Clostridium difficile
Not So Easy To Treat?

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Introduction

• Greek-kloster for spindle and Latin-difficile for difficult
• Gram positive spore forming anaerobic bacillus
• Most common cause of nosocomial diarrhea
• Rate and severity of C. difficile associated diarrhea increasing
• 4.5 cases per 1000 hospitalizations in 2001 to 8.2 cases per 1000 hospitalizations in 2010
• New strain with increased resistance and virulence
Epidemiology

- About 20 percent of hospitalized adults are C. difficile carriers who shed C. difficile in their stools but do not have diarrhea.
- In long term care facilities, carrier rate approaches 50 percent.
- These individuals serve as reservoir for environmental contamination.
- Host immune response to C. difficile may play role in determining individual's carrier status.
Clinical Manifestations

- Watery diarrhea up to 10 or 15 times daily with lower abdominal pain and cramping, low grade fever, and leukocytosis
- Fever (T>38.5) is a sign of severe infection
- Symptoms occur in the setting of antibiotic administration
- May begin during antibiotic therapy or 5 to 10 days following antibiotic administration. Infrequently, symptoms present as late as 10 weeks after cessation of therapy
- Asymptomatic carrier state to fulminant disease with toxic megacolon (cause not well understood)
Clinical Manifestations

• Physical examination ➔ lower abdominal tenderness

• Sigmoidoscopy or colonoscopy demonstrates spectrum of findings, from patchy mild erythema and friability to severe pseudomembranous colitis.

• Unexplained leukocytosis in hospitalized patients (even in the absence of diarrhea) may reflect underlying C. difficile infection
## Culprit Antibiotics

<table>
<thead>
<tr>
<th>Frequently associated</th>
<th>Occasionally associated</th>
<th>Rarely associated</th>
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<tbody>
<tr>
<td>Fluroquinolones</td>
<td>Macrolides</td>
<td>Aminoglycosides</td>
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<tr>
<td>Clindamycin</td>
<td>Trimethoprim</td>
<td>Tetracyclines</td>
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<tr>
<td>Penicillins (broad spectrum)</td>
<td>Sulfonamides</td>
<td>Chloramphenicol</td>
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<tr>
<td>Cephalosporins (broad spectrum)</td>
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<td>Metronidazole</td>
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<td>Vancomycin</td>
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Endoscopic Findings

• C. difficile toxin-induced cytoskeleton disruption → gross findings of shallow ulcerations on intestine mucosal surface
• Ulcer formation allows release of serum proteins, mucus, and inflammatory cells → colorectal mucosal surface as pseudomembranes (virtually pathognomonic for C. difficile)
• Bowel wall edema, erythema, friability, and inflammation
• Rare reports of Klebsiella and other pathogens also capable of causing pseudomembranous colitis
• Pseudomembranes may be absent in the rectosigmoid area but visualized more proximally with colonoscopy, although colonoscopy is not indicated for diagnosis of C. difficile
Endoscopic Findings
## Histopathology

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>mildest form major inflammatory changes confined to superficial epithelium and immediately subjacent lamina propria typical pseudomembranes present crypt abscesses are occasionally present</td>
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<tr>
<td>Type 2</td>
<td>more severe disruption of glands marked mucin secretion more intense inflammation of basal lamina</td>
</tr>
<tr>
<td>Type 3</td>
<td>severe, intense necrosis of full thickness of mucosa confluent pseudomembrane</td>
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CT scan appearance

Thickening of the colonic wall
(Courtesy of Jonathan Kruskal, MD, PhD)
Recurrent disease: relapse vs reinfection

- Recurrence of symptoms after successful initial therapy for C. difficile due to relapse of initial infecting strain or due to reinfection with new strain, develops in 10 to 25 percent of cases
- Recurrence may present within days or weeks of completing treatment
- Clinical presentation may be similar to or more severe than initial presentation
- Recurrence may be related to variability in host immune response to C. difficile infection
Recurrent disease: relapse vs reinfection

- Recurrent C. difficile infection often represents relapse rather than reinfection, regardless of interval between episodes.
- Some patients with recurrent diarrhea, cramping, and bloating after treatment of C. difficile may have postinfectious irritable bowel syndrome or other inflammatory colitides including collagenous or microscopic colitis, concomitant ulcerative colitis, Crohn’s disease, or celiac disease.
Fulminant colitis

- Manifestations of fulminant colitis
  - severe lower quadrant or diffuse abdominal pain
  - diarrhea
  - abdominal distention
  - fever
  - hypovolemia
  - lactic acidosis
  - hypoalbuminemia
  - marked leukocytosis (up to 40,000)
Fulminant colitis

- Diarrhea less prominent in patients with prolonged ileus due to pooling of secretions undilated, atonic colon

- Potential complications
  - Toxic megacolon
    - clinical diagnosis
    - colonic dilatation (>7 cm in its greatest diameter)
    - severe systemic toxicity
    - Abdominal plain films → small bowel dilatation, air-fluid levels and "thumb printing" (scalloping of bowel wall) due to submucosal edema
  - Bowel perforation → abdominal rigidity, involuntary guarding, diminished bowel sounds, rebound tenderness, and severe localized tenderness in left or right lower quadrants, abdominal radiographs may demonstrate free abdominal air
Toxic megacolon

Courtesy of J Thomas LaMont, MD.
Thumbprinting on plain x-ray

Courtesy of Jonathan Kruskal, MD, PhD.
Fulminant Colitis

• Aggressive diagnostic and therapeutic interventions in setting of fulminant C. difficile infection
• Bedside sigmoidoscopy or colonoscopy to make presumptive diagnosis, evaluating for presence of pseudomembranes
• Given risk of perforation, care taken to introduce minimal amounts of air to avoid exacerbating ileus or distention
• Prompt surgical consultation warranted to assess requirement for colectomy
Hypervirulent Strain

- Hypervirulent strain: NAP1/BI/027
- Responsible pathogen in selected Clostridium difficile outbreaks since the early 2000’s
- Produces binary toxin, an additional toxin not present in other C. difficile strains, role in C. difficile not fully understood
- Produces larger quantities of toxins A and B
- Partial deletion of tcdC, a gene in pathogenicity locus (PaLoc) responsible for downregulation of toxin production
Extra-colonic involvement

• Appendicitis due to C. difficile unusual
• Small bowel involvement with C. difficile enteritis unusual; manifestations → increased ileostomy output
• C. difficile involvement of small bowel tend to be elderly or patients with multiple comorbidities
• Rare cases of C. difficile cellulitis, soft tissue infection, and reactive arthritis
Differential Diagnosis

- C. difficile major infectious cause of antibiotic-associated diarrhea
- Distinguished from other infectious and noninfectious causes of diarrhea
  - S. aureus previously implicated as important cause of antibiotic-associated pseudomembranous colitis
  - Other potential pathogens: Klebsiella oxytoca, Clostridium perfringens, Candida spp, and Salmonella
Differential Diagnosis

- Among noninfectious causes, antibiotic-associated diarrhea may be attributable to osmotic mechanisms rather than C. difficile infection
  - differentiation difficult, especially in patients who also may be asymptomatic C. difficile carrier
  - cessation of symptoms with discontinuation of oral intake distinguishing feature of osmotic diarrhea
  - presence of fever and leukocytosis favor C. difficile or other infectious etiology

- Postinfectious IBS occurs in about 10% of patients successfully treated for initial bout of C. difficile

- These patients may have up to 10 watery stools per day and convinced they have relapse
Diagnosis

- Moderate to severe diarrhea or ileus
- Stool test positive for C. difficile toxins or toxigenic C. difficile
- Endoscopic or histologic findings of pseudomembranous colitis
- Diagnostic stool evaluation for the presence of C. difficile toxins in setting of clinically significant diarrhea (usually defined as three or more loose stools per day for at least two days)
- Loose, watery, or semi-formed stool should be tested
- C. difficile toxin degrades at room temperature and may be undetectable within two hours after collection
Laboratory Diagnosis

• Polymerase chain reaction (PCR)
• Enzyme immunoassay (EIA) for C. difficile glutamate dehydrogenase (GDH)
• Enzyme immunoassay (EIA) for C. difficile toxins A and B
• Cell culture cytotoxicity assay
• Selective anaerobic culture
PCR Testing

• Real-time PCR tests that detect toxin A and B genes highly sensitive and specific
• Sensitivity of PCR is greater than enzyme immunoassay and comparable to cytotoxicity assay
• PCR results available within one hour
• Given high sensitivity and potential for false positive results, some favor use of PCR in algorithm together with other assays such as EIA for GHD and EIA for toxins A and B
EIA for C. difficile GDH Antigen

- GDH antigen essential enzyme produced constitutively by all C. difficile isolates

- Detection cannot distinguish between toxigenic and nontoxigenic strains

- Testing for GDH antigen useful as initial screening step in multistep approach, which also consists of subsequent testing $\rightarrow$ PCR on specimens GDH antigen positive

- Highly sensitive and results available in less than one hour
EIA for C. difficile toxins A and B

- Most C. difficile strains produce both toxins A and B, although some strains produce toxin A or B only
- Sensitivity about 75 percent
- Specificity up to 99 percent
- Relatively high false negative rate since 100 to 1000 pg of toxin must be present for test to be positive
- If initial EIA test negative, value of repeating test limited and repeat testing discouraged
Cell culture cytotoxicity assay

• “Gold standard” test for diagnosis of C. difficile
• Performed by adding prepared stool sample (diluted, buffered, and filtered) to monolayer of cultured cells
• If C. difficile toxin present, exerts cytopathic effect characterized by rounding of fibroblasts in tissue culture
• Cytotoxicity assay more sensitive than enzyme immunoassays, but labor intensive and takes approximately two days
Selective anaerobic culture

- Culture on selective medium with toxin testing of isolated C. difficile
- Most sensitive diagnostic method
- Cannot distinguish toxin-producing strains from non-toxin producing strains
- Prior treatment with heat or alcohol to select spores sometimes used to improve yield
- Culture useful for epidemiologic studies but generally too slow and labor-intensive for clinical use
Clinical approach

- PCR either alone or as part of algorithm (including initial EIA screening for GDH, with or without EIA screening for toxins A and B)
- High sensitivity and specificity of PCR, together with rapid turn-around time, allow prompt isolation and treatment of patients reducing opportunity for nosocomial spread and improving patient outcomes.
- Algorithmic approach may be less expensive but take slightly longer and may have reduced sensitivity compared with PCR alone
- Diagnostic approach for suspected recurrent C. difficile same as approach for initial infection
- No clinical role for laboratory diagnosis among asymptomatic patients or among patients on treatment for acute disease
Endoscopy

- Colonoscopy or sigmoidoscopy and biopsy (in the setting of diagnostic uncertainty) useful in the following settings:
  - High clinical suspicion for C. difficile with negative laboratory assay(s)
  - Prompt C. difficile diagnosis needed before laboratory results can be obtained
  - Failure of C. difficile infection to respond to antibiotic therapy
  - Atypical presentation with ileus or minimal diarrhea
- Pseudomembranes on sigmoidoscopy → C. difficile infection
- Pseudomembranes not observed in 10 to 20 percent of patients with C. difficile, particularly in recurrent infection; in such cases biopsy useful
- Pseudomembranes may not be observed in the setting of other forms of colitis. Rarely seen in patients with inflammatory bowel disease and superimposed C. difficile infection → biopsy useful
- Endoscopy not warranted in patients with classic clinical findings and a positive stool toxin assay.
Indications for Treatment

- Patients with typical manifestations (diarrhea, abdominal pain, or nausea and vomiting) and positive diagnostic assay should receive antibiotics.
- Empiric therapy appropriate pending results of diagnostic testing if clinical suspicion high.
- Treatment not indicated in patients who have positive toxin assay but asymptomatic.
# Choice of Antibiotics

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment</th>
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<tr>
<td>Initial treatment of non-severe disease</td>
<td>oral metronidazole</td>
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<tr>
<td>Severe CDI</td>
<td>oral vancomycin 125 mg four times daily for 10 to 14 days</td>
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<tr>
<td>Patients with severe disease who do not demonstrate clinical improvement</td>
<td>oral vancomycin 500 mg four times daily; fidaxomicin may be considered in patients intolerant to vancomycin</td>
</tr>
<tr>
<td>In critically ill patients with fulminant or refractory disease</td>
<td>oral vancomycin 500 mg four times daily and intravenous metronidazole 500 mg every eight hours</td>
</tr>
<tr>
<td>Treatment of severe disease in patients with profound ileus</td>
<td>intracolonic vancomycin but risk of colonic perforation</td>
</tr>
<tr>
<td>Treatment of non-severe initial recurrence of CDI</td>
<td>oral metronidazole; alternatives: oral vancomycin or fidaxomicin</td>
</tr>
<tr>
<td>Treatment of second recurrence of CDI</td>
<td>intermittent and tapering vancomycin therapy or fidaxomicin</td>
</tr>
<tr>
<td>Treatment of subsequent recurrences of CDI</td>
<td>fidaxomicin or vancomycin followed by rifaximin</td>
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# Alternative Treatments

<table>
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<tr>
<th>Treatment</th>
<th>Features</th>
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<tr>
<td>nitazoxanide</td>
<td>may be as effective as vancomycin</td>
</tr>
<tr>
<td>fidaxomicin</td>
<td>non-systemic; bactericidal</td>
</tr>
<tr>
<td>anion-binding resins: colestipol</td>
<td>bowel flora not altered</td>
</tr>
<tr>
<td>and cholestyramine</td>
<td>rapid reconstitution of normal colonic flora</td>
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<tr>
<td></td>
<td>not effective as primary therapy</td>
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<tr>
<td></td>
<td>adjunctive therapy for relapsing infection</td>
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<tr>
<td></td>
<td>binds vancomycin as well as toxins</td>
</tr>
<tr>
<td>tolevamer</td>
<td>C. difficile toxin binding resin developed specifically for CDI</td>
</tr>
<tr>
<td></td>
<td>Preliminary studies show promising results but inferior to vancomycin</td>
</tr>
<tr>
<td></td>
<td>and metronidazole as primary therapy</td>
</tr>
<tr>
<td>probiotics</td>
<td>reconstitution of intestinal flora</td>
</tr>
<tr>
<td></td>
<td>ongoing studies underway to assess efficacy</td>
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Fecal Transplantation

- Relapse of C. difficile occurs in 10 to 25 percent of patients treated with metronidazole or vancomycin
- Multiple relapses in same patient common
- 10 or more bouts of relapsing colitis have occurred in some patients
- Fecal microbiota transplantation (FMT) has been used to treat relapsing C. difficile infection
Rationale for FMT

• Gastrointestinal tract harbors stable, highly complex community of microorganisms existing in symbiosis with host
• Human gut microbiota consists of 1000 to 1200 bacterial species and at least $10^{14}$ bacteria, most of which are in colon
• Beneficial roles mediated by microbiota
  – synthesis of vitamins
  – fermentation of dietary carbohydrates
  – metabolism of bile and host hormones and competitive exclusion ("colonization resistance") of pathogens taking residence in the gut community
  – development and maturation of immune system through interactions with gut epithelium
Rationale for FMT

• Composition of microbiota significantly affected by extensive use of antibiotics leading to selective removal of group of bacteria species that serve as barrier to colonization and/or persistence of pathogens

• Antibiotic-mediated changes in composition of gut microbiota lead to homeostatic imbalance via alterations in gut barrier functions and result in mucosal immune defects

• C. difficile allows environmentally acquired spores to germinate and successfully colonize gut
Rational for FMT

- Although specific antimicrobial therapy effective, recurrence of C. difficile infection increasing problem following therapy
- Recurrent C. difficile associated with decrease in fecal microbial diversity, deficiency in Bacteroides and Firmicutes → dominate within gut microbiota
- Transplantation of stool from healthy individuals to patients with recurrent C. difficile restores these strains and breaks the cycle of recurrence
Efficacy

• Meta-analysis of observational studies and a randomized trial have demonstrated efficacy of fecal microbiota transplantation (FMT) in the treatment of C. difficile-associated diarrhea in patients with recurrent disease after initial antibiotic therapy.

• Limited observational data suggests treatment with FMT associated with resolution of C. difficile-associated diarrhea in patients with severe disease.

• Several routes used to administer fecal microbiota with cure rates ranging from 81 to 94 percent in patients with recurrent disease.

• In studies where the time to response has been specified, it has been observed within 24 hours to 12 days.
Efficacy

• In 3 studies with variable follow-up ranging from 3 weeks to 9 years, response durable and well-tolerated
• Patients show immediate and complete resolution of diarrhea and associated symptoms and disappearance of pseudomembranes
• Following treatment, repeated stool tests for C. difficile and toxins were negative.
• FMT remains the only method capable of providing durable implantation of probiotics
• Attempts to reconstitute bacterial microbiota using cultured bacteria not successful
Efficacy Based on Route of Administration

• Several routes of administration of fecal intestinal microbiota have been reported but optimal protocol for FMT unclear

• Pooled analysis of 182 cases of recurrent CDI treated with FMT showed colonoscopic FMT has a slightly higher cure rate than nasogastric FMT (93 versus 85 percent), although the difference was not statistically significant
Administration via enema

- Multiple studies have shown success with FMT administered via enema
- A case series of 27 patients with refractory or recurrent C. difficile underwent FMT via retention enema using stool from two healthy donors (Kassam et al., Arch Intern Med. 2012). 25 of 27 (93 percent) patients experienced clinical resolution. Of these, 22 resolved within 24 hours of FMT
- Self-administered home fecal transplantation for recurrent C. difficile infection has also been successfully performed (Silverman et al. Clin Gastroenterol Hepatol.). 7 patients who underwent the procedure cured of C. difficile
- Efficacy of FMT may depend upon technique used to cleanse colon before administration of the fecal enema cleansing (eg, with oral polyethylene glycol lavage) may reduce density of C. difficile organisms including metabolically inactive spores that could otherwise convert to vegetative forms
Administration via colonoscope

- Enemas reach splenic flexure
- Colonoscopy allows for administration of bacteria throughout colon and distal small bowel where C. difficile can reside
- Number of studies demonstrated single administration extremely efficacious in eradicating C. difficile infection
- Given ease of administration in both inpatient and outpatient settings and delivery of introduced flora to the site where most C. difficile is located, administration via colonoscope has been proposed as the preferential route of delivery of fecal microbiota (Brandt et al., J Clin Gastroenterol. 2011)
- Colonoscopy performed extremely cautiously in this setting because of risk of perforation
Administration via nasogastric tube

- Administration via a nasogastric tube permits delivery of bacteria to distal small bowel and throughout the colon. FMT administered via nasogastric tube demonstrated to be successful in several observational studies and a randomized controlled trial.

- Open label randomized controlled trial (van Nood et al, N Engl J Med. 2013):
  - 43 patients with recurrent C. difficile infection after at least one course of antibiotic therapy randomized to duodenal infusion of donor feces preceded by an abbreviated regimen of vancomycin (vancomycin 500 mg four times daily for four days) and bowel lavage (4 L of polyethylene glycol).
  - OR a standard vancomycin regimen (vancomycin 500 mg four times daily for 14 days) or standard vancomycin regimen with bowel lavage.
  - Single infusion of donor feces was associated with significantly higher rates of resolution of CDI without relapse at 10 weeks as compared with a standard vancomycin regimen with or without bowel lavage (81, 23, and 31 percent, respectively). Mild diarrhea, cramping, and belching quickly resolved most common side effects.
Safety

- FMT appears to be safe
- Major complications have not been reported in published series
- Adverse effects transient and mild (and consist mainly of abdominal gurgling, gas, and noise)
- Concern: potential of transmission of infectious agents contained in the stool. Risk reduced by obtaining stool from healthy donors with normal bowel function and by testing both stool and blood for common viral and bacterial pathogens and parasites
Suggested Protocol

• Treatment hampered by lack of standardization in the preparation and administration

• Efficacy depends upon number of factors including freshness of donated stool, frequency of enema administration, use of colonic lavage, and re-population of entire colon
Exclusion Criteria

- Donor stool and blood screened for pathogens and viruses before infusion
  - CBC
  - Hepatitis A, B, and C
  - HIV
  - Syphilis
  - Stool tests: fecal Giardia antigen, cryptosporidium antigen, acid fast stain for Cyclospora, Isospora, and H. pylori fecal antigen
  - Stool cultures are obtained to look for enteric bacterial pathogens and for ova and parasites.
  - Donor stool screened for C. difficile
  - Donor needs to have normal, daily stools, no recent antibiotics, no history of inflammatory bowel disease, and be clinically well
  - Relative or friend may be a donor but should not share living quarters with patient, as likelihood they will share same defective microbiota
  - Recipient's HIV and hepatitis A and B status is also checked prior to receipt of FMT
Management Principles

- Stop inciting antibiotic as soon as possible
- Treatment with concomitant antibiotics (ie, antibiotics other than those given to treat C. difficile infection) associated both with significant prolongation of diarrhea and with increased risk of recurrent C. difficile infection
- If ongoing antibiotics essential for treatment of primary infection, select antibiotics less frequently implicated in CDI like aminoglycosides, sulfonamides, macrolides, vancomycin, or tetracycline
- Implementation of infection control policies
- Patients with suspected or proven C. difficile infection should be placed on contact precautions
Management Principles

- Healthcare workers should wash hands before and after patient contact.
- Hand hygiene with soap and water more effective than alcohol-based hand sanitizers in removing C. difficile spores, since C. difficile spores are resistant to killing by alcohol.
- Antimotility agents such as loperamide and opiates avoided.
- Supportive care with attention to correction of fluid losses and electrolyte imbalances.
- Regular diet as tolerated, unless surgery or other procedure planned.
- Treatment options: metronidazole, oral vancomycin, fidoxamicin, anion-binding resins, alternative therapies, and FMT.