-abdominal Abscess
- Result from chronic inflammation and often occur without generalized peritonitis.
- Located within peritoneal cavity or visceral organs.
- May range from a few milliliters to a liter in volume.
- Often have a fibrinous capsule and take days to yrs to form.
- Appendicitis is the most common cause.
- Ultrasound or CT scan may be used for evaluation

Clinical Manifestations:
- Symptoms less dramatic than peritonitis
  +/- pain
  +/- fever
  +/- abdominal distention
- Common Bacteria: (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 out put (0.5 ml/kg/hr)
  - Appropriate antimicrobial therapy

Antibiotic Therapy
Empiric Therapy must include aerobic/anaerobic coverage.
- **Aerobic and Anaerobic activity**
  - Ampicillin/sulbactam (Unasyn) (enterococci)
  - Piperacillin/tazobactam (Zosyn) (enterococci)
  - Cefotetan (Cefotan) Astra Zeneca has discontinued production
  - Cefoxitin (Mefoxin) [In production by Baxter]
  - Imipenem/cilastatin (Primaxin)
  - Meropenem (Merrem)
  - Ertapenem (Invanz)
  - Tigecycline (Tygacil)
  - Moxifloxacin (Avelox)

**TYGACIL®**
(tigecycline) for injection
Approved June 15, 2005

**Complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin-susceptible isolates only), Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus anginosus gff (includes S. anginosus, S. intermedius, and S. constellatus), Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, and Peptostreptococcus species.**

**DOSAGE AND ADMINISTRATION**
The recommended dosage regimen for TYGACIL is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of TYGACIL should be administered every approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with TYGACIL for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient’s clinical and bacteriological progress.

FDA Approves New Indication for AVELOX(R) (moxifloxacin HC) for Treatment of Complicated Intra-Abdominal Infections (cIAI)
November 2005

- AVELOX is indicated for the treatment of adults with cIAI, including abscesses caused by:
  - Escherichia coli, Bacteroides fragilis, Streptococcus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron or Peptostreptococcus species.

- FDA approval was based on results from clinical studies in cIAI patients showing that sequential I.V. or oral monotherapy with AVELOX once daily was as effective as the widely used I.V. therapy piperacillin-tazobactam four times daily followed by oral amoxicillin-clavulanate twice daily. In this study, the overall success rates in evaluable patients for AVELOX versus the comparator were 79.8 % and 78.1 %, respectively.

- AVELOX was effective at eradicating key pathogens, including E. coli and B. fragilis, which are the most commonly encountered bacteria in cIAI
Antibiotic Therapy

Empirical Therapy must include aerobic/anaerobic coverage.

- **Anaerobic activity:**
  - 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)
    - Levofloxacin (Levaquin) (Gram +/- and some anaerobic coverage)
    - Vancomycin/Linezolid/Synercid (Enterococci, MRSA)

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 for 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*.

Pseudomembranous Colitis

"Antibiotic Associated Diarrhea"

An Epidemic, Toxin Gene-Variant Strain of *Clostridium difficile*
Pseudomembranous Colitis

- **Clostridium difficile.**
- **toxin mediated disease**
  - Toxin A (major)
    - Overproduction in outbreak strains of *C. difficile* due to deletion in tetA 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

Pseudomembranous Colitis

- Associated with broad spectrum antibiotics
- Patients may develop diarrhea after 3 or more days of hospitalization or within 2 months of antibiotic therapy.
- 3 to 5% of adults are carriers of *C. difficile*
- Metronidazole (oral) treatment of choice with vancomycin (oral only) +/- rifampin for recurrences.
- Recurrence in 7 to 20% of patients.

?????Clinical Questions?????

- A pseudomembranous colitis caused by oral cefuroxime.

- “What is the cause?”
- “What are the antibiotic treatment options for Pseudomembranous colitis?”

Investigational Therapies

- Nitazoxanide vs. metronidazole
- Rifaximin
- Linezolid
- Cholestyramine

Probiotics in human infections

- *Lactobacillus* (*L. acidophilus*)
- *Bifidobacterium*
- *Saccharomyces* (*S. boulardii*)

- Probiotics thought to counteract disturbances and reduce the risk of colonization by pathogenic bacteria.
Conclusions

- Intra-abdominal infections demand immediate evaluation based on patient history and presentation.
- Management includes three components:
  - Surgical evaluation
  - Vital Support
  - Appropriate antimicrobial selection
- Antibiotic selection is based on likely source of infection and should always include aerobic and anaerobic bacterial coverage.

Ruptured Appendix

- Immediately begin empiric antibiotic with aerobic and anaerobic coverage and continue following appendectomy.
  - Ampicillin/sulbactam (Unasyn) +/- Aminoglycoside
  - Piperacillin/tazobactam (Zosyn) +/- Aminoglycoside
  - Tigecycline (Tigecil) +/- Aminoglycoside
  - Clindamycin + Ampicillin + Aminoglycoside
  - Ampicillin + Metronidazole
  - Moxifloxacin + Metronidazole
  - And many other combinations

Clinical Questions

“Recommend an empiric antibiotic treatment for a ruptured appendix?”