Updated *Clostridium difficile* Treatment Guidelines

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Disclosures

- Nothing to disclose

Learning Objectives

- Indicate the severity of *clostridium difficile* infection based on clinical features
- Identify the medication and dosing regimens *for clostridium difficile* infection treatment
- Summarize the trials that led to the changes in the IDSA/SHEA guideline recommendations

Clostridioides difficile

- Gram-positive, spore-forming, toxic producing bacterium
- Opportunistic pathogen
- Two major toxins
  - TcdA
  - TcdB

Clinical Pharmacist. February 2017, Vol 9, No 2, online

McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.
Di Bella, S., et al. *Toxins*, *8*(5), 134. doi.org/10.3390/toxins8050134

Clostridioides difficile infection (CDI)

- Suspect in patients with acute diarrhea (3 loose stools in 24 hours)
  - Confirmatory diagnostic evaluation
- Repeat testing
- Pediatric testing
- Transmission is person-to-person, or environmental
- Incubation time
- Annual impact in US:
  - ~ 500,000 cases
  - 15,000-30,000 deaths
  - $4.8 billion

McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.
Di Bella, S., et al. *Toxins*, *8*(5), 134. doi.org/10.3390/toxins8050134

CDI Risk Factors

Acquiring Disease
- Advanced age
- Duration of hospitalization
- Exposure to antibiotic agents
  - 3rd/4th generation cephalosporins
  - Fluoroquinolones (FQs)
  - Carbapenems
  - Clindamycin
  - Highest risk during and in first month after exposure
- Chemotherapy
- Gastrointestinal surgery
- Manipulation of GI tract

Recurrence
- Advanced age
- Antibiotics during follow-up
- Proton Pump Inhibitors
- Strain type
- Previous exposure to FQs

Mortality
- Advanced age
- Comorbidities
- Hypoalbuminemia
- Leukocytosis
- Acute renal failure
- Infection with ribotype 027

McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

IDSA/SHEA Guidelines for CDI

- Updated in 2017 and published in 2018
- Key differences compared to 2010 guidelines
  - Treatment duration 10 days
    - 14 days only if patient not improving
  - Vancomycin and fidaxomicin are first line for initial episodes
    - non-severe and severe
  - Metronidazole is an alternative in non-severe
  - Pediatric antibiotic therapy recommendations
  - Severity changes

McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.
Cohen SH, et al. Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.

Severity of CDI

Clinical Definition	Supportive Clinical Data
Non-severe	Leukocytosis with a WBC ≤15000 cells/mL and SCr < 1.5 mg/dL
Severe	Leukocytosis with a WBC ≥15000 cells/mL and/or SCr > 1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon
Recurrence	Resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms 2-8 weeks after treatment

McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Assessment Question #1

BD is a 75 year old male complaining of severe diarrhea; having approximately 6 loose stools in the last 24 hours. He is afebrile, BP 142/85, HR 72, RR 16. His laboratory data includes WBC 14000 cells/mL, albumin 2.8 g/dL, BUN 45 mg/dL, SCr 1.6 mg/dL. He was seen in the ED 9 days ago and started on ciprofloxacin for a suspected UTI. He tests positive for CDI. Based on the new IDSA/SHEA Clinical Practice Guidelines for CDI, which one of the following best describes the level of severity of BD's CDI?

A. Initial episode, non- severe
B. Initial episode severe
C. Initial episode, fulminant
D. First recurrence

Recommendations for Treatment of CDI in Adults- Initial episode

Clinical Definition	Recommended Treatment
Initial episode, non-severe	• Vancomycin 125 mg QID x 10 days • Fidaxomicin 200 mg BID x 10 days • Alternative: metronidazole 500 mg TID x 10 days
Initial episode, severe	• Vancomycin 125 mg QID x 10 days • Fidaxomicin 200 mg BID x 10 days
Initial episode, fulminant	• Vancomycin 500 mg QID PO or NG • If ileus, consider adding rectal vancomycin • IV metronidazole 500 mg TID + oral/rectal vancomycin, particularly if ileus present

Adapted from Table 1: McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Recommendations for Treatment of CDI in Adults- Recurrence

Clinical Definition	Recommended Treatment
First recurrence	• Vancomycin 125 mg QID x 10 days if metronidazole used for initial episode • Tapered/pulsed vancomycin regimen if standard regimen was used for initial episode • Fidaxomicin 200 mg BID x 10 days if vancomycin used for initial episode
Second or subsequent recurrence	• Tapered/pulsed vancomycin regimen • Vancomycin 125 mg QID x 10 days followed by rifaximin 400 mg TID x 20 days • Fidaxomicin 200 mg twice daily x 10 days • Fecal microbiota transplantation

Adapted from Table 1: McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Recommendations for Treatment of CDI in Pediatrics- Initial episode

Clinical Definition	Recommended Treatment	Maximum Dose
Initial episode, non-severe	Vancomycin 10 mg/kg/dose QID (PO)	125 mg QID
	Metronidazole 7.5 mg/kg/dose TID/QID (PO) x 10 days	500 mg TID/QID
Initial episode, severe/ fulminant	Vancomycin 10 mg/kg/dose QID (PO/PR) x 10 days	500 mg QID
	+/- Metronidazole 10 mg/kg/dose TID (IV) x 10 days	500 mg TID

Adapted from Table 1: McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Recommendations for Treatment of CDI in Pediatrics- Recurrence

Clinical Definition	Recommended Treatment	Maximum Dose
First recurrence, non-severe	Metronidazole 7.5 mg/kg/dose TID/QID x 10 days	500 mg TID/QID
	Vancomycin 10 mg/kg/dose QID (PO)	125 mg QID
Second or subsequent recurrence	Vancomycin in a tapered and pulsed regimen	500 mg QID
	Vancomycin 10 mg/kg/dose QID x 10 days followed by rifaximin 400 mg TID x 20 days	500 mg TID
	Fecal microbiota transplantation	

Adapted from Table 1: McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Vancomycin Taper/Pulsed Recommendations

- Adults
  - Vancomycin 125 mg QID x 10-14 days, then BID x 7 days, then daily x 7 days, then every 2-3 days for 2-8 weeks
- Pediatrics
  - Vancomycin 10 mg/kg with max of 125 mg QID x 10-14 days, then 10 mg/kg with max of 125mg BID x 7days, then 10 mg/kg with max of 125 mg daily x 7 days, then 10 mg/kg with max 125 mg every 2-3 days for 2-8 weeks

Adapted from Table 1: McDonald LC, et al. Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Assessment Question #2

Which of the following regimens would you recommend for BD given his diagnosis of CDI?

A. Vancomycin 125 mg PO four times daily x 10 days
B. Fidaxomicin 200 mg PO twice daily x 14 days
C. Vancomycin 125 mg PO twice daily x 10 days
D. Metronidazole 500 mg PO three times daily x 10 days

Fidaxomicin versus vancomycin for *Clostridium difficile* infection

Fidaxomicin versus vancomycin for *Clostridium difficile* infection

Design
Phase 3, prospective, multicenter double-blind, randomized, parallel-group

Primary Endpoint
Clinical cure

Secondary Endpoints
Recurrence
Global cure

Inclusion Criteria
≥16 years old; acute, toxin +(A or B) CDI

Statistical Analyses
Modified intent-to-treat (mITT) and per-protocol (PP)

Methods
Stratified first or second episode and then randomized into treatment arms: fidaxomicin 200 mg q12 h x 10 days, OR oral vancomycin 125 mg q6 h x 10 days

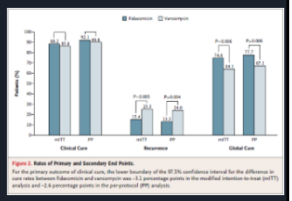
Demographics and Baseline Characteristics
No statistical difference between groups in any measured characteristic

Louie TJ, et al. N Engl J Med. 2011 Feb 3;364(5):422-31. doi: 10.1056/NEJMoa0910812.

Fidaxomicin versus vancomycin for *Clostridium difficile* infection

Results

- Non-inferior to vancomycin for clinical cure
- Significant reduction in recurrence
- Significant increase in global cure
- Subgroup analyses showed no differences for clinical cure rates
- AEs: primarily GI symptoms for fidaxomicin
- MIC ≤ 0.25 mcg/mL for 90% for fidaxomicin vs 2.0 mcg/mL for vancomycin



Louie TJ, et al. N Engl J Med. 2011 Feb 3;364(5):422-31. doi: 10.1056/NEJMoa0910812.

Fidaxomicin versus vancomycin for *Clostridium difficile* infection

Conclusions

- Fidaxomicin was non-inferior to vancomycin for clinical cure rates
- Fidaxomicin had a significantly lower rate of recurrence in the 4 weeks after completion
- Fidaxomicin had a significantly higher rate of global cure
- Narrow spectrum and minimum side effect on gut flora
- Fidaxomicin is bactericidal vs vancomycin is bacteriostatic for *c. difficile*
- Fidaxomicin has a prolonged post-antibiotic effect against *c. difficile*

Louie TJ, et al. N Engl J Med. 2011 Feb 3;364(5):422-31. doi: 10.1056/NEJMoa0910812.

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Design
Multicentre, double-blind, randomised, non-inferiority trial

Inclusion Criteria
≥16 years old; acute, toxin +(A or B) CDI

Methods
1:1 randomization to either:
fidaxomicin 200 mg q12 h x 10 days, OR
oral vancomycin 125 mg q6 h x 10 days

Primary Endpoint
Clinical cure

Secondary Endpoints
Recurrence
Sustained Response

Statistical Analyses
Modified intent-to-treat (mITT) and per-protocol (PP)

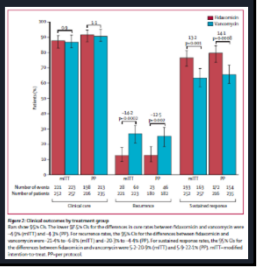
Demographics and Baseline Characteristics
No statistical difference between groups in any measured characteristic

Cornely OA, et al.; Lancet Infect Dis. 2012 Apr;12(4):281-9. doi: 10.1016/S1473-3099(11)70374-7. Epub 2012 Feb 8.

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Results

- Non-inferior to vancomycin for clinical cure
- Significant reduction in recurrence
- Significant increase in sustained response
- Time to resolution of diarrhea not significantly different
- Time to resolution of diarrhea did differ in subgroup analysis, with those receiving concomitant antibiotics having longer times to resolution
- AEs: primarily GI symptoms for fidaxomicin



Cornely OA, et al.; Lancet Infect Dis. 2012 Apr;12(4):281-9. doi: 10.1016/S1473-3099(11)70374-7.

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Conclusions

- Fidaxomicin was non-inferior to vancomycin in clinical cure rates
- Fidaxomicin had a significantly lower rate of recurrence in the 4 weeks after completion
- Fidaxomicin had a significantly higher rate of sustained response
- Narrow spectrum and minimum side effect on gut flora
- Concomitant antibiotics reduced clinical cure rate for patients given vancomycin but had no apparent effect on those given fidaxomicin
- Concomitant antibiotics reduced time to resolution of diarrhea
- Subgroup analyses showed fidaxomicin superior to vancomycin for recurrence and sustained response only for those not on concomitant antibiotics

Cornely OA, et al.; Lancet Infect Dis. 2012 Apr;12(4):281-9. doi: 10.1016/S1473-3099(11)70374-7. Epub 2012 Feb 8.

Assessment Question #3

According to the both of the fidaxomicin vs vancomycin studies presented today (NEJM and Lancet), which statement best fits the authors conclusions?

A. Fidaxomicin was superior to vancomycin in initial clinical cure response, recurrence and global cure/sustained response.
B. Fidaxomicin was non-inferior to vancomycin in initial clinical cure response, and superior for recurrence and global cure/sustained response.
C. Fidaxomicin was non-inferior to vancomycin in initial clinical cure response, recurrence and global cure/sustained response.
D. Fidaxomicin was non-inferior to vancomycin in initial clinical cure response and inferior for recurrence and global cure/sustained response.

Questions

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