Clostridioides (prev: clostridium) difficile

July 4, 2019 by Josh Farkas

CONTENTS

- Prevention and C. Diff-o-genic antibiotics (#prevention)
- Presentation & diagnosis (#presentation_&_diagnosis)
- Lab testing (#lab_testing)
- Colonoscopy (#colonoscopy)
- Imaging (#imaging)
- Risk-stratification (#risk-stratification)
- Treatment (#treatment)
  - Non-standard therapies (#other_potential_therapies)
- Epilogue: The future of C. Difficile? (#epilogue_the_future_of_c_difficile?)
- Checklist (#checklist)
- Podcast (#podcast)
- Questions & discussion (#questions_&_discussion)
- Pitfalls (#pitfalls)

#1. avoid/limit antibiotics

- Recent guidelines have pared back the use of prophylactic antibiotics for most indications.
- Emerging evidence suggests that the duration of antibiotic courses may often be reduced.
- Procalcitonin measurement within the appropriate context may help reduce antibiotic exposure.
- Antibiotics shouldn’t be used blindly except under specific circumstances (e.g. septic shock, neutropenic fever).

#2. know which antibiotics cause C. Difficile

https://emcrit.org/ibcc/cdiff/
Slimmings 2014 performed a meta-analysis to determine the odds ratio (OR) of getting C. Difficile following treatment with different antibiotics. This allows antibiotics to be arranged roughly in order of increasing risk. The most problematic antibiotics are generally fluoroquinolones, clindamycin, and advanced-generation cephalosporins (29462280).

- **Tetracyclines** (OR 0.77)
- **Macrolides** (OR 1.14)
- **Aminoglycosides** (OR 1.17)
- **Penicillins** (OR 1.23)
- **G1-cephalosporins** (OR 1.36)
- **Piperacillin-tazobactam** (OR 1.5)
- **Fluoroquinolones** (OR 1.66)
- **Trimethoprim-sulfamethoxazole** (OR 1.78)
- **Carbapenems** (OR 1.84)
- **G4-cephalosporins** (OR 2.14)
- **Clindamycin** (OR 2.86)
- **G3-cephalosporins** (OR 3.2)

A few comments:

- Macrolides and tetracyclines have very low risk, making them good choices for COPD exacerbation (where a broad spectrum antibiotic isn't needed).
- There is a substantial difference between various cephalosporins, so when possible a first-generation cephalosporin is preferred.
- Piperacillin-tazobactam has the lowest C. difficile rate of any broad-spectrum antibiotic. Shortage of piperacillin-tazobactam has been associated with doubling the rate of C. difficile (Alston 2004).

### #3. Excellent hygiene

- One meaning of “first do no harm” is to try to avoid C. difficile transmission.
- C. difficile spores aren't sterilized by ethanol-based hand cleansers. Better approaches include the use of gloves and traditional hand-washing.
- Any clothing that isn't laundered daily can transmit C. difficile spores (e.g. white coats, ties, vests). Ideally, all external clothing in the ICU should be hospital-issued and cleaned daily (e.g. scrubs and anesthesia “warm-up” jackets).
- Hospital-laundered scrubs are cleaner than home-washed scrubs (hospitals clean them industrially at high temperatures).

### #4. Isolation of patients with C. Difficile

- Patients with known or suspected C. Difficile should be placed under contact isolation. Signage should remind staff to wash their hands (rather than using ethanol-based hand cleansers).
- Continuing contact isolation until hospital discharge could help limit the spread of C. difficile (carriage of spores may persist for weeks).

### Presentation & Diagnosis

#### Broad range of severity

- Mild disease: diarrhea only.
- Moderate disease: diarrhea plus colitis, causing fever and pain.
- Severe disease: toxic megacolon, septic shock, peritonitis, multiorgan failure.

#### When to consider testing for C. difficile

1. Any hospitalized patient with new-onset diarrhea (unless there is an obvious cause, such as over-enthusiastic laxative use).
2. Any patient admitted to the hospital for acute diarrhea (C. difficile is now being seen in patients from the community without any recent antibiotic use).
   - Risk factors include inflammatory bowel disease, healthcare exposure, cancer chemotherapy, and other chronic comorbidities (e.g. liver or kidney disease).
3. Patients with clinical/imaging evidence of colitis or toxic megacolon.
(4) Any patient you notice developing a profoundly elevated white blood count that you cannot explain.
   
   C. difficile patients may have markedly elevated white blood counts, which are disproportionate to their degree of clinical illness.

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**lab testing**

*the menu of various lab tests*

**glutamate dehydrogenase antigen**

- Present in all strains of C. difficile (both toxigenic strains & benign, non-toxigenic strains).
- May be used as a screening test (sensitive for clinical infection, but nonspecific).

**PCR for C. difficile toxins A or B**

- More specific than glutamate dehydrogenase (found only in toxigenic strains of C. difficile).
- Not entirely specific for clinical infection (the bacterium may simply be a colonizing organism).

**Enzyme immunoassay (EIA) to detect C. difficile toxin A or B**

- Most specific for clinical disease (bacteria which are actually secreting toxin in the colon).
- Less sensitive (~80%), but >95% specific.
- Toxin breaks down rapidly, so samples should be refrigerated or transported rapidly to the lab.

**the strategy of using different tests**

Every hospital will have a preferred diagnostic strategy for detecting C. difficile. Discuss with your infectious disease colleagues which assay your hospital uses and the best strategy for its application. Some potential algorithms are as follows:

1. Accept only unformed stool for testing (to screen out patients with low pre-test probability). Then use the PCR to test for C. difficile toxin A or B. If positive, assume that the patient has clinical C. difficile and treat as such.
2. Start with glutamate dehydrogenase or PCR as a screening test. If positive, then use an ELISA assay to detect toxins as a confirmatory test.

**potential pitfalls**

- A patient on treatment for C. difficile may have a false-negative toxin assay (due to suppression of bacterial replication).
- After successful treatment for C. difficile, patients may continue to have positive tests (especially the PCR test). For this reason, testing to confirm cure is not recommended.

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**colonoscopy**

*not generally helpful (especially in the critically ill)*

- Diagnosis can usually be secured based on stool analysis with or without CT scanning of the abdomen.
- Colonoscopy of a patient with severe colitis may risk perforation, so this should be avoided if possible.
- Endoscopic visualization (+/- biopsy) may be of benefit in situations with an unusually broad differential diagnosis:
  - Infectious colitis vs. inflammatory bowel disease
  - Possible immune checkpoint-mediator induced colitis
- If performed, the study should probably be limited to an unprepped sigmoidoscopy with minimal insufflation of air into the colon (especially if the CT scan shows involvement of the sigmoid colon).

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**classic finding is pseudomembranes ("pseudomembranous colitis")**

- Neither 100% sensitive nor 100% specific for C. diff.
- Other causes of pseudomembrane formation include inflammatory bowel disease, ischemic colitis, cytomegalovirus (CMV), enterohemorrhagic E. coli O147:H7, or collagenous colitis (30945014).

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**Charles Van Hook**
@LeftHandPulmCC

Repeating to @emcrit and 2 others

Loved Dr. Farkas Sr on the IBCC podcast!! This is the gross specimen of a 70 y.o. female who presented in shock with a surgical abdomen and underwent total colectomy for C diff/toxic megacolon 2 weeks after receiving azithromycin for a URI.
plain film for megacolon

- There should be a low threshold for abdominal X-ray to screen for toxic megacolon (e.g. in patients with significant abdominal tenderness or distension).
  - Dilation > 6 cm is worrisome for the possibility of impending perforation (especially if associated with other markers of severe disease).
  - May be repeated in a serial fashion to follow colonic distension.

CT scan

- Allows for identification of toxic megacolon, as well as other complications (e.g. perforation).
- Better study than abdominal X-ray, but be careful – patients may evolve rapidly. Absence of megacolon at one point in time doesn’t mean this cannot evolve over time.

risk-stratification

Risk-stratification may help determine the appropriate disposition and how aggressive care should be. Unfortunately, there is little solid data on this. The following factors bear consideration:

lab markers of severity

- Marked leukocytosis (e.g. >15,000-20,000 white blood cells/ml).
- Hyperlactatemia
- Elevated creatinine

organ failure

- Acute kidney injury (especially if unresponsive to volume resuscitation, with persistently low urine output).
  - Note: Anuria may be more worrisome than creatinine level.
- Hypotension requiring vasopressor
**local signs of advanced disease**

- Marked colonic distension (frank or threatened toxic megacolon)
- Ileus, distension
- Severe pain, peritonitic abdominal examination

**treatment**

- Patients experiencing septic shock should be resuscitated accordingly.
- If there is a history of extensive diarrhea, these patients may have true hypovolemia and require more fluid than the average septic patient.

**diarrhea & discontinuation of anti-motility agents**

- The major cause of mortality in C. Difficile is ileus and toxic megacolon.
- All anti-motility agents should be discontinued (including avoidance of opioids) (31105766).
- Diarrhea in these patients is a good thing: it removes C. Difficile from the colon (one form of "source control").
- Patients with substantial volumes of diarrhea may require additional IV fluid to compensate for these losses.

**nutrition**

- Diet may be continued in patients with diarrhea and no evidence of ileus or megacolon (e.g. no abdominal distension or colonic dilation on abdominal x-ray).
- In ileus or megacolon, oral intake should be held.

**antibiotics**

- Vancomycin
  - Front-line for all patients with C. difficile.
  - For non-fulminant infection treat with 125 mg PO q6hr; for fulminant infection use 500 mg PO q6hr.

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Jerad Gardner, MD
@JMGardnerMD

Toxic megacolon. HUGE. Due to IBD or C. Diff. Sepsis, death if untreated. #pathology #surgery #medicine #GIPath
- An alternative to vancomycin is fidaxomicin 200 mg BID.
- For fulminant infection (e.g. hypotension, shock, ileus, or megacolon)
  - Vancomycin 500 mg PO q6hr orally or via NG tube
  - IV metronidazole 500 mg q8hr (may have improved performance in context of ileus).
  - Rectal instillation of vancomycin may be considered if ileus (500 mg Q6hr PR in 100 ml of normal saline as a retention enema). This is associated with a potential risk of colonic perforation (30945014). Articles disagree regarding when rectal vancomycin is appropriate; there is no evidence to support this practice.
- Treatment duration generally 10-14 days. May extend course longer in patients who require ongoing antibiotics for another infection.

**pare back antibiotics which aren’t helping (if possible)**
- Ongoing use of antibiotics directed towards other infections may exacerbate C. difficile.
- If patient requires ongoing antibiotic therapy, try to shift antibiotics to agents which disrupt the bowel flora less and promote C. difficile less (see list above).

**surgery**
- Colectomy represents definitive source control.
- Surgery should be involved early for patients admitted to ICU with septic shock due to C. difficile.
- Potential indications for colectomy may include:
  - Toxic megacolon
  - Colonic perforation
  - Peritonitis
  - Deterioration despite medical therapy
  - Lactate >5 mM, WBC >25,000
- Surgical outcomes are best if performed relatively early, prior to the development of end-organ damage.

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**Case of a patient with a history of organ transplant who developed fulminant C. difficile following ciprofloxacin therapy for a urinary tract infection**

(Alterman et al., [https://pdfs.semanticscholar.org/46b1/38fb5d5152571f069529df5e2aa3ad3fdd68.pdf?_ga=2.203036370.277760284.1561752897-72910372.1544537166](https://pdfs.semanticscholar.org/46b1/38fb5d5152571f069529df5e2aa3ad3fdd68.pdf?_ga=2.203036370.277760284.1561752897-72910372.1544537166))
### Tigecycline
- Tigecycline offers various theoretical benefits (29363242, 29713630):
  - a) It has activity against C. Difficile, including suppression of toxin secretion.
  - b) It has activity against enteric pathogens, so it could provide some degree of coverage for bacteria which translocate into the bloodstream.
  - c) Good penetration of bile and intestinal contents.
  - d) Activity against resistant strains of C. difficile.
- Tigecycline is supported by case-series level evidence in the treatment of C. Difficile, with mixed results. A study was attempted but couldn't be completed due to slow recruitment.
- More on tigecycline in the antibiotics chapter [here](https://emcrit.org/ibcc/antibiotics/#tigecycline).

### Bezlotoxumab
- Monoclonal antibody that binds to C. difficile toxin B.
- Evaluated to help prevent recurrent infection.
- Theoretically should be useful in fulminant C. difficile infection. Unfortunately, there isn't data on this currently.
- IV immunoglobulin (IVIG) may be considered if bezlotoxumab is unavailable, but there isn't high-level data on this either.

### Fecal Microbiota Transplantation (FMT)
- Stool transplant is a promising treatment for *outpatients* to prevent recurrent C. difficile.
- The use of stool transplant for *acute, fulminant* infection in the ICU is dubious, for numerous reasons:
  - (a) These patients will generally be on several antibiotics (e.g. metronidazole and vancomycin at a bare minimum). Such antibiotics are likely to destroy transplanted bacteria, negating any benefit from the transplant.
  - (b) Severe C. difficile leads to *ileus (often with toxic megacolon)*, which may make it impossible or dangerous to deliver a stool transplant. Stool delivered via upper endoscopy or oral route is unlikely to traverse into the colon (carrying a risk of stool aspiration). Delivering stool via colonoscopy may increase the risk of colonic dilation and perforation. Enemas may be safer but less effective.

### Epilogue: The Future of C. Difficile?
This is a slightly off-topic, but two developments on the horizon are worth mentioning. These therapies could promise to substantially curtail C. difficile infection.

1. **Stool transplant**: More aggressive use of this therapy following recovery from C. difficile could prevent recurrent episodes. The numerous recurrences that often follow the initial C. difficile infection can over time weaken the patient and eventually precipitate death. Stool transplant could interrupt this process by resetting the colonic microbiome.
2. **Non-toxigenic C. difficile**: Strains of non-toxigenic C. difficile have been developed, which may prevent infection by toxigenic C. difficile. Non-toxigenic C. difficile is perfectly positioned to compete with toxigenic C. difficile strains for its specific niche in the colon (30093897). Non-toxigenic C. difficile spores could conceivably be administered to patients in the ICU as a prophylactic strategy to prevent disease. Unlike stool transplant, non-toxigenic C. difficile carries no risk of introducing other infection.
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Checklist: ICU-severity C. Difficile

- **Sepsis resuscitation**
- **Imaging** (Abdominal X-ray +/- CT scan)
  - Consider serial abdominal X-ray to follow for megacolon, especially if diarrhea stops (ominous sign).
- **Antibiotics**
  - Vancomycin 500 mg PO q6hrs
  - Metronidazole 500 mg IV q8hrs IV
  - Discontinue unnecessary antibiotics (may aggravate tx)
- **Promotion of gut motility** (patients die from ileus & megacolon)
  - D/c anti-motility agents (e.g. loperamide)
  - Avoid opioid analgesia like the plague (e.g. use multimodal non-opioid tx)
  - Encourage ambulation if possible
- **Surgery consultation**
- **Other potential treatments** (e.g. in refractory disease)
  - Tigecycline
  - Bezlotoxumab (if available)

-The Internet Book of Critical Care, by @PulmCrit

podcast


The Podcast Episode

Want to Download the Episode?
[Right Click Here and Choose Save-As](http://traffic.libsyn.com/ibcppodcast/IBCC_Episode_43_Clostridium_Difficile.mp3)

questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/cdiff/).

Consider C. difficile early for any hospitalized patient with new-onset diarrhea, as this may limit spread to other patients.

- Under-utilization of primary prevention strategies to prevent C. difficile in the ICU (e.g. permissive wearing of white coats, alcohol-based hand hygiene, liberal utilization of antibiotics).
- Failure to provide dual antibiotic therapy for fulminant C. difficile (oral vancomycin plus intravenous metronidazole).
- Excessive use of opioids in patients with C. difficile, increasing the risk of toxic megacolon.

**Going further:**

- [C. Difficile & pseudomembranous colitis](https://litfl.com/clostridium-difficile-enterocolitis-and-pseudomembranous-colitis/) (Chris Nickson, LITFL)
- [C. Difficile colitis](http://www.emdocs.net/em3am-clostridium-difficile-colitis/) (EM@3AM, Erica Simon)
- [C. Difficile](https://wikem.org/wiki/Clostridium_dicile) (WikiEM)
- [C. difficile colitis](https://radiopaedia.org/articles/clostridium-difficile-colitis) (Radiopaedia)