Acute diarrheal Infections and Clostridium dificile

Negin N Blattman

Infectious Diseases

Phoenix VA Healthcare System

What is acute diarrhea

ACUTE DIARRHEA

- What is ?
  - Diarrhea- passage of loose or watery stools typically at least 3/24hr period.
    - Increased water content of stool
  - Invasive diarrhea=dysentery- diarrhea with visible blood or mucus. Commonly associated with fever and abdominal pain

BRISTOL STOOL CHART

	Type 1	Separate hard lumps	**SEVERE CONSTIPATION**
	Type 2	Lumpy and sausage like	**MILD CONSTIPATION**
	Type 3	A sausage shape with cracks in the surface	**NORMAL**
	Type 4	Like a smooth, soft sausage or snake	**NORMAL**
	Type 5	Soft blobs with clear-cut edges	**LACKING FIBRE**
	Type 6	Mushy consistency with ragged edges	**MILD DIARRHEA**
	Type 7	Liquid consistency with no solid pieces	**SEVERE DIARRHEA**

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- Etiology

Causes of acute infectious diarrhea in adults in resource-rich settings

	Likely pathogens	Mean incubation period	Classic/common food sources	Other epidemiologic clues
Watery diarrhea	Norovirus	24 to 48 hours	Shellfish, prepared foods, vegetables, fruit	▪ Outbreaks in: • Restaurants • Health care facilities • Schools and childcare centers • Cruise ships • Military populations
	*Clostridium difficile**	N/A	N/A	▪ Antibiotic use ▪ Hospitalization ▪ Cancer chemotherapy ▪ Gastric acid suppression ▪ Inflammatory bowel disease
	Clostridium perfringens	8 to 16 hours	Meat, poultry, gravy, home-canned goods	
	Enterotoxigenic *Escherichia coli*	1 to 3 days	Fecally contaminated food or water	▪ Travel to resource-limited settings
	Other enteric viruses (rotavirus, enteric adenovirus, astrovirus, sapovirus)	10 to 72 hours	Fecally contaminated food or water	▪ Daycare centers ▪ Gastroenteritis in children ▪ Immunocompromised adults
	Giardia lamblia	7 to 14 days	Fecally contaminated food or water	▪ Daycare centers ▪ Swimming pools ▪ Travel, hiking, camping (particularly when there is contact with water in which beavers reside)
	Cryptosporidium parvum	2 to 28 days	Vegetables, fruit, unpasteurized milk	▪ Daycare centers ▪ Swimming pools and recreational water sources ▪ Animal exposure ▪ Chronic diarrhea in advanced HIV infection
	Listeria monocytogenes	1 day (gastroenteritis)	Processed/delicatessen meats, hot dogs, soft cheese, pâtés, and fruit	▪ Pregnancy ▪ Immunocompromising condition ▪ Extremes of age
	Cyclospora cayetanensis	1 to 11 days	Imported berries, herbs	▪ Chronic diarrhea in advanced HIV infection
Inflammatory diarrhea (fever, mucoid or bloody stools)¶	Nontyphoidal *Salmonella*	1 to 3 days	Poultry, eggs, and egg products, fresh produce, meat, fish, unpasteurized milk or juice, nut butters, spices	▪ Animal contact (petting zoos, reptiles, live poultry, other pets) ▪ Travel to resource-limited settings
	Campylobacter spp	1 to 3 days	Poultry, meat, unpasteurized milk	▪ Travel to resource-limited settings ▪ Animal contact (young puppies or kittens, occupational contact)
	Shigella spp	1 to 3 days	Raw vegetables	▪ Daycare centers ▪ Crowded living conditions ▪ Men who have sex with men ▪ Travel to resource-limited settings
	Enterohemorrhagic *E. coli*	1 to 8 days	Ground beef and other meat, fresh produce, unpasteurized milk and juice	▪ Daycare centers ▪ Nursing homes ▪ Extremes of age
	Yersinia spp	4 to 6 days	Pork or pork products, untreated water	▪ Abnormalities of iron-metabolism (eg, cirrhosis, hemochromatosis, thalassemia) ▪ Blood transfusion
	Vibrio parahemolyticus	1 to 3 days	Raw seafood and shellfish	▪ Cirrhosis
	Entamoeba histolytica	1 to 3 weeks	Fecally contaminated food or water	▪ Travel to resource-limited settings ▪ Men who have sex with men

* *Clostridium difficile* can also present with inflammatory diarrhea.
¶ Pathogens that are more classically associated with inflammatory diarrhea can also cause watery diarrhea, particularly early in the course of infection.

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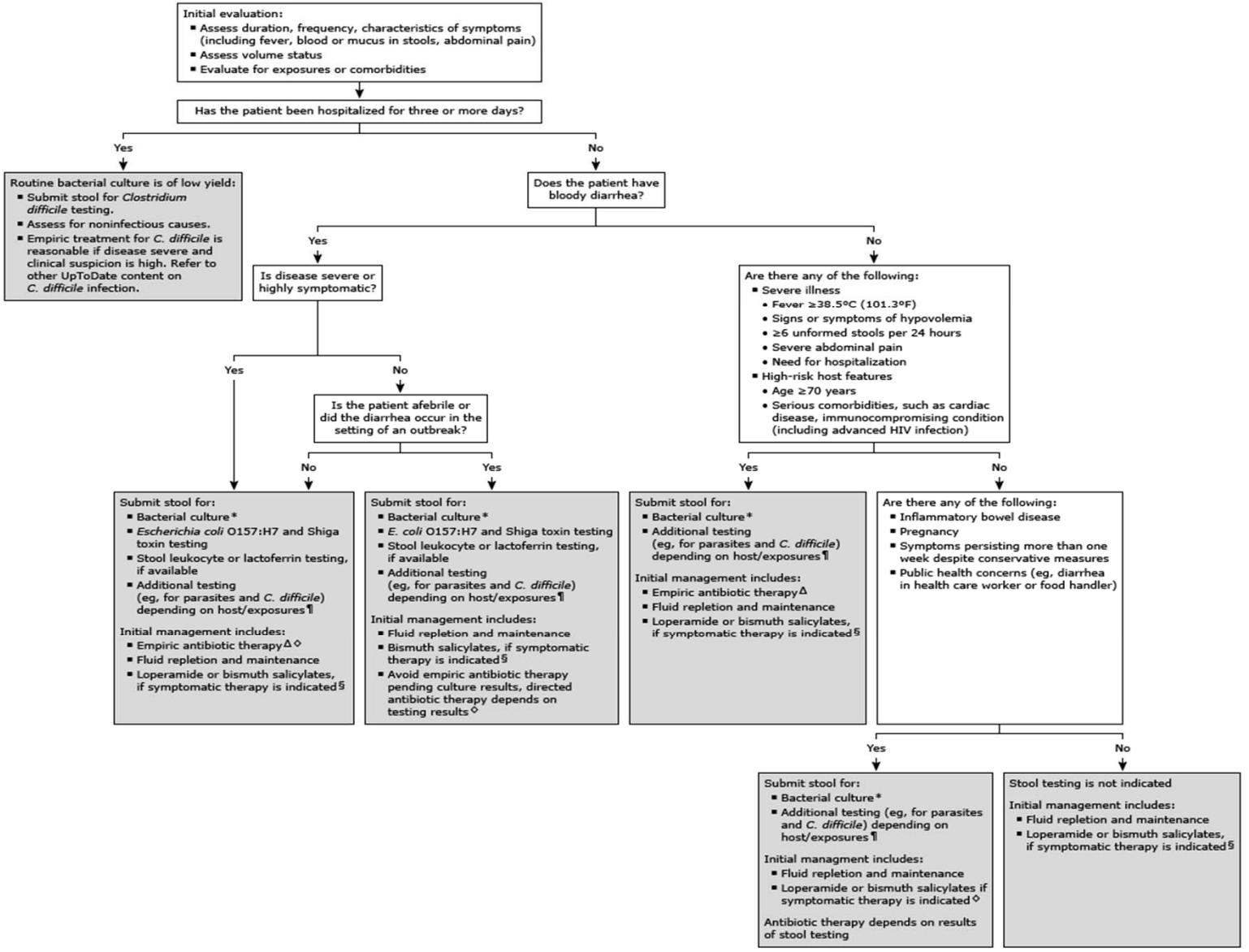
- Etiology
- Diagnosis
  - History
  - History
  - History
  - Ok send a stool culture/molecular

Management

- Fluids- oral rehydration therapy
  - Gatorade sucks
  - Needs to have water salt and sugar in appropriate concentrations
    - diluted fruit juice flavored soft drinks along with saltine crackers and broths or soups may work
    - Rehhydrate or Ceralyte

TREATMENT


Initial evaluation:
Assess duration, frequency, characteristics of symptoms (including fever, blood or mucus in stools, abdominal pain)
Assess volume status
Evaluate for exposures or comorbidities
Has the patient been hospitalized for three or more days?
Yes
No
Routine bacterial culture is of low yield:
Submit stool for Clostridium difficile testing.
Assess for noninfectious causes.
Empiric treatment for C. difficile is reasonable if disease severe and clinical suspicion is high. Refer to other UpToDate content on C. difficile infection.
Does the patient have bloody diarrhea?
Yes
No
Is disease severe or highly symptomatic?
Are there any of the following:
Severe illness
Fever ≥38.5°C (101.3°F)
Signs or symptoms of hypovolemia
≥6 unformed stools per 24 hours
Severe abdominal pain
Need for hospitalization
High-risk host features
Age ≥70 years
Serious comorbidities, such as cardiac disease, immunocompromising condition (including advanced HIV infection)
Yes
No
Is the patient afebrile or did the diarrhea occur in the setting of an outbreak?
No
Yes
Submit stool for:
Bacterial culture*
Escherichia coli O157:H7 and Shiga toxin testing
Stool leukocyte or lactoferrin testing, if available
Additional testing (eg, for parasites and C. difficile) depending on host/exposures¶
Initial management includes:
Empiric antibiotic therapy△◇
Fluid repletion and maintenance
Loperamide or bismuth salicylates, if symptomatic therapy is indicated§
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Bacterial culture*
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Fluid repletion and maintenance
Bismuth salicylates, if symptomatic therapy is indicated§
Avoid empiric antibiotic therapy pending culture results, directed antibiotic therapy depends on testing results◇
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Bacterial culture*
Additional testing (eg, for parasites and C. difficile) depending on host/exposures¶
Initial management includes:
Empiric antibiotic therapy△
Fluid repletion and maintenance
Loperamide or bismuth salicylates, if symptomatic therapy is indicated§
Are there any of the following:
Inflammatory bowel disease
Pregnancy
Symptoms persisting more than one week despite conservative measures
Public health concerns (eg, diarrhea in health care worker or food handler)
Yes
No
Submit stool for:
Bacterial culture*
Additional testing (eg, for parasites and C. difficile) depending on host/exposures¶
Initial managment includes:
Fluid repletion and maintenance
Loperamide or bismuth salicylates if symptomatic therapy is indicated◇
Antibiotic therapy depends on results of stool testing
Stool testing is not indicated
Initial management includes:
Fluid repletion and maintenance
Loperamide or bismuth salicylates, if symptomatic therapy is indicated§

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 mild diarrhea with levofloxacin and admitted for 24 hour period after being around her sick daycare attending granddaughter
  - 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 oral vancomycin clears infection/symptoms

- Testing is part of the algorithm

Diagnosis

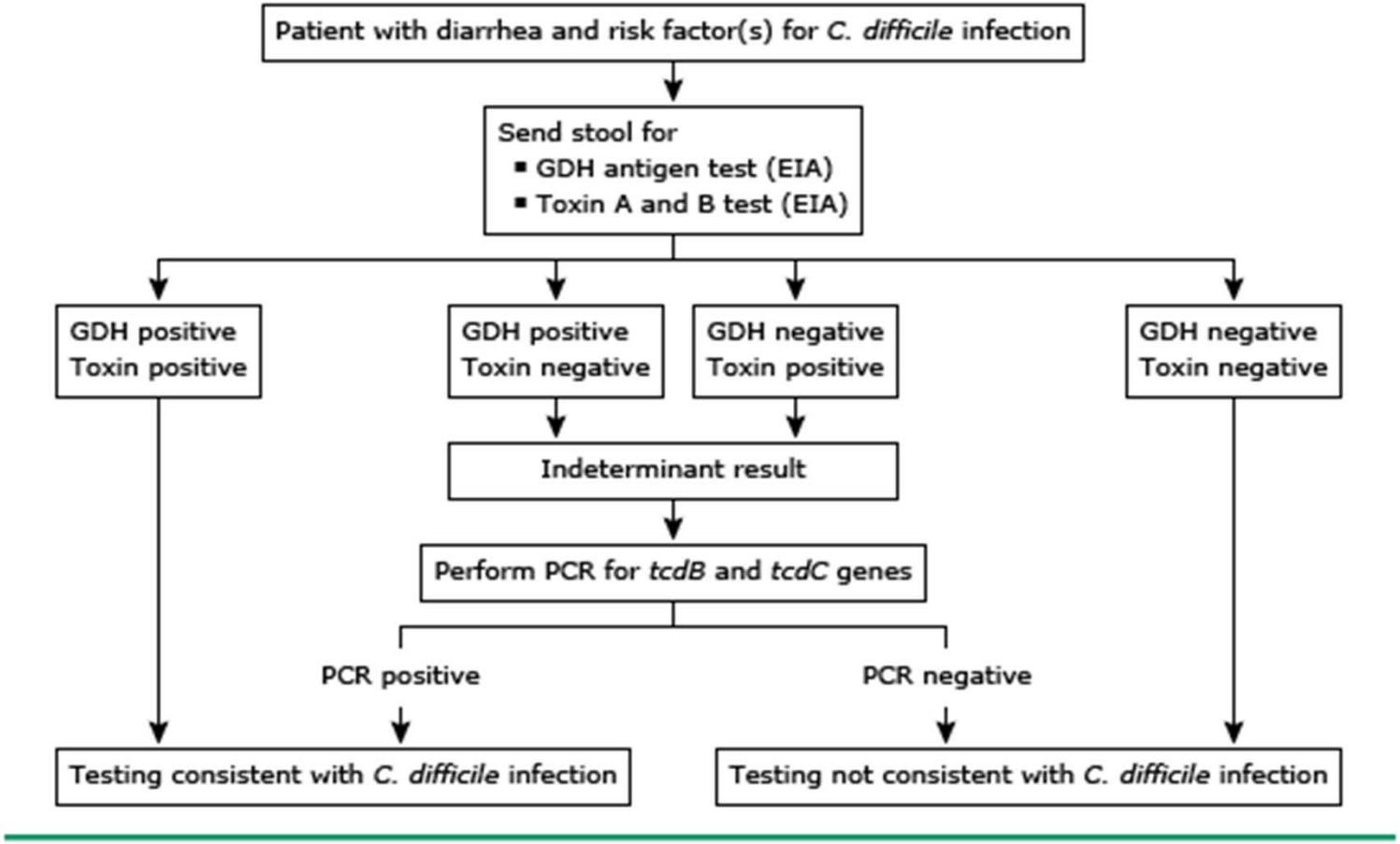
- Diagnosis requires:
  - Moderate to severe diarrhea

    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



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Patient C

- 45 year old female recently treated with amoxicillin/clavulaunate 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

Classification of disease

For the purposes of the treatment decisions in the following discussion, determination of disease severity is left to clinician judgment and may include any or all of the above criteria.

Classification	Presentation
Nonsevere	WBC≤15,000 cells/mL and sCr<1.5 mg/dL
Severe	WBC>15,000 cells/mL and SCr ≥1.5 mg/dL
Fulminant (severe complicated)	Hypotension or shock, ileus, or megacolon

TREATMENT: NON-SEVERE

- General management
  - Stop inciting antibiotic as soon as possible
  - Infection control
- Antibiotic therapy*
  - Initial therapy
    - Vancomycin
    - fidaxamicin
    - 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

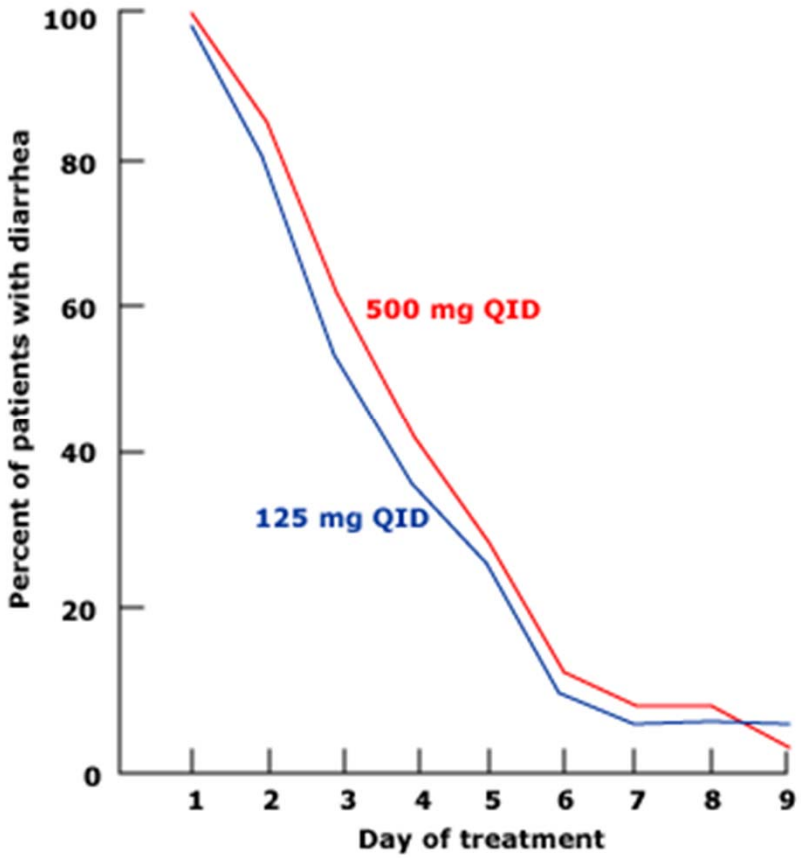
Patient D

- 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: fulminant

- 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 Options for First episode

Clinical definition	Treatment*
Nonsevere disease Supportive clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL	
Initial episode	▪ Vancomycin 125 mg orally four times daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days ▪ If above agents are unavailable: Metronidazole 500 mg orally three times daily for 10 days¶
First recurrence	▪ If vancomycin was used for the initial episode: • Vancomycin pulsed-tapered regimen: ○ 125 mg orally four times daily for 10 to 14 days, then ○ 125 mg orally twice daily for 7 days, then ○ 125 mg orally once daily for 7 days, then ○ 125 mg orally every 2 or 3 days for 2 to 8 weeks, **OR** • Fidaxomicin 200 mg orally twice daily for 10 days ▪ If fidaxomicin or metronidazole was used for the initial episode: Vancomycin 125 mg orally four times daily for 10 days
Second or subsequent recurrence	▪ Vancomycin pulsed-tapered regimen (outlined above), **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days, **OR** ▪ Vancomycin followed by rifaximin: • Vancomycin 125 mg orally four times per day for 10 days, then • Rifaximin 400 mg three times daily for 20 days, **OR** ▪ Fecal microbiota transplantation∆
Severe disease◇ Supportive clinical data: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL	▪ Vancomycin 125 mg orally four times daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days
Fulminant disease (previously referred to as severe, complicated *C. difficile* infection)◇ Supportive clinical data: Hypotension or shock, ileus, megacolon	▪ Enteric vancomycin plus parenteral metronidazole: • Vancomycin 500 mg orally or via nasogastric tube four times daily, **AND** • Metronidazole 500 mg intravenously every 8 hours ▪ If ileus is present, rectal vancomycin may be administered as a retention enema (500 mg in 100 mL normal saline per rectum; retained for as long as possible and readministered every 6 hours)§

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

- I highly recommend “The Blattman Taper”