Clostridioides Difficile Colitis: Update on Guidelines

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No disclosures
April 6, 2018
Outline

- Overview of CDI
- Diagnosis of C Difficile - updates
- Infection Prevention and C Difficile - updates
- Treatment of C Difficile - updates
**Clostridium (now Clostridioides) difficile**

- Most common cause of hospital-acquired infection in U.S.
  - Hospitals $\rightarrow \$4.8$ billion for acute care facilities
  - $\$3427-\$9960$ per episode acute care hospital cost
- 2011 *C. difficile* associated with 29,000 deaths

Kwon. Infect Dis Clin N Am. 2015
Antibiotic and *C. Difficile*

**High risk**
- Clindamycin
- Cephalosporins (2\textsuperscript{nd} and 3\textsuperscript{rd} generation)
- Carbapenems
- Fluoroquinolones
- Broad-spectrum penicillins
- Ampicillin/amoxicillin

**Medium risk**
- Penicillin
- Trimethoprim/sulfonamides
- Macrolides

**Low risk**
- Aminoglycosides
- Metronidazole
- Rifampin
- Vancomycin
- Tetracycline

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**Risk of CDI TRIPLES after any antibiotic exposure, with increased cumulative risk**

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Increased toxin production

Fluoroquinolone

Lower cure rates

Increased recurrence rates

Severe disease/outcomes

Death

New terminology for CDI case definitions

- Healthcare facility-onset (HO) CDI
- Community-onset, healthcare facility-associated (CO-HCFA) CDI
- Community-associated (CA) CDI

McDonald. Clin Infect Dis. 2018
Healthcare facility-onset (HO) CDI

- C difficile carriage 8-50% of adults in hospitals and LTACs
  - 20% of patients with negative C diff stool cultures become infected

- Asymptomatic carriers can increase risk of CDI to other patients
  - No recommendation to screen asymptomatic carriers and place in contact precautions

- However newly infected patients are more likely to develop CDI

Zacharioudakis. Am J Gastro. 2015
McDonald. Clin Infect Dis. 2018
Blixt. Gastroenterol. 2017
Shim. Lancet. 1998
Diagnosis of CDI

- **Diarrhea** (≥ loose stools in 24 hours)
- No other explanation (laxative)
- + Risk factors: antibiotics, age, hospitalized
C difficile Diagnosis Evolution

1. Culture
2. Toxin EIA
3. PCR (NAAT)
4. EIA GDH + Toxin → PCR
## Different CDI diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT (PCR)</td>
<td>Very sensitive</td>
<td>Moderate</td>
<td>Can’t distinguish infection from carriage</td>
</tr>
<tr>
<td>EIA C. difficile GDH</td>
<td>High</td>
<td>Moderate</td>
<td>Can’t distinguish toxin +/- strains</td>
</tr>
<tr>
<td>EIA C. difficile toxins A/B</td>
<td>75%</td>
<td>99%</td>
<td>High false neg rate</td>
</tr>
<tr>
<td>Selective anaerobic culture</td>
<td>Very sensitive</td>
<td></td>
<td>Takes days Can’t distinguish toxin+/- strains</td>
</tr>
<tr>
<td>Cell culture cytotoxic assay</td>
<td>Very sensitive</td>
<td>Very specific</td>
<td>Takes days Gold standard</td>
</tr>
</tbody>
</table>
Recommended Testing Strategies

- GDH + Toxin
- GDH + Toxin → NAAT
- NAAT + Toxin

McDonald. Clin Infect Dis. 2018
Sample testing algorithm

1. Patient with diarrhea and risk factor(s) for *C. difficile* infection
   - Stool is tested by EIA (Alere Quik Chek Complete®)
     - GDH antigen
     - Toxin A/B

2. GDH positive
   - Toxin positive
   - GDH negative
   - Toxin negative

3. Indeterminant result
   - PCR for *C. difficile* toxin

4. PCR positive
   - POSITIVE
     - Testing is consistent with *C. difficile* infection

5. PCR negative
   - NEGATIVE
     - Testing not consistent with *C. difficile* infection
Infection Prevention Measures

- Private room
- Gowns and gloves
- Pre-emptive contact precautions

  Continue until 48 hours after resolution of diarrhea

  Prolong contact precautions until discharge if high CDI rates

McDonald. Clin Infect Dis. 2018
**Hand Hygiene Recommendations**

<table>
<thead>
<tr>
<th>Routine/endemic</th>
<th>Outbreaks/Hyper endemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Before and after</td>
<td></td>
</tr>
<tr>
<td>• Soap/water OR alcohol-based hand sanitizer</td>
<td></td>
</tr>
<tr>
<td>• Before and after</td>
<td></td>
</tr>
<tr>
<td>• Soap and water</td>
<td></td>
</tr>
</tbody>
</table>

McDonald. Clin Infect Dis. 2018
Room cleaning recommendations

Terminal room cleaning with sporicidal agent – during endemic high rates or outbreaks

Incorporate measures of cleaning effectiveness

No data to recommend automated, terminal disinfection using sporicidal method

Consider daily cleaning with sporicidal agent + other measures during hyperendemic/outbreaks

McDonald. Clin Infect Dis. 2018
Recurrent *Clostridium difficile* infections (CDI)

- **RISK FACTORS**
  - Prior CDI
  - Repeat exposure to contaminated environment
  - Resistant spores
  - Extreme/prolonged alteration of microbiome
  - Age > 65
  - Defective immune response to toxin A

Huebner et al. Gastroenterol Hepatol. 2006
Treatments for CDI

- Metronidazole
- Vancomycin
- Colestipol/cholestyramine/tolevamer
- Rifaximin
- Nitazoxanide
- IVIG
- Teicoplanin
- Tigecycline
- Probiotics
- Fidaxomicin
- Bezlotoxumab
- FMT
Fundamentals of CDI management (IDSA and ACG)

Cessation of inappropriate antibiotics

Infection prevention measures

Not all positive C diff tests = CDI (Only test diarrhea)

No test of cure

Avoid use of anti-diarrheals

Cohen et al. Infect Control & Hospital Epi. 2010
Surawicz. Am J Gastroenterol. 2013
What should be initial therapy for mild/moderate CDI?

Diarrhea + WBC < 15,000 cells/μL + creatinine < 1.5x pre-morbid level (+/- fever)
Metronidazole

- Not FDA approved
- First-line per IDSA guidelines 2010 and ACG guidelines 2013:
  - 500 mg po tid
- Cheap: $15 10 day course

Cohen et al. Infect Control & Hospital Epi. 2010
Surawicz. Am J Gastroenterol. 2013
Vancomycin

- FDA approved based on 1978 RCT
- High concentration in the colon
- Expensive: $225-1200

10 day course

Gonzales. BMC Infect Dis. 2010
Vancomycin superior to metronidazole ($p < 0.020$)
Meta-analysis of RCTs: no difference for mild CDI but favors vancomycin

85% cure vancomycin vs 77% metronidazole

**Di. Brazil J Infect Dis. 2015**
Cochrane Review antibiotics for mild-mod CDI

“Moderate quality evidence suggests that vancomycin is superior to metronidazole”

Nelson. Cochrane Database Syst Rev. 2017
Fidaxomicin

- FDA approved for treatment of mild/mod CDI 2011: 200mg po bid x 10 days

- Expensive $3700 for 10 day course
Fidaxomicin non-inferior to vancomycin, but less recurrence

Fidaxomicin non-inferior to vancomycin, but less recurrence

Patients with concomitant antibiotics: cure rate fidaxomicin 90.2% vs. vancomycin 73.3%, p = 0.031
Reduced recurrence or death with fidaxomicin

Fidaxomicin

Cochrane meta-analysis: fidaxomicin modestly more effective than vancomycin for initial response (71% vs 61%)

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): recommends fidaxomicin for all CDI patients suitable for oral antibiotics, severe and non-severe

IDSA guidelines recommend fidaxomicin for mild-moderate CDI

Nelson. Cochrane Database Syst Rev. 2017
McDonald. Clin Infect Dis. 2018
Summary of first-line therapy for mild/mod CDI

Vancomycin
125mg po qid
x 10 days

Fidaxomicin
200mg po bid
x 10 days

McDonald. Clin Infect Dis. 2018
What should we use to treat severe CDI?

Leukocytosis > 15,000 cells/mm³, serum albumin < 3 g/dL, abdominal tenderness, fever, age > 65
Vancomycin

IDSA, ACG, and ESCMID guidelines recommend vancomycin as initial treatment for severe CDI

Cochrane Review 2017: “Moderate quality evidence suggests that vancomycin is superior to metronidazole”

Cohen et al. Infect Control & Hospital Epi. 2010
Surawicz. Am J Gastroenterol. 2013
Nelson. Cochrane Database Syst Rev. 2017
Vancomycin superior to metronidazole for severe CDI

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Mtz group</th>
<th>Vm group</th>
<th>Total</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>37/41 (90)</td>
<td>39/40 (98)</td>
<td>76/81 (94)</td>
<td>.36</td>
</tr>
<tr>
<td>Severe</td>
<td>29/38 (76)</td>
<td>30/31 (97)</td>
<td>59/69 (86)</td>
<td>.02</td>
</tr>
<tr>
<td>All</td>
<td>66/79 (84)</td>
<td>69/71 (97)</td>
<td>135/150 (90)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Mtz, metronidazole; Vm, vancomycin.

<sup>a</sup> P values were calculated using Fisher’s exact test.
Reduced 30-day mortality with vancomycin compared to metronidazole

Retrospective propensity-matched cohort study
47,471 patients VA cohort 2005-2012

Vancomycin significantly reduced the risk of all-cause 30 day mortality amongst patients with severe CDI
(Adjusted relative risk, 0.79;95%CI, 0.65-0.97; adjusted risk difference , -0.04;95% CI, -0.07 to -0.01)

Stevens. JAMA Intern Med. 2017
Fidaxomicin

ESCMID guidelines offer fidaxomicin for severe CDI without complications (level B recommendation)

IDSA guidelines 2017 recommend fidaxomicin for severe CDI

McDonald. Clin Infect Dis. 2018
Treatment of severe CDI

- Vancomycin 125-250mg po qid x 10-14 days
- Consider fidaxomicin 200mg po bid x 10 days (B)
What should we use to treat fulminant CDI (aka severe with complications)?

Criteria for severe CDI PLUS hypotension/shock, ileus, megacolon, ICU admission, elevated lactate, abdominal distension
Different recs for severe CDI with complications

<table>
<thead>
<tr>
<th>IDSA</th>
<th>ACG</th>
<th>ESCMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Vancomycin</strong> 500mg po qid</td>
<td>• <strong>Vancomycin</strong> 125mg (500mg if abd distension) po qid</td>
<td>• <strong>Vancomycin</strong> 125mg po qid</td>
</tr>
<tr>
<td>• <strong>+ IV metronidazole</strong> 500mg q 8h</td>
<td>• <strong>+ IV metronidazole</strong> 500mg q 8h</td>
<td>• <strong>+ IV metronidazole</strong> 500mg q 8h (if no po)</td>
</tr>
<tr>
<td>• <strong>+ vancomycin</strong> 500mg pr qid if + ileus</td>
<td>• <strong>+ vancomycin</strong> 500mg pr qid if + ileus</td>
<td>• <strong>+ surgery</strong></td>
</tr>
<tr>
<td>• <strong>Surgery consult</strong></td>
<td>• <strong>Surgery consult</strong></td>
<td></td>
</tr>
</tbody>
</table>

No RCTs!!

McDonald. Clin Infect Dis. 2018
Surawicz. Am J Gastroenterol. 2013
What should we use to treat recurrent CDI?
<table>
<thead>
<tr>
<th>Treatment of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st</strong></td>
</tr>
<tr>
<td><strong>IDSA:</strong> vancomycin (if flagyl used), vanco taper + pulse), or fidaxomicin</td>
</tr>
<tr>
<td><strong>ACG:</strong> same drug</td>
</tr>
<tr>
<td><strong>ESCMID:</strong> vancomycin, fidaxomicin</td>
</tr>
</tbody>
</table>

| **2nd**                  |
| **IDSA:** vancomycin taper/pulse, vanco + rifaximin chaser, fidaxomicin, or FMT |
| **ACG:** pulsed vancomycin |
| **ESCMID:** vancomycin taper, fidaxomicin |

| **3rd**                  |
| **IDSA:** N/A            |
| **ACG:** Fecal Microbiota Transplant (FMT) |
| **ESCMID:** vancomycin pulse/taper, fidaxomicin, FMT |

McDonald. Clin Infect Dis. 2018  
Surawicz. Am J Gastroenterol. 2013  
### Vancomycin Tapers

#### Taper with Pulse
- 125mg po qid x 14 days
- 125mg po bid x 7 days
- 125mg po q day x 7 days
- 125mg po q 3 days x 2 weeks
- **81% cure rate**

#### Prolonged Taper plus Kefir
- 125mg po qid x 14 days
- 375mg po q M/W/F x 14 days
- 250mg po q M/W/F x 14 days
- 125mg po q M/W/F x 14 days
- PLUS ½ cup kefir po tid x 15 weeks total
- **85% sustained cure by 9 months**

Rifaximin

- **Dosed:** 400mg po bid or tid x 14-20 days
- **Expensive:** $1000/14 days
- **High level resistance**
- **Adding rifaximin “chasers”** to vancomycin may be effective treatment for rCDI, phase II 68 pts: 15% rifaximim vs 31% placebo with rCDI (p = 0.087)
- **Phase III trial** 130 pts: 16% rifaximim vs 30% placebo with rCDI (p = 0.06)
- **Second phase III trial (RAPID study)** completed, analysis pending

Garey. J antimicrob Chemother. 2011
Major. Gut. 2017
**Monoclonal antibodies: Bezlotoxumab**

**Phase II**
- Multicenter, double-blind RCT of rCDI bezlotoxumab vs placebo: 7% vs 25% (p < 0.001).
- No difference in number of days to resolution or severity of CDI.

**Phase III (MODIFY 1 & MODIFY 2)**
- Lower rate of recurrence (17% vs 28%).
- Higher rate of SAEs and death in actoxumab group—stopped.
- Bezlotoxumab as effective as combo actoxumab/bezlotoxumab.
- Note caution in patients with cardiovascular disease or CHF.

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FDA approved 2016 for secondary prevention of CDI in high risk patients (> 65, severe/prior CDI, immunocompromised, NAP1, use of other antibiotics).

Reduced rate of recurrence with Bezlotoxumab

<table>
<thead>
<tr>
<th>Participants with Infection Recurrence through Wk 12 (%)</th>
<th>Actoxumab-bezlotoxumab</th>
<th>Bezlotoxumab</th>
<th>Placebo</th>
<th>Actoxumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODIFY I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events</td>
<td>61</td>
<td>67</td>
<td>109</td>
<td>60</td>
</tr>
<tr>
<td>No. of Participants at Risk</td>
<td>383</td>
<td>386</td>
<td>395</td>
<td>232</td>
</tr>
<tr>
<td><strong>MODIFY II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events</td>
<td>58</td>
<td>62</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>No. of Participants at Risk</td>
<td>390</td>
<td>395</td>
<td>378</td>
<td></td>
</tr>
<tr>
<td><strong>Pooled Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Events</td>
<td>119</td>
<td>129</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>No. of Participants at Risk</td>
<td>773</td>
<td>781</td>
<td>773</td>
<td></td>
</tr>
</tbody>
</table>

Fecal Microbiota Transplant

Fig. 6. Administration of FMT in syringes through the biopsy channel. FMT procedure. (Courtesy of The Centre for Digestive Diseases, Five Dock, New South Wales, Australia; with permission.)
Role of Antibiotics in Perturbation of Intestinal Microbiota with restoration via FMT

Overall Efficacy of FMT

- **48%-100%** overall efficacy → up to 95-100% with 2nd FMT
- **91%** primary cure rate (resolution of symptoms w/o recurrence in 90 days)
- **No** randomized blinded controlled clinical trials but at least 3 RCTs
- **No** standardized processes
  - EGD
  - Colonoscopy
  - Rectal tubes
  - Capsules – OpenBiome, RePOOPulate

FMT (NGT) superior to oral vancomycin

- Open-labeled RCT comparing vancomycin with FMT (duodenal):
  - Vancomycin 500mg po qid x 4 days → bowel lavage → FMT
  - Vancomycin 500mg po bid x 14 days
  - Vancomycin 500mg po bid x 14 days + bowel lavage

- **Study terminated early (@43 of 120 pts)** due to significant improvement in FMT group

van Nood et al. NEJM. 2013
FMT (colonoscopy) superior to oral vancomycin

- Open-label randomized
- 49 patients
  - Vanco + FMT
  - Vanco treatment + 3 week taper
- 18/20 (90%) FMT cured vs. 5/19 (26%) vanco → study stopped at 1 year

% of patients cured

Cammarota. Aliment Pharmacol & Ther. 2015
FMT via colonoscopy vs NGT

- 20 patients (5 donors)
- 8/10 (80%) colonoscopy group without rCDI
- 6/10 (60%) in NGT group without rCDI


**Table 2. Summary Results for Reported Resolution of Symptoms After Initial FMT for Recurrent CDI, Overall and by FMT Method**

<table>
<thead>
<tr>
<th>FMT Method</th>
<th>Patients With Resolution of Symptoms Without Recurrence, %*</th>
<th>Studies/Total Studies Analyzed, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI tract</td>
<td>77</td>
<td>7/187†</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>90</td>
<td>11/257†</td>
</tr>
<tr>
<td>Enema</td>
<td>78</td>
<td>5/45</td>
</tr>
<tr>
<td>Upper GI tract and colonoscopy</td>
<td>100</td>
<td>1/27</td>
</tr>
<tr>
<td>All methods</td>
<td>85</td>
<td>23/516‡</td>
</tr>
</tbody>
</table>

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal.
* Because of small sample sizes and the abundance of data from case-series studies, 95% CIs were considered to be unreliable and were not calculated.
† Includes 10 patients from reference 18.
‡ Total number of studies is 1 less than the sum of individual rows.
FMT capsules effective treatment for CDI

- 180 patients received FMT from 7 donors
  - 15 capsules/day x 2 days
  - 8 week f/u
- **93% cure rate by 3rd dose**
- 3 serious adverse events:
  - 1 fever
  - 2 new diagnosis of ulcerative colitis

FMT capsules noninferior to FMT via colonoscopy

- 116 with h/o CDI x 3 randomised:
  - 360mL fecal slurry via colonoscopy
  - 40 capsules of FMT (80-100g)
- @12 weeks → 96.2% patients in both groups without recurrence

Kao. JAMA. 2017
FMT leads to long-lasting efficacy

- 82% (113/137) FMT recipients without recurrence
- 75% with rCDI received antibiotics compared to 38% in non-rCDI
- 33% with new medical condition or symptom post-FMT
- 95% would undergo FMT again, 70% as first line

Mamo. Open Forum Infect Dis. 2017
FMT – adverse reactions

- Upper GI hemorrhage (1) (Wettstein et al. United European Gastroenterol Federation. 2007)
- Infectious IBS symptoms (1) (Hellemans et al. Acta Gastroenterol Belg. 2009)
- Constipation (1) (Louie et al. ICAAC/IDSA. 2008)
- Signs of irritable colon (1) (Schwan et al. Lancet. 1983)
- Mild transient enteritis (3) (van Nood. NEJM. 2013)
- Diverticulitis (1) (Mandalia. Am J Gastro. 2014)
- Peritonitis after colonoscopy (2) (Sofi. Scand J Gastroenterol. 2012)
- Fatal aspiration pneumonia (1) (Baxter. CID. 2015)
- Norovirus transmission (2) (Schwartz. Am J Gastroenterol. 2013 in press)
- Bacteremia 2/2 E. coli (1) (Quera et al. J Crohns Colitis. 2013)
- Weight gain (34 lbs) (Alang. Open Forum Infect Dis. 2015)
FMT for CDI is cost effective

- Decision-analysis computer simulation model comparing tapered vancomycin to FMT
- FMT less costly ($1669 vs $3788) and more effective than vancomycin for recurrent CDI

Varier. Infect Control & Hospital Epi. 2015
Frozen Donor Stool - Openbiome

- Nonprofit founded 2012 by an MIT grad student
- Donors are “MIT, Harvard, & Tufts communities”
- Donors paid $40/sample $13,000/year
- Only 4% pass screening $5000
- Charge $500-$900 per treatment

THE MOST IMPORTANT THING YOU’LL DO ALL DAY!
FMT for CDI

- Effective for rCDI
- Need more studies
- Reimbursement?
- ACG & ESCMID & IDSA: FMT for recurrence

Cammarota. Gut. 2017
Vancomycin prophylaxis is effective in preventing CDI

Van Hise study

- Vancomycin 125 or 250mg po bid prophylaxis in patients on antibiotics
- CDI 4.2% prophylaxis vs 26.6% w/o prophylaxis; OR, 0.12; 95% CI, 0.04-0.4; p < 0.001

Carignan study

**Summary for management of rCDI**

<table>
<thead>
<tr>
<th>Option</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>pulse or taper (+/- kefir)</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>taper after vancomycin</td>
</tr>
<tr>
<td>Consider rifaximin</td>
<td>“chaser”</td>
</tr>
<tr>
<td>Bezlotoxumab</td>
<td>for those at risk of rCDI</td>
</tr>
<tr>
<td>Consider FMT</td>
<td></td>
</tr>
<tr>
<td>Consider vancomycin prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>
Summary re CDI updates

- New terminology for case definitions
- Updated strategies for CDI diagnosis include GDH + toxin or NAAT + toxin
- Slight revisions to hand hygiene for CDI
- Oral vancomycin, fidaxomicin should be considered first-line therapy for mild/mod CDI
- Consider bezlotoxumab, fidaxomicin for prevention of rCDI
- Vancomycin taper or FMT can also be considered for refractory or recurrent CDI
Thank you