Clostridium dificile

Negin N Blattman

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

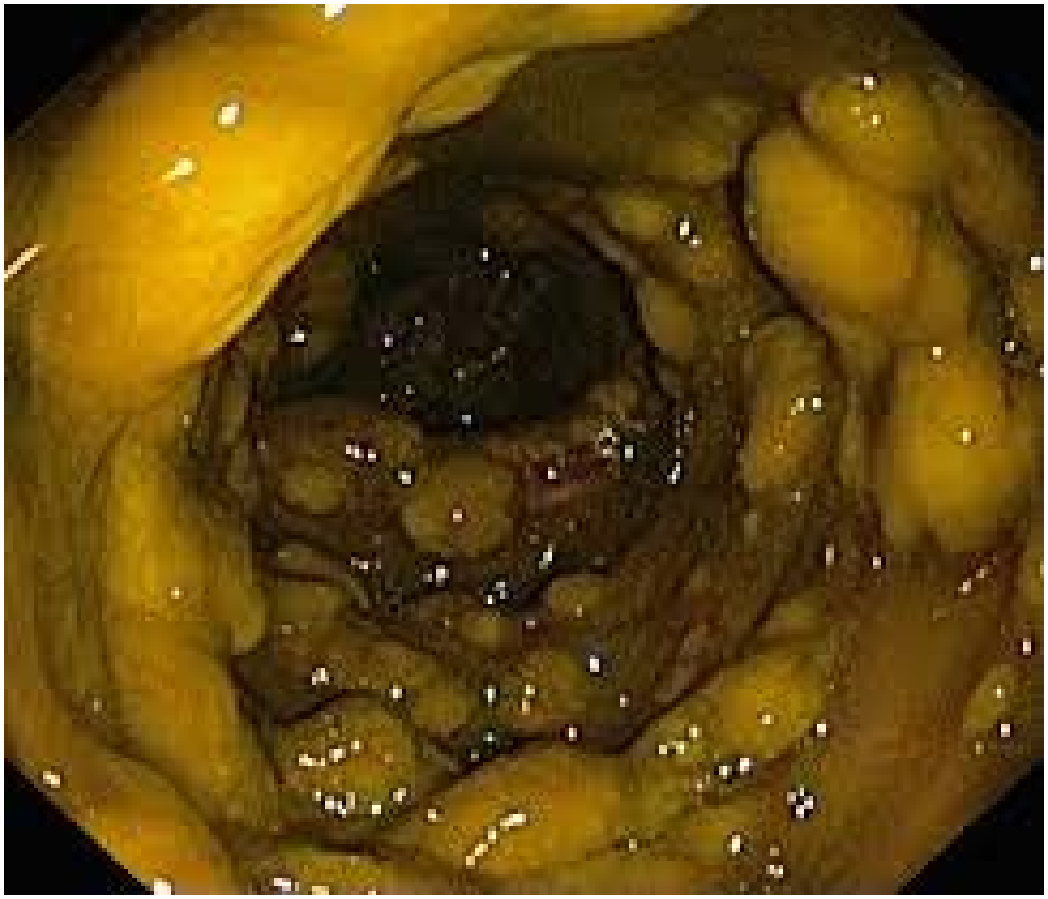
Relapse vs Reinfection

- 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.
- Extra-colonic involvement
  - Appendicitis (3 cases)
  - Small bowel involvement usually patients with prior colectomy with ileostomy

C diff and Inflammatory bowel Disease

- High level of carriage in patient with IBD (8%vs1%)
- Diagnosis can be difficult as symptoms and presentation of both diseases very similar
- Can often be underlying cause for a flare
- Treatment with metronidazole or oral vancomycin clears infection
  - response to treatment in IBD patients is variable because of refractory response to metronidazole

Diagnosis

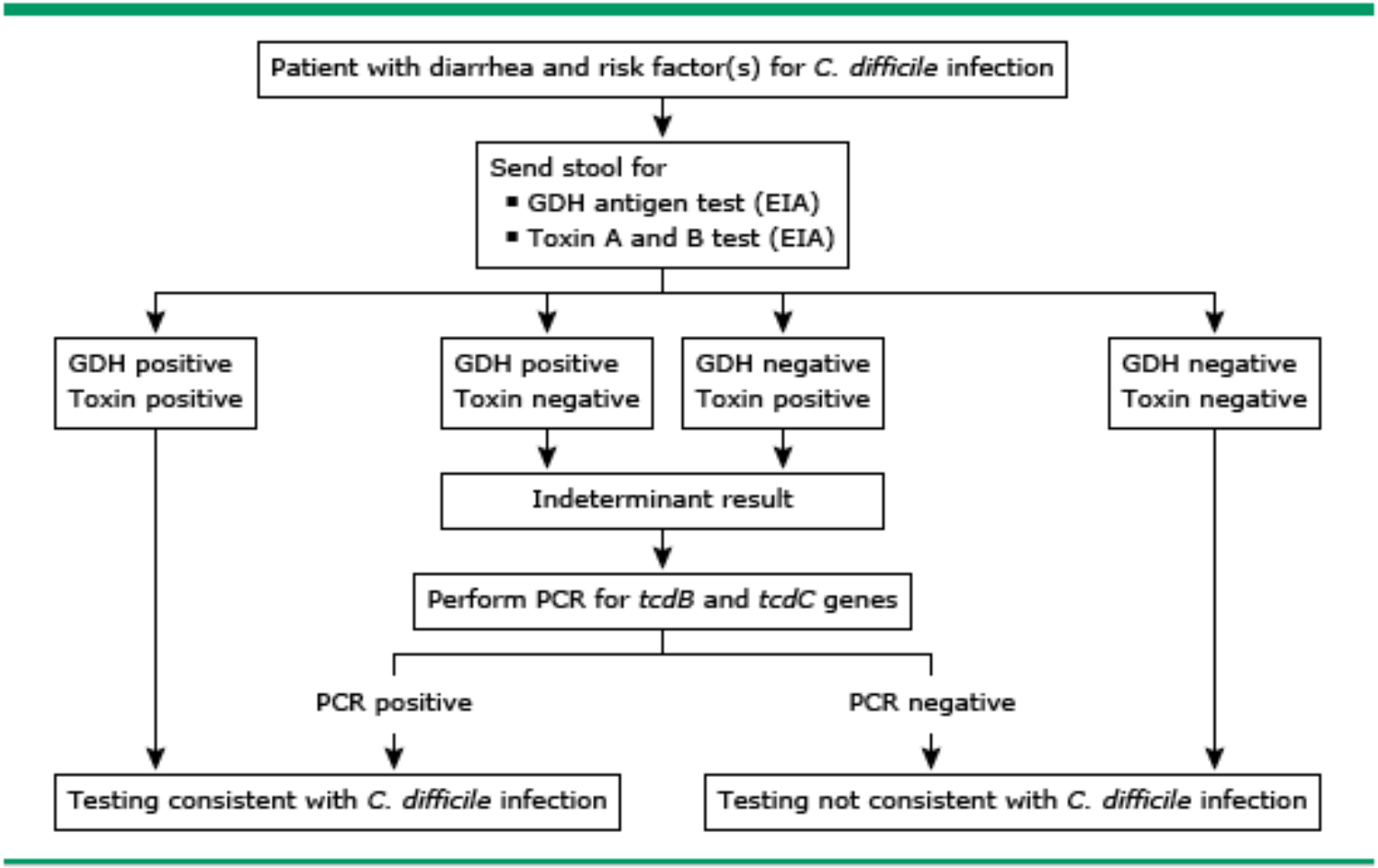
- Diagnosis requires:
  - Moderate to severe diarrhea

    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

Approach to diagnosis of CDI



UpToDate

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 1. Classification of CDI by Severity for Determining Appropriate Therapy[10,11,88]

Clinical Severity	Clinical Findings
Nonsevere illness (mild to moderate)	Must have all: Nonbloody diarrhea (passage of <6 watery stools/day), afebrile, mild abdominal pain, creatinine level <1.5 × baseline, and WBC <15,000/mm^3
Severe illness	Must have at least one: Advanced age, mental changes, serum albumin ≤2.5 g/dL, WBC >15,000/mm^3, creatinine level >1.5 × baseline, or abdominal tenderness and ileus
Severe complicated illness	Must have at least one: Hypotension/shock with serum lactate levels >2.2 mmol/L, need for ICU confinement for CDI, organ failure, or WBC ≥35,000/mm^3 or <2000/mm^3

CDI, *Clostridium difficile* infection; ICU, intensive care unit; WBC, white blood cells.

Treatment: non-severe

- General management
  - Stop inciting antibiotic as soon as possible
  - Infection control
- Antibiotic therapy*
  - Initial therapy
    - Metronidazole (mild outpatient ONLY)
      - Dose dependent peripheral neuropathy
      - Nausea and metallic taste
    - 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

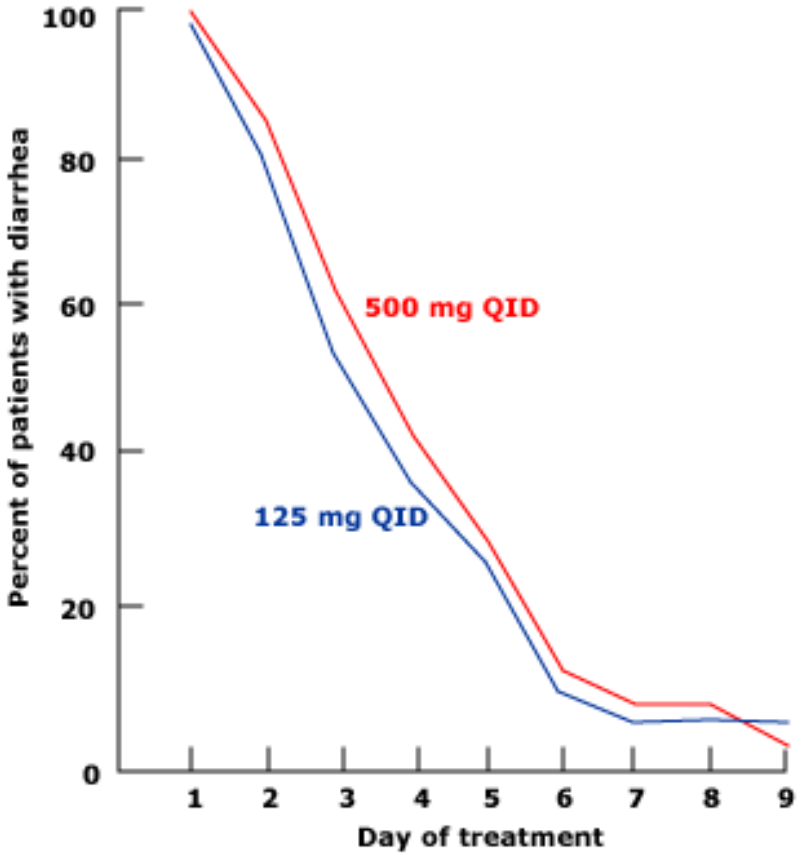
Patient D

- 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

Treatment Options for First episode

Table 2. Recommended Treatment Options for the First Episode of CDI[a]

Recommended Therapy	Dose/Schedule	Comment(s)
Metronidazole	Mild CDI: 500 mg 3 times daily for 10 days (PO or IV)	• Less effective than other options for treating CDI • Only used in the mildest cases and only via IV route if the patient is unable to take oral medications
Vancomycin	Mild to severe cases: 125 mg 4 times daily for 10-14 days PO Severe complicated cases: 250-500 mg 4 times daily. Consider 500 mg of vancomycin in 100 mg normal saline per rectum every 6 hours as a retention enema in the face of ileus.	• Superior to metronidazole for moderate to severe CDI • Increases the risk of VRE[89]
Fidaxomicin	All forms of CDI: 200 mg PO twice daily for 10 days	• Lower rate of recurrence than other treatments • Less likely than vancomycin to promote acquisition of VRE[25] • More expensive than other treatments
Tigecycline	Refractory cases of CDI: 100 mg IV, then 50 mg IV twice daily	• Not approved for treatment • Can be used as rescue treatment for patients with severe CDI when treatment with vancomycin and metronidazole fails[29]
Nitazoxanide	All forms of CDI: 500 mg PO twice daily for 10 days	• Not approved for treatment • In preliminary study, as effective as metronidazole or vancomycin[31,32] • More studies are needed.
Rifaximin	All forms of CDI: 400-550 mg twice daily for 14 days	• Not approved for treatment • Has been used with tigecycline with or without vancomycin for refractory cases of CDI[36,37] • More studies are needed.
Colonic surgery (colectomy or colon bypass)	Indicated with shock, respiratory failure, lactate levels >5 mmol/L, signs of end organ damage. Associated with refractory CDI and fulminant colitis.	• Colon-sparing approach has been described in the literature to reduce mortality and preserve the colon.

[a]Initial antibiotics causing CDI should be stopped if possible, and patients should be hydrated.

CDI, *Clostridium difficile* infection; IV, intravenous; PO, oral; VRE, vancomycin-resistant enterococci.

Adjunctive therapies

- 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
  - Now 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 for recurrent CDI

Initial episode
Metronidazole 500 mg orally three times daily or 250 mg four times daily for 10 to 14 days
Vancomycin 125 mg orally four times daily for 10 to 14 days
First relapse
Confirm diagnosis (refer to text)
If symptoms are mild, conservative management may be appropriate
If antibiotics are needed, repeat treatment as in initial episode above. Alternative: fidaxomicin 200 mg orally twice daily for 10 days.[1,2]
Second relapse[3,4]
Confirm diagnosis (refer to text)
Tapering and pulsed oral vancomycin (below), with or without probiotics (for example, *Saccharomyces boulardii* 500 mg orally twice daily). The probiotics may be overlapped with the final week of the taper and continued for two additional weeks in the absence of antibiotics.
125 mg orally four times daily for 7 to 14 days
125 mg orally twice daily for 7 days
125 mg orally once daily for 7 days
125 mg orally every other day for 7 days
125 mg orally every 3 days for 14 days
Alternative: fidaxomicin 200 mg orally twice daily for 10 days[1,2]
Subsequent relapse[1,2,5]
Confirm diagnosis (refer to text)
Fidaxomicin 200 mg orally twice daily for 10 days if not used previously
Fecal bacteriotherapy (fecal microbiota transplant)