Stony Brook Adult Clostridium difficile Management Guidelines

Summary:

Use of the “C Diff Infection (CDI) PowerPlan (Adult)” Required

Patient with clinical findings suggestive of *Clostridium difficile* infection including the following:
- Diarrhea (3+ liquid BM, Bristol stool 7)
- AND
- No laxative use in the past 48 hours

Check *C. difficile* Stool PCR
- Discontinue unnecessary PPI
- Discontinue all unnecessary antibiotics

Recurrent Episode (symptom onset following an episode with positive testing within the previous 8 weeks)

Initial Episode

Fulminant Disease (CDI with hypotension, shock, ileus, or megacolon)

Vancomycin Taper and Pulse Therapy (see below)
- Consultation with ID and/or GI recommended

Vancomycin 125mg po q6h x 10 days

Vancomycin 500mg po q6h
- Metronidazole 500mg IV q8h
- [if ileus] Vancomycin retention enema
- Consultation with ID and/or GI recommended
- Consultation with General Surgery if toxic megacolon

Recommend Vancomycin taper regimen:
- Vancomycin 125mg po q6h x 14 days
- Vancomycin 125mg po q12h x 7 days
- Vancomycin 125mg po daily x 7 days
- Vancomycin 125mg po q48h x 4 doses
- Vancomycin 125mg po q72h x 5 doses

Use of fidaxomycin in the management of CDI requires consultation with either Infectious Diseases or Gastroenterology as well as approval from the Antimicrobial Stewardship Program.

*Updated February 28, 2018.*
Discussion:

*Clostridium difficile* infection (CDI) is the most commonly recognized cause of infectious diarrhea in healthcare settings and one of the most common causes of nosocomial infections. The estimated number of incident CDI cases in the United States was 453,000, of which 293,300 (64.7%) were considered to be healthcare-associated. The burden of disease is high in both the hospital setting as well as in long term care facilities. The severity of CDI has been reported to have increased with the emergence of the PCR ribotype NAP1/BI/027 epidemic strain in the 2000s. Recurrent disease is a challenge in the management of CDI with 10-30% of patients developing at least one recurrence, and the risk of recurrence increasing with successive episodes. Current evidence suggests an increasing incidence of CDI in the community, even in healthy persons at low risk. Specific patient populations at increased risk for initial and recurrent disease include those with inflammatory bowel disease (especially ulcerative colitis), solid organ transplants, and hematopoietic stem cell transplants.

Case Definitions

Case definitions for CDI requires that there is (1) the presence of diarrhea or evidence of megacolon or severe ileus and (2) either a positive laboratory diagnostic test result or evidence of pseudomembranes demonstrated by endoscopy or histology. Case defined are further as follows:

- An incident case is defined as a new primary episode of symptom onset (i.e. no episode of symptom onset with positive result within the previous 8 weeks) and positive assay result.
- A recurrent case is defined as an episode of symptom onset and positive assay result and an episode of symptoms with positive result within the previous 8 weeks.
- Fulminant disease is defined

For institutional surveillance, the following definitions are used:

- Healthcare facility-onset (HO-CDI) cases are defined as a laboratory identified event collected >3 days after admission to the facility. HO-CDI cases are reported to the CDC’s National Healthcare Safety Network (NHSN).
- Community-onset, healthcare facility associated (CO-HCFA) cases are defined as CDI occurring within 28 days after discharge from a healthcare facility.

Epidemiology

The route of transmission is via person-to-person contact, spread through the fecal-oral route, or direct exposure to the contaminated environment with *Clostridium difficile* spores. This can be on the hands of healthcare personnel who are transiently contaminated with *C. difficile* spores. Objects in the patient’s room such as the bed, table have been shown to harbor spores. Spores have been identified on numerous objects within a hospital room, including the floor, bedrails, bedsheets, call buttons, and blood pressure cuffs. *C. difficile* spores can be long lived, persisting for months, and are resistant to killing by alcohol based cleansers. Evidence also suggests that simply occupying a room where a prior
occupant had CDI is a significant risk factor for CDI acquisition.\(^5\) The high potential for transmission of spores highlights the importance of strict hygiene, handwashing, and environmental cleaning.

Several risk factors for disease have been identified in various studies. **The most important modifiable risk factor for the development of CDI is exposure to antibiotic agents.** Virtually all antibiotics have been associated with CDI, but the higher risk is associated with the use of third/fourth generation cephalosporins, quinolones, carbapenems, and clindamycin. This increased risk is attributed to the disruption of intestinal microbiota, and the effect can be long-lasting. The risk of CDI increases both during therapy and in the 3-month period following the cessation of therapy, with the highest risk in the first month after antibiotic exposure.\(^6\)

Advanced age (>65) is one of the most important risk factors for CDI, potentially as a surrogate for severity of illness and presence of comorbidities. Duration of hospitalization is another major risk factor (likely owing to increased exposure to the organism, likelihood of receiving antibiotics, and severity of underlying illness). Inflammatory bowel disease, especially ulcerative colitis, and the receipt of either a solid organ transplant or a hematopoietic stem cell transplant are also recognized risk factors.

Links have been made between gastric acid suppressing medications, particularly proton pump inhibitors (PPI), though this remains controversial as this association may be confounded by the underlying severity of illness, non-CDI diarrhea, and the duration of hospital stay.\(^4\)

Adding to the challenge of diagnosing CDI is the recognition of asymptomatic colonization of *C. difficile*. It is well recognized that there are high rates of colonization in infants <12 months of age.\(^7\) While colonization rates decrease with increasing age, the prevalence of asymptomatic colonization is still elevated in the second year of life. Studies have found that the asymptomatic carriage of *C. difficile* among hospitalized adult patients can range from 3-26% and from 5-7% among elderly persons in long term care facilities.

### Diagnosis and Laboratory Testing

Differentiating a true CDI from asymptomatic carriage can be challenging. While a variety of options are available for laboratory testing, there is no consensus on the optimal testing strategy. In alignment with the 2018 IDSA guidelines, Stony Brook Medicine uses NAAT/PCR testing with screening for appropriate stool samples. Prior to considering *C. difficile* testing, the patient should have the following:

1. At least three documented episodes of diarrhea (defined as Bristol Stool Chart Type 7) unless there is ileus
2. No laxative use within the past 24 hours

The PCR has high sensitivity (>90%) and a negative predictive value of >95%. The positive predictive value has been estimated as being less than 50%, likely owing to the presence of asymptomatic carriage.\(^4\) As such, testing for *C. difficile* should only be done in the setting of clinical symptoms that are likely due to CDI.

Repeat testing during the same diarrheal episode should not be done within 7 days given the high negative predictive value of the PCR test.
None of the available *C. difficile* laboratory tests can be used as a test of cure. Abnormal results can persist for weeks after clinical resolution.

Recurrence of symptoms following successful treatment and clinical resolution should be assessed by repeat testing given the high incidence of recurrent CDI.

**Management**

A recommended treatment algorithm is displayed on page 1.

As the use of any antibiotic and prolonged antibiotic exposure have been associated with CDI, all unnecessary antibiotics should be discontinued.

While the role of acid suppressing medications is controversial, eliminating unnecessary medications is an overall good clinical practice. **Unnecessary PPI and H2 blockers should be discontinued. Opiate use should be reviewed and the use should be limited if possible.**

**Initial Episode of CDI**

In contrast to earlier guidelines, **metronidazole is not a first line therapy for CDI.** Comparing oral vancomycin compared to oral metronidazole, recent clinical studies have demonstrated superiority of vancomycin for clinical response rates and for the resolution of diarrhea at the end of therapy without CDI recurrence. Metronidazole can be considered in the situation of an initial episode of non-severe CDI in which other agents are contraindicated or not available.

**Oral vancomycin is the recommended first therapy for the initial episode of CDI.** A dose of 125mg every 6 hours is recommended for 10 days. **Higher doses (i.e. 250mg) have not been shown to have additional clinical benefit.**

Findings of fever (>38.5 °C), WBC count >15 x 10⁹/L, and creatinine >1.5 mg/dL have been associated with severe CDI and have been correlated with treatment failure. Consultation with Infectious Diseases or Gastroenterology is recommended for severe CDI.

**Recurrent Episode of CDI**

For recurrent CDI, **oral vancomycin as a tapered and pulsed regimen over at least 6 weeks is recommended.** Prolonged therapy with oral vancomycin may be beneficial as this may keep the vegetative forms of *C. difficile* in check while the microbiota is reconstituted. A suggested tapering regimen is shown on page 1, though variations have been used successfully by clinicians. Consultation with Infectious Diseases or Gastroenterology is recommended for recurrent CDI.

Metronidazole alone or in combination has not been shown to have a benefit with CDI as response rates are lower than that for oral vancomycin. Prolonged therapy with metronidazole also has the potential
for cumulative neurotoxicity. The role of probiotics in the management of recurrent episodes of CDI is unclear as reproducible efficacy has not been demonstrated in clinical trials.

**Fulminant CDI**

Fulminant disease is characterized by CDI with associated hypotension or shock, ileus, or megacolon is a potentially life threatening condition. Despite the limited available data, high dose oral vancomycin (500mg every 6 hours) and intravenous metronidazole (500mg every 8 hours) is recommended.

For patients with ileus attributed to CDI, a vancomycin retention enema is also recommended.

Consultation with Infectious Diseases or Gastroenterology is strongly recommended in cases of fulminant CDI.

Subtotal colectomy can be lifesaving in patients with megacolon, colonic perforation, acute abdomen, or septic shock due to CDI. In those patients with findings of megacolon, a rising WBC (>25,000), or a rising lactate, General Surgery consultation is strongly recommended.

**Alternate and Adjunctive Therapies**

Fidaxomicin is another approved agent that can be considered for the management of initial and recurrent episodes of CDI. In studies measuring the resolution of diarrhea as a clinical end point, fidaxomicin was found to be noninferior to oral vancomycin. The benefit of fidaxomicin was reduced in cases involving the BI strain. Consultation with Infectious Diseases or Gastroenterology is required if fidaxomicin is being considered.

While adjunctive therapies such as nitazoxanide, rifaximin, and tigecycline may have a benefit, high quality evidence is lacking to recommend their routine use.

Fecal microbiota transplantation (FMT) has emerged as a treatment option for recurrent CDI cases. Consultation with Gastroenterology for FMT should be considered after at least two recurrences.

Bezlotoxumab is a recently approved monoclonal antibody against toxin B produced by C. difficile that has been approved as an adjunctive therapy for those persons who are receiving antibiotic therapy for CDI and who are at high risk for recurrence. The role of bezlotoxumab in a management algorithm is not clear at this time; consultation with Infectious Diseases is required for use in the hospital.

**Preventative Strategies**

For clinicians, the best way to prevent CDI involves the following:

1. Limiting a patient’s exposure to unnecessary antibiotics
2. Hand hygiene with soap and water
3. Use of personal protective devices (gown and gloves) when caring for a patient with CDI

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Contact precautions should be placed on all patients with confirmed CDI or suspected disease (awaiting test results) as recommended by the Hospital Infection Control guidelines. Patients and visitors should be encouraged to practice good hygiene and to wash their hands with soap and water.

Probiotic therapy (*Lactobacillus* spp., *Acidophilus* spp.) can be considered in patients in the primary prevention of CDI. Recent meta-analyses suggest a potential benefit with probiotic use. As probiotic use has been associated with infections in the hospital, clinicians should be cautious in their use particularly in immunosuppressed and severely debilitated patients.

**References**