Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the IDSA and SHEA

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Co-Medical Director of Antimicrobial Stewardship
Baptist Health
Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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A panel of experts was convened by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to update the 2010 clinical practice guideline on Clostridium difficile infection (CDI) in adults. The update, which has incorporated recommendations for children (following the adult recommendations for epidemiology, diagnosis, and treatment), includes significant changes in the management of this infection and reflects the evolving controversy over best methods for diagnosis. Clostridium difficile remains the most important cause of healthcare-associated diarrhea and has become the most commonly identified cause of healthcare-associated infection in adults in the United States. Moreover, C. difficile has established itself as an important community pathogen. Although the prevalence of the epidemic and virulent ribotype 027 strain has declined markedly along with overall CDI rates in parts of Europe, it remains one of the most commonly identified strains in the United States where it causes a sizable minority of CDIs, especially healthcare-associated CDIs. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, infection prevention, and environmental management.

Keywords. Clostridium difficile; Clostridioides difficile; Guidelines; CDI; CDAD.
About Clostridium difficile
About *Clostridium difficile*

1. Normal microbiota gets disturbed (by antibiotics, or even poor diet)
2. Gut is exposed to *Clostridium difficile* spores (which can survive stomach acid)
3. Without “good bacteria” to keep it in check, C diff grows and releases Toxins (Toxin-A and Toxin-B)
4. Those toxins damage the gut, cause inflammation, diarrhea, and pseudomembranes

Not all *Clostridium difficile* have the gene to make toxins, and even the ones that have the gene aren’t necessarily making the toxin all the time.
Epidemiology

• How are CDI cases best defined?
  • 1) the presence of diarrhea (or ileus, or megacolon) **AND**
  • 2) a positive lab diagnostic test or pseudomembranes demonstrated on endoscopy or histology

• An **incident** case is \{symptoms + lab test\} with no episodes in the previous 8 weeks

• A **recurrent** case is defined as \{symptoms + lab test\} when there has been another episode of \{symptoms + lab test\} in the last 8 weeks
Epidemiology Definitions

- CDI = *Clostridium difficile* Infection
- HO = Healthcare facility-onset
- CO-HCFA = Community-onset healthcare facility-associated
- CA = Community-associated
- NHSN = National Healthcare Safety Network
- LabID-CDI = Laboratory Identified *C diff* infection
- SIR = Standardized infection ratio
- HAI = Healthcare associated infection
Epidemiology

• **HO-CDI** cases are defined as LabID events collected >3 days after admission (on or after day 4)

• **CO-HCFA CDI** cases are defined as \{symptoms + lab test\} that occur within 28 days after discharge from a healthcare facility

• **CA-CDI** cases are defined as \{symptoms + lab test\} that are not associated with admission/discharge in the last 4 weeks

**HO**: Healthcare facility onset  
**CO-HCFA**: Community-onset Healthcare facility associated  
**CA**: Community associated
Epidemiology

From 2010 guidelines
Prevalence, Incidence, Morbidity, Mortality

• 2010 rate of LabID-CDI was 7.4 per 10,000 patient-days
• In 2011, there were an estimated 453,000 cases (147/100,000person)
• Of those, 64.7% were considered healthcare associated:
  • 37% were hospital onset
  • 36% had their onset in long-term care facilities
  • 28% were CO-HCFA (i.e. with admission in the prior 12 weeks)
• Of the 35.3% that were considered community-associated:
  • 82% were associated with outpatient healthcare exposure
• Therefore, 94% of all CDI cases had a recent healthcare exposure
Prevalence, Incidence, Morbidity, Mortality

- *C difficile* is the **most common causative pathogen** in HAIs
- After a first episode, 10-30% of patients develop recurrence
- Endemic periods: CDI-attributable mortality is 4.5% - 5.7%
- Epidemic periods: CDI-attributable mortality is 6.9% - 16.7%
- CDI attributable **cost** is $3427 - $9960 per episode
Increased Risk

- Advanced age
- Antibiotics
- PPIs
- Cancer
- Inflammatory bowel disease
- Solid organ transplant
- CKD and ESRD
- Hematopoietic stem cell transplant (9x greater risk than other hospitalized patients)
Colonization

• Asymptomatic colonization in adult inpatients is 3%-26%
• (in the general population without healthcare exposure, it is <2%)
• Colonization ➔ Infection is probably 3-7 days
• Prolonged colonization increases risk for infection, but that risk of progression decreases over time (that is, if you’ve been colonized for 2 weeks, your risk of progression is higher than if you’ve been colonized for 6 weeks).
• Colonization with a nontoxigenic strain confers protection against CDI
Diagnosis

• Who to test:
  • Patients with **unexplained new-onset diarrhea**, with **≥3 unformed stools in 24 hours**

• Examples of “explained diarrhea”
  • Inflammatory bowel disease
  • Enteral tube feeding
  • Intensive chemotherapy for cancer
  • Laxatives

“However, some of these conditions and interventions associated with diarrhea in their own right, such as IBD and enteral tube feeding, have been shown to have increased risk of CDI when compared with a matched cohort. So, in practice it is difficult to exclude the possibility of CDI on clinical grounds alone”
Improving laboratory test relevance

• Do not routinely test stool within 48 hours after a laxative

• Laboratory can reject specimens that are not liquid

• Include criteria for testing (# of unformed stools in 24 hours, or include other clinical risk factors/signs/symptoms of CDI)
About *C diff* testing

Table 3. Summary of Available Tests for *Clostridium difficile* Infection, in Decreasing Order of Sensitivity

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*Must be combined with a toxin test.*
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Diagnostic testing

5. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected (B-II).

6. Testing of stool from asymptomatic patients is not clinically useful, including use as a test of cure. It is not recommended, except for epidemiological studies (B-III).

7. Stool culture is the most sensitive test and is essential for epidemiological studies (A-II).

8. Although stool culture is not clinically practical because of its slow turnaround time, the sensitivity and specificity of stool culture followed by identification of a toxigenic isolate (i.e., toxigenic culture), as performed by an experienced laboratory, provides the standard against which other clinical test results should be compared (B-III).

9. Enzyme immunoassay (EIA) testing for *C. difficile* toxin A and B is rapid but is less sensitive than the cell cytotoxin assay, and it is thus a suboptimal alternative approach for diagnosis (B-II).

10. Toxin testing is most important clinically, but is hampered by its lack of sensitivity. One potential strategy to overcome this problem is a 2-step method that uses EIA detection of glutamate dehydrogenase (GDH) as initial screening and then uses the cell cytotoxicity assay or toxigenic culture as the confirmatory test for GDH-positive stool specimens only. Results appear to differ based on the GDH kit used; therefore, until more data are available on the sensitivity of GDH testing, this approach remains an interim recommendation. (B-II)

11. Polymerase chain reaction (PCR) testing appears to be rapid, sensitive, and specific and may ultimately address testing concerns. More data on utility are necessary before this methodology can be recommended for routine testing. (B-II)

12. Repeat testing during the same episode of diarrhea is of limited value and should be discouraged (B-II).

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**2017 Update**

- Only test unformed stools
- Do not test asymptomatic patients, and do not test for cure
- (New guidelines mention stool culture deep in the “summary of evidence”, not in the recommendations)
- (New guidelines end with NAAT testing rather than cell cytotoxicity assay or toxigenic culture)
- PCR takes a much more prominent role
- Repeat testing is still discouraged
Diagnostic testing

• VII. What is the **best-performing method** (ie, in use positive and negative predictive value) for detecting patients at increased risk for clinically significant C. difficile infection in commonly submitted stool specimens?

• Use a stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission
VIII. What is the **most sensitive** method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms? Recommendation

- Use a NAAT alone or a multistep algorithm for testing (ie, GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone **when there are pre-agreed institutional criteria for patient stool submission**
Figure 2. *Clostridium difficile* infection laboratory test recommendations based on preagreed institutional criteria for patient stool submission. Abbreviations: CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test.
When to test for *C diff*...
If yes...

BestPractice Advisory - Pate, Disco

⚠️ Patient has received a laxative or stool softener in the past 3 days. It is NOT recommended to order C-Diff testing.

No current facility-administered medications for this encounter.

**Remove** the following orders?

 carta C Diff by Nucleic Acid Amp. NAAT

Routine, ONCE First occurrence Today at 0710 Has the patient had any laxatives or stool softeners in the last 3 days? Yes Are there 3 watery stools documented in the last 24 hours? Yes

Remove Keep

[✓ Accept] [Cancel]
If no (but you’re fibbing)...

Patient has received a laxative or stool softener in the past 3 days. It is NOT recommended to order C-Diff testing.

Remove the following orders?

Remove

Keep

C Diff by Nucleic Acid Amp. NAAT
Routine, ONCE First occurrence Today at 1026
When to test for *C diff*
If they’ve had fewer than 3 watery stools, it’s not time to test yet...

BestPractice Advisory - Observation, Testtwo

Patient has not had 3 watery stools in the past 24 hours. It is NOT recommended to order C-Diff testing.

Remove the following orders?

- C Diff by Nucleic Acid Amp. NAAT

Routine, ONCE First occurrence Today at 10:14 Has the patient had any laxatives or stool softeners in the last 3 days? No Are there 3 watery stools documented in the last 24 hours? No

[ ] Accept  [ ] Cancel
About repeat testing...

• If using 2-stage algorithm or stand-alone NAAT, a single tests has a negative predictive value of >99%

• **DO NOT REPEAT TESTING WITHIN 7 DAYS**

• Testing for recurrence (following successful treatment and diarrhea) should include **toxin detection** (since PCR can remain positive for a long time after CDI)

• Empiric treatment for recurrence is discouraged (and may be harmful to microbiome restoration)
But I agree, real *C diff* is real bad
Infection Control

• Private rooms and dedicated toilets
  • Prioritize private rooms for patients with incontinence
• Gown and gloves
• Isolate when CDI is suspected “if test results cannot be obtained on the same day”
• Continue isolation for at least 48 hours after diarrhea has resolved
  • Keep it going until discharge if CDI rates remain high
  • C diff is suppressed to undetectable levels in stool samples by the time diarrhea resolves, in most patients, but skin/environmental contamination remains high
Routes of transmission

- Hands of healthcare personnel
- Environmental contamination
- High-risk fomites (electronic rectal thermometers, bedpans, commodes)
- Asymptomatically colonized patients
- For most cases, the exact route of transmission is never determined
Infection control - Hand hygiene

• “In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand hygiene product”

• In CDI outbreaks or hyperendemic settings, use soap and water preferentially over alcohol-based products

• If there is direct contact with feces, wash with soap and water.
Infection control

- “Encourage patients to wash hands and shower to reduce the burden of spores on the skin”
- Use disposable patient equipment when possible, and ensure that reusable equipment is cleaned and disinfected with sporicidal products (that are equipment compatible)
- “Terminal room cleaning with sporicidal agent should be considered in conjunction with other measure to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room”
  - Data on *automated* disinfection are too limited to make a recommendation for now
Infection control

- Daily sporicidal disinfection “should be considered” during outbreaks

- There is no recommendation to screen/isolate asymptomatic patients
Antimicrobial Stewardship

### Risk factors for C. difficile colonization
- Previous hospitalization
- Exposure to antibiotics
- Chemotherapy treatment
- Corticosteroid use
- Dialysis/renal disease

### Factors that protect against progression to symptomatic CDI
- Increased levels of IgG and IgA
- Intact indigenous microbiome
- Colonization by less virulent C. difficile strain

### Risk factors for symptomatic CDI
- Increased age
- Exposure and duration of antibiotics
- Presence of nasogastric tube
- Severe underlying disease
- Prolonged hospital admission
- Exposure to drugs that reduce stomach pH

Healthy intestinal epithelial cells with intact microbiome in an individual with asymptomatic C. difficile colonization

**Legend**
- *Clostridium difficile* cell
- Normal colonic flora
- *Clostridium difficile* spore
- Toxin A
- Toxin B

Damaged intestinal epithelial cells in an individual with symptomatic CDI
Antimicrobial Stewardship

• Minimize the frequency and duration of high-risk antibiotic therapy, and the number of agents prescribed

• Implement an antibiotic stewardship program

• Antibiotics to be targeted should be based on local epidemiology and strains of C diff in the community.

• Restrictions of fluouroquinolones, clindamycin, and cephalosporin (except for surgical antibiotic prophylaxis) should be considered
Receipt of antibiotics in hospitalized patients and risk for *Clostridium difficile* infection in subsequent patients who occupy the same bed

**Original Investigation | LESS IS MORE**

**Hospital Ward Antibiotic Prescribing and the Risks of *Clostridium difficile* Infection**

Kevin Brown, PhD; Kim Valenta, PhD; David Fisman, MD, MSc; Andrew Simor, MD; Nick Daneman, MD, MSc
Probiotics

• “There is insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials”
Treatment

Laughter is the best medicine... except for treating diarrhea.
<table>
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<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
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<tr>
<td>Initial episode, mild or moderate</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or lower and a serum creatinine level less than 1.5 times the premorbid level</td>
<td>Metronidazole, 500 mg 3 times per day by mouth for 10–14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode, severe&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level</td>
<td>Vancomycin, 125 mg 4 times per day by mouth for 10–14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>Same as for initial episode</td>
<td>A-II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>...</td>
<td>Vancomycin in a tapered and/or pulsed regimen</td>
<td>B-III</td>
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<sup>1</sup> The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.
# New guidelines

## Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

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| **Initial episode, non-severe** | Leukocytosis with a white blood cell count of ≤15,000 cells/mL and a serum creatinine level <1.5 mg/dL | • VAN 125 mg given 4 times daily for 10 days, OR  
• FDX 200 mg given twice daily for 10 days  
• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days | Strong/High  
Strong/High  
Week/High |
| **Initial episode, severe** | Leukocytosis with a white blood cell count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL | • VAN, 125 mg 4 times per day by mouth for 10 days, OR  
• FDX 200 mg given twice daily for 10 days | Strong/High  
Strong/High |
| **Initial episode, fulminant** | Hypotension or shock, ileus, megacolon | • VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus is severe, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present. | Strong/Moderate (oral VAN);  
Weak/Low (rectal VAN);  
Strong/Moderate (intravenous metronidazole) |
| **First recurrence** | ... | • VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR  
• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR  
• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode | Weak/Low  
Weak/Low  
Week/Moderate |
| **Second or subsequent recurrence** | ... | • VAN in a tapered and pulsed regimen, OR  
• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR  
• FDX 200 mg given twice daily for 10 days, OR  
• Fecal microbiota transplantation* | Weak/Low  
Weak/Low  
Strong/Moderate |

Abbreviations: FDX, fidaxomycin; VAN, vancomycin.

*All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

*The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

*The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.
Initial episode

• Initial episode, non-severe
  • Vancomycin 125mg 4x/d for 10 days
  • Fidaxomycin 200mg BID x 10 days
  • If those are unavailable, metronidazole 500mg TID x 10d

• Initial episode, severe
  • Vancomycin 125mg 4x/d for 10 days
  • Fidaxomycin 200mg BID x 10 days

• Initial episode, fulminant
  • Vancomycin 500mg 4x/d, plus rectal instillation, plus IV metronidazole
Fulminant disease

- PO Vancomycin *500mg* 4x/d + IV metronidazole 500mg Q8h
- If ileus is present, vancomycin can be administered PR (500mg/100mL q6h as a retention enema)

- “it may be appropriate to monitor trough serum concentration to rule out drug accumulation” when high doses are used
Recurrent CDI

- First recurrence: tapered/pulsed Vancomycin, not another 10-day course

  OR

- Treat a first recurrence with 10-day fidaxomicin

  OR

- If you (wrongly) used flagyl the first time around, try 10 days of PO Vanc
Multiple recurrences

- PO Vanc tapered + pulsed (weak, low quality)
- PO Vancomycin followed by PO Rifaximin (weak, low quality)
- PO Fidaxomicin (weak, low quality)
- Fecal microbiota transplantation (strong, moderate quality)
Take-Home Message

• Prevent C diff by making better antibiotic choices to begin with
• Prevent spread of C diff with excellent Infection Control adherence
• Our test is overly sensitive, so we need to be pickier about when we use it (not for patients on laxatives, or with less than 3 stools in 24h)
• First line treatment has changed (PO Flagyl is no longer recommended)
Questions?

LOVE IS IN THE AIR...

...NOPE! THAT'S C.DIFF...