CLOSTRIDIUM DIFICILE

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Infectious Diseases

Phoenix VA Healthcare System

Antibiotic Associated Diarrhea

- 1978: C diff first identified
- 1989-1992: Four large outbreaks in the US caused by J strain (clindamycin resistant)
- 2003-2006: more frequent, severe and refractory to standard therapy with likely relapse than previously described
  - New strain called NAP1/B1/027 (hyper-virulent strain)- related to increase toxin production
  - Wider studies did not confirm significant prediction of severe disease.

Patient A

- 75 year old female admitted four days ago with abdominal pain, diarrhea, and leukocytosis to 22. She is febrile and has greater than 10 stools per day.
  - 2 weeks ago she was treated for CAP with levofloxacin and admitted for 24 hour period
  - 3 months ago treated for a UTI with TMP-SMX x 3 days

EPIDEMIOLOGY

- Who are carriers?
  - Patients are carriers and the source in the presence of absence of active infection
  - Healthy 3%
  - Hospitalized and long term care facilities 20-50%

- How is infection acquired
  - Hospital: Fecal oral transmission generally of spores that live on surfaces, clothing, stethoscopes, etc.
  - Community acquired infections: also fecal oral exact source unclear
    - Younger and healthier
    - **More** likely to be female
    - **Less** likely to have antibiotic exposure, acid suppressants, cancer, severe
    - Recurrence rates are the same
    - ??? Pets and industrial meat

Risk Factors

- Antibiotics
  - Disruption of barrier function of normal colonic flora
  - C diff antibiotic resistance to clindamycin and quinolone seem to play a role in increase virulence
- Age
- Gastric suppression
  - Both PPI and H2 blockers

ANTIMICROBIAL AGENTS

FREQUENT	OCCASIONAL	RARE
Flouroquinolones	Macrolides	Aminoglycosides
Clindamycin	Trimethoprim	Tetracyclines
Penicillins(broad)	Sulfonamides	Chloramphenicol
Cephalosporins(broad)		Metronidazole
		Vancomycin

Patient B

- 59 year old male with inflammatory bowel disease controlled by low dose steroids who presents with three days of abdominal pain, diarrhea (he thinks it might be worse than his usual), and low grade fever of 100.4. His WBC is ~13K. He completed a course of antibiotic therapy about three weeks ago for CAP.
  - He has had C diff in the past

Disease Pathophysiology

- Toxins: production correlates with disease severity
  - Toxin A
    - Enterotoxin
    - Fluid secretion, injury to mucosa, inflammation and activates neutrophils
  - Toxin B
    - Cytotoxin
    - 10x more powerful than A
    - Similar cell injury and inflammation
    - There can be C diff strains that only produce B and are still pathogenic
- Antibody production is protective

INTIAL CLINICAL MANIFESTATIONS

- Watery diarrhea
  - Mild 3-5
  - Moderate 6-9
  - Severe >10
- Abdominal pain
- Cramping
- Fever
- Leukocytosis
  - On average >15K
- Endoscopy: shallow ulceration as this progresses get leakage of serum proteins, mucus, and inflammatory cells which congeal on the mucosal surface making pseudomembranes

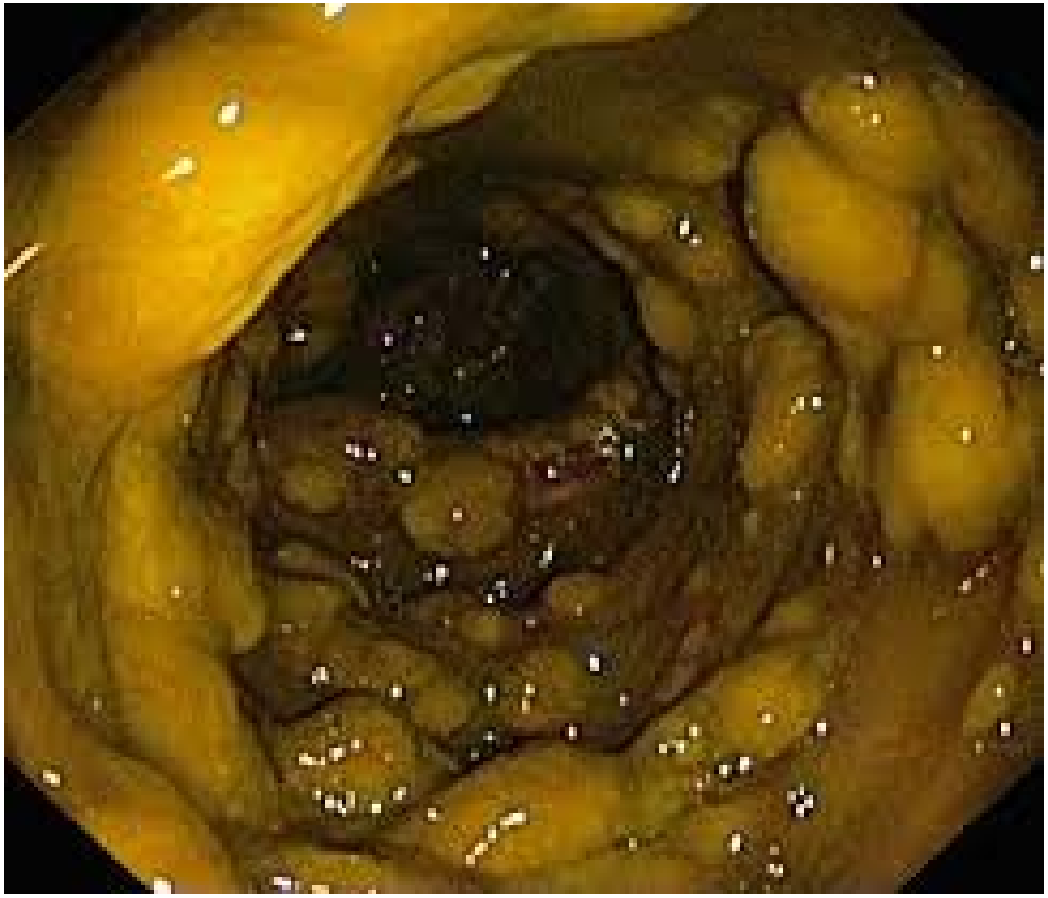
Relapse vs Reinfection

- Occurs in 10-25% of cases
- Recurrence may present in days to weeks
- Clinical presentation similar to or more severe than initial.
- Usually recurrence (~88%)
- May be related to variability in host immune response.

COMPLICATIONS

- Fulminant colitis
  - Severe LQ abdominal pain
  - Diarrhea
  - Abdominal distension
  - Fevers hypovolemia
  - Lactic acidosis
  - Hypo-albuminemia
  - Leukocytosis up to 40K
- Toxic megacolon and perforation
  - Colonic dilatation >7cm
  - Severe systemic toxicity
  - Thumb printing on abdominal films
  - Diarrhea may be less prominent as there is pooling of fluids in atonic colon

Pseudomembranes Colitis



Unusual presentations or complications

- Protein-losing enteropathy with ascites
  - Rapid protein loss leading to hypoalbuminemia
- Post infectious irritable bowel syndrome: in ~10% of patients who have been successfully treated.
- C diff and inflammatory bowel disease
  - High level of carriage in patient with IBD (8% vs 1%)
- Extra-colonic involvement
  - Appendicitis (3 cases)
  - Small bowel involvement usually patients with prior colectomy with ileostomy

Diagnosis

- Diagnosis requires:
  - Moderate to severe diarrhea

    AND
  - Stool test + for C difficile toxins (PCR or EIA) or toxigenic C difficile (cell culture cytotoxicity assay)

    OR
  - Endoscopic or histologic findings of pseudomembranous colitis

- Test only loose, watery or semi-formed stool

Patient C

- 45 year old female recently treated with moxifloxacin for acute sinusitis developed abdominal pain and diarrhea for the last three days increasing in frequency to about 6-8 per day. She is having trouble getting to the restroom in time. She is febrile 100.8 and her WBC 16K.

TREATMENT: NON-SEVERE

- General management
  - Stop inciting antibiotic as soon as possible
  - Infection control
- Antibiotic therapy*
  - Initial therapy
    - Metronidazole
      - Dose dependent peripheral neuropathy
      - Nausea and metallic taste
    - Vancomycin
      - DO NOT USE IV

TABLE 3. Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level less than 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	A-I
Initial episode, severe[a]	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin	C-III
First recurrence	…	Same as for initial episode	A-II
Second recurrence	…	Vancomycin in a tapered and/or pulsed regimen	B-III

[a] The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

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    - Vancomycin
      - DO NOT USE IV
- Duration and testing
  - 10-14 days
  - If underlying infection may need to treat longer
  - Repeat stool assays are NOT warranted during or following treatment in patients who are recovering and/or are symptom free

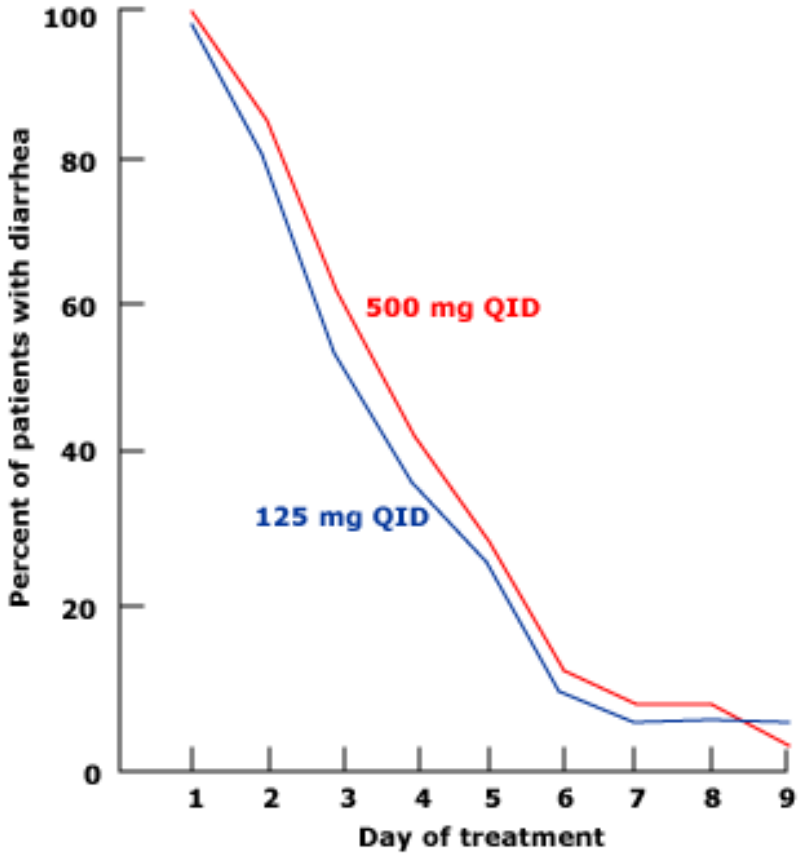
Patient D

- 68 year old female on dialysis admitted with HAP on therapy with vancomycin and piperacillin/tazobactam. Two days into therapy she develops diarrhea and abdominal pain, on day 4 she develops leukocytosis to 23,000 and is febrile to 102. Her diarrhea had increased to about 12 -14 episodes per day.

Treatment: severe

- Oral vancomycin first line
  - Low vs. high dose*

High and low dose oral vancomycin are equally effective in acute C. difficile colitis



Disappearance of diarrhea was identical in patients with acute *Clostridium difficile* colitis who received either high (500 mg four times daily, red line) or low (125 mg four times daily, blue line) dose oral vancomycin for 10 days.
Fekety R, Silva J, Kauffman C, et al. Am J Med 1989; 86:15.

TREATMENT: SEVERE

- Oral vancomycin first line
  - Low vs. high dose*
  - PO vs. intracolonic vs both
- Alternative antibiotics
  - Fidaxomicin*
    - Most expensive antibiotic on the market >$2800/10 day
  - Tigecycline

Adjunctive therapies

- Anion binding resins
  - Tolevamer*
- Probiotics:
  - Prevention: for patient felt to be at increased risk
  - Patient with recurrent disease that is not severe and no sig. comorbidities.
  - *Saccharomyces boulardii* and *Lacobacillus rhamnosus GG*
- Monoclonal antibodies against Toxins A and B
  - Not yet clinically available
- Fecal microbiota transplantation
  - Upper or lower (enema vs colonoscope)
  - There is now a pill for that
  - >92-95% cure rates
  - Did well even in immunocompromised settings

Recurrence

- Persistent spores
- Change in colonic microenvironment
- Immunity
- NOT antibiotic resistance

- Treatment
  - Same as initial
  - Fidoxamicin with lower recurrence rates vs vancomycin (18-20% vs 35%)