Clostridium difficile Infection: Diagnosis and Management

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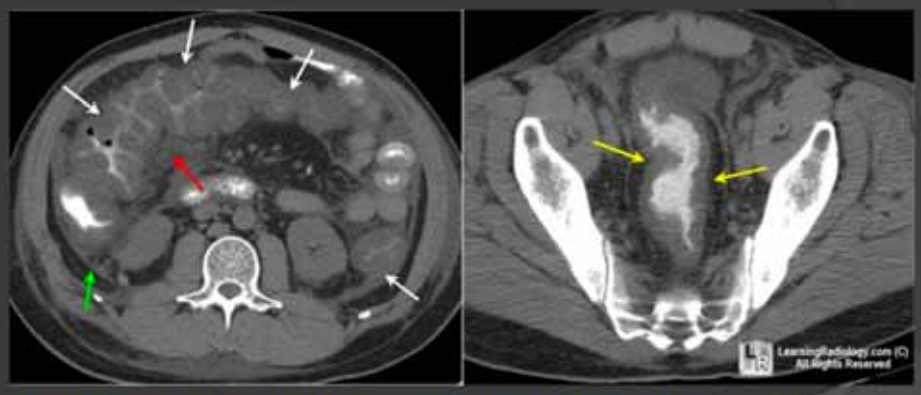
Case study

- 42 year old female with history of essential hypertension and COPD presents to ED complaining of 24 hours of intractable, diffuse abdominal pain and diarrhea. Patient reports 10-12 foul smelling stools over the previous 24 hours. Blood work revealed WBC-24,000 and CT showed diffuse colonic thickening. Patient has been in normal health with the exception of a URI treated with antibiotic 6 weeks ago.

Pseudomembranous colitis- cont'd



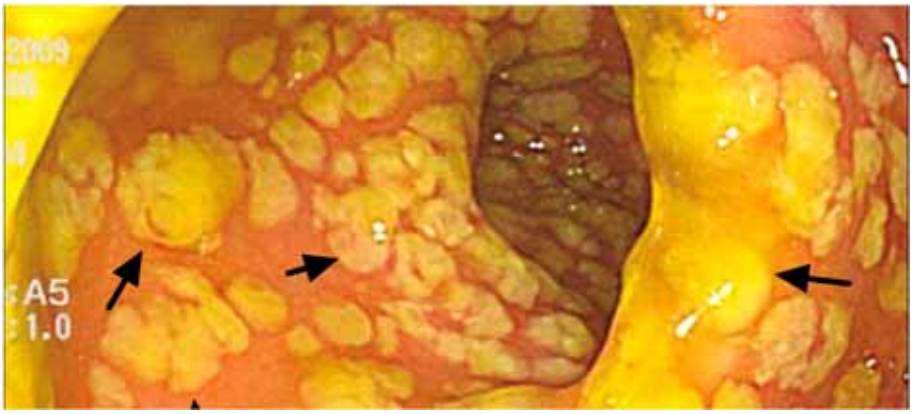
(Left) Axial CT scan of the midabdomen utilizing oral but not intravenous contrast demonstrates marked thickening of the colonic wall (white arrows) producing the so-called "accordion sign." There is a small amount of pericolonic stranding (red arrow) and ascites (green arrow). **(Right)** Axial CT scan through the pelvis shows marked thickening of the wall of the rectum (yellow arrows) indicating this is a pan-colitis.

Clostridium Difficile

- Spore-forming rod
- Infection typically follows use of broad spectrum antibiotics- ampicillin, clindamycin, cephalosporins
  - Wipe out the normal intestinal bacterial flora, allowing the pathogenic Clostridium difficile to superinfect the colon
- Symptoms are causes by exotoxins
  - Toxin A- causes diarrhea
  - Toxin B- cytotoxic to colonic cells

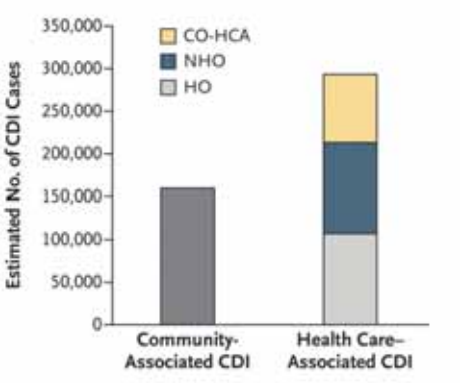
Clostridium difficile

- Infection is defined by the presence of symptoms (diarrhea) and either a positive stool toxin or colonoscopic/histologic findings consistent with pseudomembranous colitis (next slide).
- Presence of symptoms are necessary and patients without symptoms should not be tested as they can be carriers and do not require treatment.
  - Unnecessary cost and treatment



Pseudomembranous colitis

Estimated Annual U.S. Burden



Estimated U.S. Burden of CDI, According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

CO-HCA: Community onset healthcare-associated
NHO: Nursing home onset
HO: Hospital onset

- **453,000 CDI cases[1]**
  - **293,000 healthcare-associated**
    - **107,000 hospital-onset**
    - **104,000 nursing home-onset**
    - **81,000 community-onset, healthcare-facility associated**
  - **160,000 community-associated**
    - **82% associated with outpatient healthcare exposure**

Overall, 94% of CDI cases related to healthcare

- **29,000 deaths**
- **$4.8 billion in excess healthcare costs[2]**

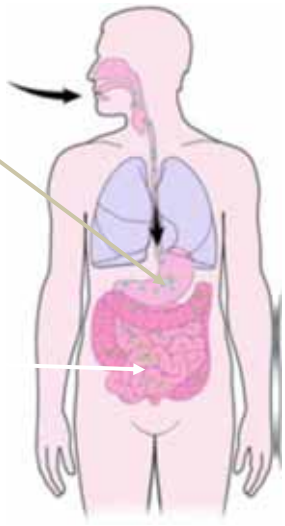
1. Lessa et al. N Engl J Med 2015; 372(9):825-834.
2. Dubberke et al. Clin Infect Dis 2012; 55:988-92.

Clostridium difficile- Incidence

- An estimated 500,000 cases yearly in United States
- Increased risk with the following
  - Age > 65
  - Female
  - Caucasian
  - Healthcare exposure
  - Antibiotic exposure
  - Inflammatory bowel disease- also carries increased risk of recurrence and colectomy
  - PPI?- 50% increase risk of recurrence
  - Stem cell (9-fold increased risk) and solid organ transplant recipients (5-fold increased risk)
  - ESRD on dialysis. (2-2.5-fold increased risk)
  - Malignancy- especially if actively treated with chemotherapy
- C-dif has surpassed MRSA as most common cause of healthcare associated infection

Pathogenesis of CDI

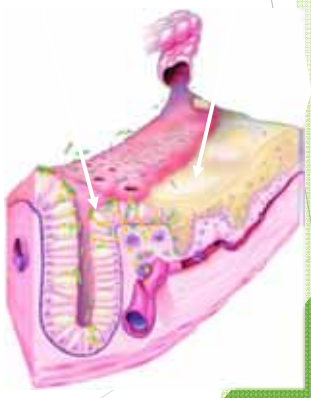
1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.



2. Spores germinate within the intestine

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.

4. Toxin A & B Production leads to colon damage +/- pseudomembrane.



Sunenshine & McDonald Cleve Clin J Med 2006; 73(2):187-197.

9

Clostridium difficile- Routes of transmission

- Hands of healthcare personnel, transiently contaminated with spores, and environmental contamination are predicted as main vectors
- Instruments- rectal thermometers etc.
- Family members

Clostridium Difficile- Diagnosis

- Who should we test- patients with 3 unformed stools in 24 hours
- Types of stool tests
  - **Enzyme immunoassay.** The enzyme immunoassay (EIA) test is faster than other tests but isn't sensitive enough to detect many infections and has a higher rate of falsely normal tests.
  - **Polymerase chain reaction.** This sensitive molecular test can rapidly detect the C. difficile toxin B gene in a stool sample and is highly accurate.
  - **GDH/EIA.** Some hospitals use a glutamate dehydrogenase (GDH) in conjunction with an EIA test. GDH is a very sensitive assay and can accurately rule out the presence of C. difficile in stool samples.
  - **Cell cytotoxicity assay.** A cytotoxicity test looks for the effects of the C. difficile toxin on human cells grown in a culture. This type of test is sensitive, but it is less widely available, more cumbersome to do and requires 24 to 48 hours for test results. Some hospitals use both the EIA test and cell cytotoxicity assay to ensure accurate results.

Available Tests

Table 1. **Tests Available for Laboratory Confirmation of *Clostridium difficile* Infection***

Test	Description	Sensitivity, %	Specificity, %	Speed of Reports	Cost, $†
EIA	Detects toxin A or toxins A plus B	70–80	>97	Hours	5–17
GDH	Detects a common antigen, not a toxin, of *Clostridium difficile*; immunoassay is preferred over latex agglutination	70–80	<90	Hours	17
qPCR	Detects toxin B or toxin regulator genes; commercial and locally developed tests are available	>90	>97	Hours	7–50
Anaerobic culture for toxigenic *C. difficile*	Detects toxin B	>90	95–97	2 to >3 d	10–22
Direct stool cytotoxin with tissue culture	Detects toxin B	70–80	>97	2 to >3 d	7–13

EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; qPCR = quantitative real-time polymerase chain reaction.
* Adapted from references 6 and 10–13.
† Range of manufacturer's suggested retail prices for 2007–2008 (6, 12).

Guidance from the American Society for Microbiology

- Toxin A/B enzyme immunoassays have low sensitivity and should not be used as stand alone tests.[1]
- Highly sensitive screening tests like glutamate dehydrogenase antigen assays (GDH) should have positive results confirmed.
- Nucleic acid amplification that detects *C. difficile* toxin genes may be used as a stand alone test.
- Repeat testing, testing of formed stool, and testing for cure should be avoided.[2]

Regardless of testing method, ensure appropriate testing to optimizing test performance!

1. Am Soc Microbiol, 2010.

2. Dubberke et al. Infect Control Hosp Epidemiol 2014; 35 (6):628-645.

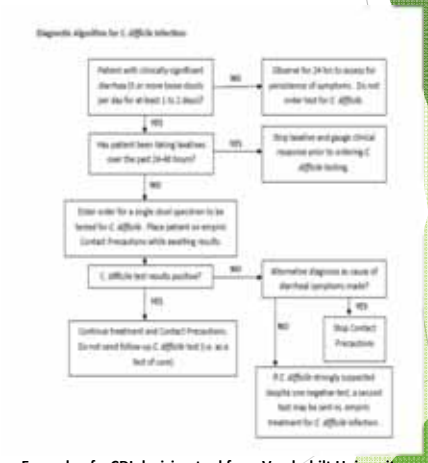
13

Clostridium Difficile- Diagnosis

- Important to remember, if CDI is suspected, do not delay treatment. Empiric treatment is extremely important in preventing complications
- Do not perform repeat testing (within 7 days) during the same episode
  - Increases diagnostic yield only 2%
  - If epidemic is suspected- repeat testing may be warranted vs empiric treatment

Guidance for Appropriate Testing

- Tools that guide clinical decision making, such as algorithms, can assist in ensuring appropriate testing



Example of a CDI decision tool from Vanderbilt University Medical Center

1. Dubberke et al. Infect Control Hosp Epidemiol 2014; 35(6):628-645.
2. Vanderbilt University Medical Center: http://www.mc.vanderbilt.edu/documents/infectioncontrol/files/Guidance%20for%20Providers%20FINAL%202011.pdf

15

Fulminant Clostridium Difficile Infection

- In prior guidelines this was referred to severe, complicated CDI
- Hypotension
- Shock
- Ileus
- Megacolon
- Important to identify early because treatment is different initially

Infection prevention and control

- Accommodate patients with CDI in a private room with a dedicated toilet to prevent transmission
- Healthcare personnel must use gloves and gowns upon entry to a room of a patient with CDI
- These precautions should be instituted if CDI suspected while testing completed
- Continue contact precautions for 48 hours after resolution of diarrhea
- Hand washing prior and after patient contact is required. If direct contact with stool, handwashing with soap and water preferred
- Patient should wash hands and shower when able
- Disposable equipment should be used if possible and reusable equipment should be thoroughly cleaned sporicidal disinfectant

Infection prevention and control

- Minimize the frequency and duration of high risk antibiotic therapy
  - Fluoroquinolones, clindamycin, cephalosporins
  - Most institutions should have antibiotic stewardship program
- Proton pump inhibitors
  - There is an epidemiologic associated with PPI and CDI
  - Minimize use in high risk patients
  - Insufficient evidence for discontinuation of PPI's
- Probiotics- Insufficient evidence that they reduce CDI
  - Does reduce antibiotic associated diarrhea

Treatment

- Discontinue therapy with the inciting antibiotic agent as soon as possible
  - Evidence shows this will decrease clinical response and increase recurrence rates
- Antibiotic therapy for CDI should. Be started empirically for situations where a substantial delay in laboratory confirmation is expected or severe disease

Treatment

- Vancomycin or fidaxomicin is now first line
  - Vanco 125mg PO QID
  - Fidaxomicin 200mg PO BID
  - Treat for 10 days
- Prior guidelines used disease severity to guide treatment decisions
  - Studies since then have showed decreased response and high recurrence in metronidazole groups

Fulminant Clostridium Difficile Infection

- Initial treatment of choice- Vancomycin 500mg PO QID
  - Metronidazole 500mg IV q 8 hours
- If ileus present- Vancomycin 500mg in 100mL NS per rectum q 6 hours
  - Metronidazole 500mg IV q 8 hours
- If ileus or toxic megacolon patient should admitted to ICU with surgical consultation
  - Surgery of choice- subtotal colectomy with rectal sparing
  - Diverting loop ileostomy with colonic lavage may lead to improved outcomes
  - Rising WBC (>25,000) or rising lactate level is associated with high mortality and if occurs early surgery indicated

Recurrent Clostridium Difficile Infection

- Prior guidelines state repeat C-dif treatment with same regimen as initial infection
- Now…
- First recurrence treated with one of the following
  - Vancomycin taper/pulse dosing
  - Fidaxomicin 200mg BID x 10 days
  - Vancomycin can be used in a standard 10 day treatment if metronidazole was used initially
- If additional recurrence occurs-
  - Vancomycin taper/pulse dosing
  - Standard Vancomycin followed by rifaximin 400mg for 20 days
  - Fecal transplant

Vancomycin taper/pulse dose

- 125mg QID for 10-14 days then
- 125mg BID for 7 days then
- 125mg daily for 7 days then
- 125mg q2-3 days for 2-8 weeks

- Mechanism- C. Difficile vegetative forms will be kept in check while allowing restoration of normal microbiota

Fecal Microbiota Transplant

- Patient with recurrent have significant disruption of the intestinal microbiome diversity and decreased bacterial population numbers
- Instillation of processed stool collected from a healthy donor into the intestinal tract of patients with recurrent CDI
  - Effective 77-100% depending on route of instillation
  - Studies of route of transmission and long term consequences are ongoing
- The designated stool donor should undergo screening of blood and feces prior to the stool donation
  - Disqualifying factors- antibiotic in prior 3 months, IBD, malignancy, chronic infection, autoimmune disease, immunosuppressive medications
- Typically induction course of 3-4 days of vancomycin prior

Probiotics

- Several have shown promise in preventing CDI recurrence but none have shown reproducible efficacy in clinical trials
- Saccharomyces boulardii
- Lactobacillus

Cholestyramine

- In patients with refractory disease give 4g PO 3-4 times daily
- Works by binding Toxin A/B
- Use in adjunct with antibiotics- Must separate by 3 hours as it will bind
- Can continue for several weeks after antibiotic regimen if needed.

Clostridium difficile

- Following treatment, there is no reason to retest stool as patient may have colonized and would result in unnecessary treatment
- May discontinue contact precautions once diarrhea free for 48 hours
- Antibiotic overuse has led to increase in Clostridium difficile colitis and recurrence.
  - Limiting usage through self monitoring and antibiotic stewardship programs

Summary

- Review your facilities diagnostic studies and understand the S/S of each
- Only test patient's with diarrhea
- Initiate contact precautions once CDI suspected
- First line treatment is now vancomycin
- Prevention is key- contact precautions, hand washing, limit antibiotic usage

Questions…