

# Recent changes in CDI treatment guidelines

Educational Workshop: Changing perspectives in the treatment of *C. difficile* infection (CDI)

29<sup>th</sup> ECCMID

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# Disclosures

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- Advisory boards: Bio-K+, Acurx Pharmaceuticals
- Co-Chair of the IDSA/SHEA\* CDI guidelines committee

*\*Infectious Diseases Society of America/  
Society for Healthcare Epidemiology of America*

# History of CDI guideline recommendations and clinical practice in the USA

1970s

- Vancomycin established as effective treatment for pseudomembranous colitis<sup>1</sup>

1980s

- Metronidazole shown to be effective for CDI<sup>2</sup>

1995

- Reduce vancomycin use in hospitals (concern for emergence of vancomycin resistance in other pathogens) *HICPAC recommendations*<sup>3</sup>
- Vancomycin or metronidazole for 10 days is effective; metronidazole may be preferred *SHEA position paper on CDAD*<sup>4</sup>

2010

- Vancomycin is the drug of choice for severe disease, metronidazole is drug of choice for mild-to-moderate CDI. 10–14 day course recommended (concern for slow response to metronidazole) *SHEA/IDSA CDI guidelines*<sup>5</sup>

2018

- Either vancomycin or fidaxomicin is recommended over metronidazole for the initial CDI episode; Treatment duration is 10 days for either drug. *IDSA/SHEA CDI guidelines*<sup>6</sup>

# CDI Guidelines from other Societies

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- 2013: American College of Gastroenterology
- 2013: Public Health England
- 2014: European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
- 2016: Australasian Society of Infectious Diseases
- 2017: Scottish Health Protection Network

# American College of Gastroenterology recommendations (2013):

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## Initial CDI episode:

- Mild-to-moderate- metronidazole 500 mg orally 3 x daily for 10 d\*  
Strong recommendation, high-quality evidence
- Severe CDI- vancomycin 125 mg 4 x daily for 10 d  
Conditional recommendation, moderate-quality evidence

< Severe: ALB < 3 g / dl +  
either:  
WBC ≥ 15,000 cells / mm<sup>3</sup>,  
Abdominal tenderness

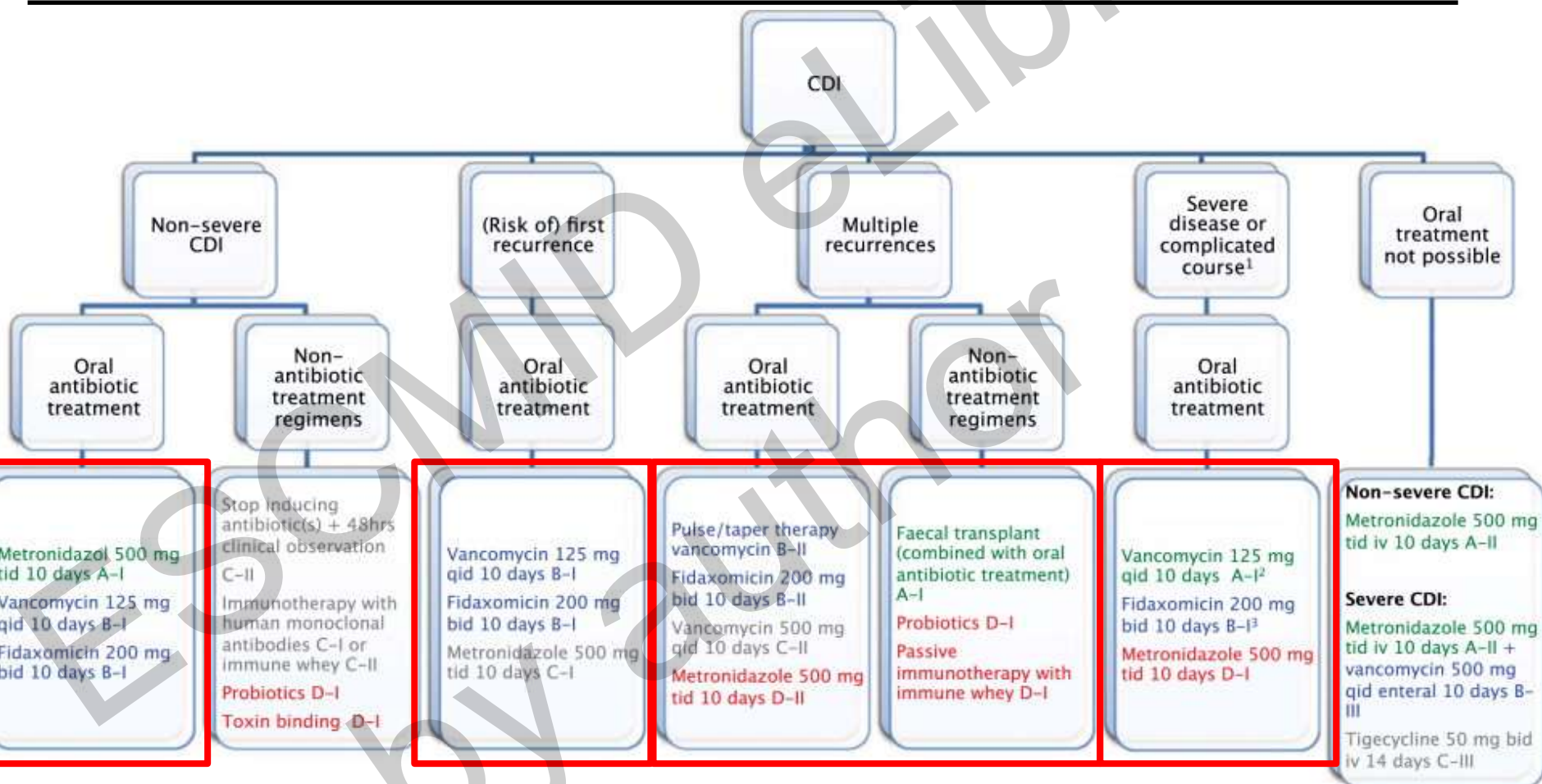
*\*Failure to respond to metronidazole therapy within 5-7 days  
should prompt consideration of a change in therapy to vancomycin  
at standard dosing*

## Recurrent CDI (RCDI):

- 1st recurrence: same regimen was used for the initial episode  
Conditional recommendation, low-quality evidence
- 2nd recurrence: pulsed vancomycin regimen  
Conditional recommendation, low-quality evidence
- 3rd recurrence: fecal microbiota transplant should be considered  
Conditional recommendation, moderate-quality evidence

# ESCMID\* update of treatment guidance document for CDI (2014):

\*European Society of Clinical Microbiology and Infectious Diseases



Strength of recommendation:

Green- strong; Blue- moderate; Grey- marginal; Red- do not use

# ESCMID update of treatment guidance document for CDI (2014): Severity definition

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- Severe or life-threatening CDI is defined as an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death.
- One or more of the following unfavourable prognostic factors can be present:
  - Marked leucocytosis (leucocyte count  $>15 \times 10^9/L$ )
  - Decreased blood albumin ( $<30 \text{ g/L}$ )
  - Rise in serum creatinine level ( $\geq 133 \text{ uM}$  or  $\geq 1.5$  times the premorbid level)

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

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- Published on line in *Clinical Infectious Diseases* 2/8/18
- Updates the 2010 clinical practice guidelines
- *C. difficile* infection (CDI) has become increasingly relevant:
- ~500,000 cases, 15,000–30,000 deaths, and excess costs of > \$4.8 billion annually in the US
- The epidemic 027/BI strain has decreased in prevalence but is still one of the most common strains identified.
- National efforts to control CDI include incentives for public reporting of hospital rates and hospital “pay for performance”:

*US Centers for Medicare and Medicaid Services. CMS requirements: CMS resources for NHSN users 2015.*

*US Centers for Medicare and Medicaid Services. Fiscal year (FY) 2016 results for the CMS hospital value-based purchasing program. 2015.*



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

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- Literature reviewed through Dec 2016
- The 2017 update now incorporates:
  - Recommendations for children
  - Quality of evidence and strength of recommendations weighed using GRADE\* methodology
  - New recommendations for epidemiology, diagnosis, infection prevention & control, and treatment of CDI
  - *Significant changes* in the diagnosis and treatment recommendations

\**Grading of Recommendations Assessment, Development, and Evaluation*

## Previous SHEA/IDSA recommendations (2010):

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- *Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10-14 days (A-I)*
- *Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10-14 days (B-I)*

**^Severe:** WBC  $\geq$  15,000 cells/mL or Cr  $\geq$  1.5 times the premorbid level

- *Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity .. (C-III)*
- *Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III)*

# New IDSA/SHEA recommendations (2018):

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What are the best treatments of an initial CDI episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations:

-**Either vancomycin or fidaxomicin** is recommended over metronidazole for an initial episode of CDI. The dosage is vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days

strong recommendation, high quality evidence (⊕⊕⊕⊕)

-In settings where access to vancomycin or fidaxomicin is limited, we suggest using metronidazole for an initial episode of non-severe CDI only

Severe: WBC  $\geq$  15,000 cells/mL or Cr  $\geq$  1.5 mg/dL

weak recommendation, high quality evidence (⊕⊕⊕⊕)

# Evidence for treatment recommendations of initial CDI episode *(Randomized, controlled trials)*

Outcome	N Participants (studies)	Percent resolution	Relative Risk (95%CI)	P	Quality of evidence (GRADE)
<b>Metronidazole (MTR) vs. vancomycin (VAN)</b>					
Initial cure	843 (5*)	78 (MTR) 87 (VAN)	0.89 (0.85, 0.96)	0.0008	⊕⊕⊕⊕ high
Sustained response	843 (5*)	63 (MTR) 73 (VAN)	0.87 (0.79, 0.96)	0.003	⊕⊕⊕⊕ high
<b>Fidaxomicin (FDX) vs. vancomycin (VAN)</b>					
Initial cure	1,005 (2**)	88 (FDX) 86 (VAN)	1.0 (0.98, 1.1)	0.36	⊕⊕⊕⊕ high
Sustained response	1,005 (2**)	71 (FDX) 57 (VAN)	1.2 (1.1, 1.4)	<0.0001	⊕⊕⊕⊕ high

\*Teasley Lancet 1983, Wenisch CID 1996, Zar CID 2007, Johnson CID 2014

\*\*Louie NEJM 2011, Cornely Lancet ID 2012

# New IDSA/SHEA recommendations (fulminant CDI):

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-Vancomycin administered orally

strong recommendation, moderate quality of evidence (⊕⊕⊕⊖)

-If ileus is present, vancomycin administered per rectum

weak recommendation, low quality evidence (⊕⊕⊖⊖)

-Intravenously administered metronidazole should also be administered, particularly if ileus is present

strong recommendation, moderate quality of evidence (⊕⊕⊕⊖)

*-Dosages: vanco: 500 mg orally 4x daily and 500 mg in 100 mL normal saline per rectum every 6 hr as a retention enema; metro: 500 mg iv q 8hr*

-If surgical management is necessary, perform subtotal colectomy with preservation of the rectum

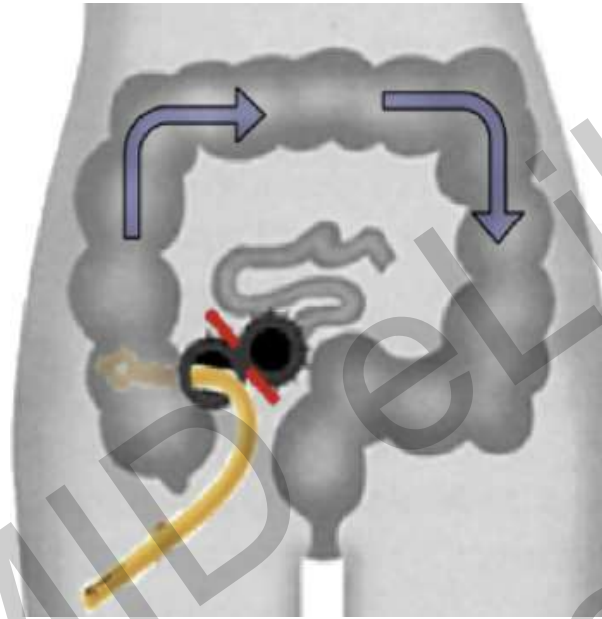
strong recommendation, moderate quality of evidence (⊕⊕⊕⊖)

-Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach

weak recommendation, low quality of evidence (⊕⊕⊖⊖)

# Diverting loop ileostomy

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42 patients at one center with severe complicated CDI underwent:

- Diverting loop ileostomy (laparoscopically in 83%)
- Intraoperative colonic irrigation with PEG3350/E-lyte solution
- Postoperative colonic enemas with vancomycin x 10 d
- IV metronidazole x 10 d

## Outcome

- Resolution of leukocytosis & bowel function: mean, 2.6d p-op
- 3 patients underwent subsequent colectomy
- 8 patients (19%) died w/in 30d p-op (historical rate: 50% after colectomy)
- Reversal of ileostomy w/in 6 months in 79%

# New IDSA/SHEA recommendations (recurrence):

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-Treat a first recurrence of CDI with **oral vancomycin as a tapered and pulse regimen** rather than a second standard 10-day course of vancomycin

weak recommendation, low quality evidence ( $\oplus\oplus\ominus\ominus$ )

**OR:**

-Treat a first recurrence of CDI with a **10-day course of fidaxomicin** rather than a standard 10-day course of vancomycin

weak recommendation, moderate quality evidence ( $\oplus\oplus\oplus\ominus$ )

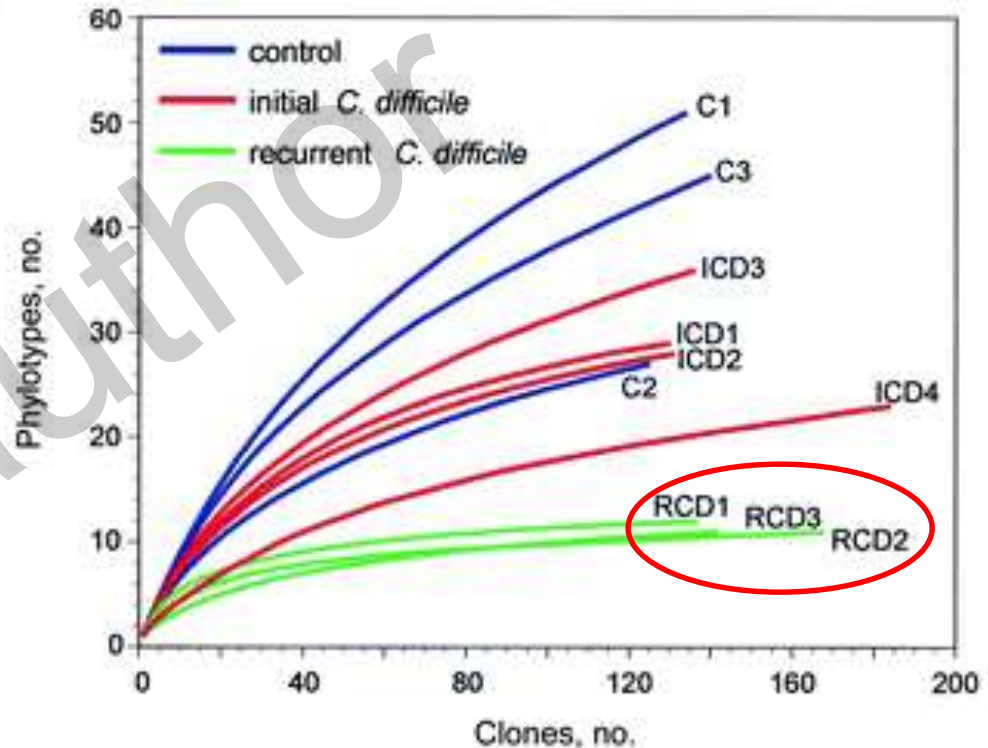
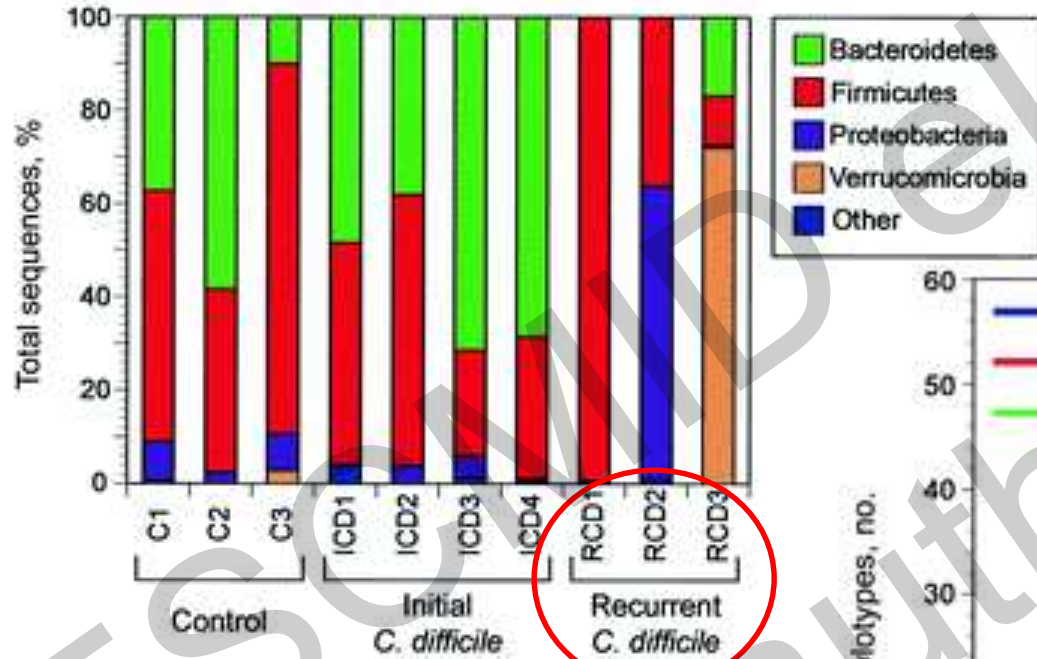
**OR:**

-Treat a first recurrence of CDI with a **standard 10-day course of vancomycin** rather than a second course of metronidazole if metronidazole was used for the primary episode

weak recommendation, low quality evidence ( $\oplus\oplus\ominus\ominus$ )

# Decreased diversity of fecal microbiome in CDI

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# New IDSA/SHEA recommendations (multiple recurrences):

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-Antibiotic treatment options for patients with more than one recurrence of CDI include:

- oral vancomycin therapy using a tapered and pulse regimen,
- a standard course of oral vancomycin followed by rifaximin, or
- fidaxomicin

weak recommendations, low quality evidence ( $\oplus\oplus\ominus\ominus$ )

-Fecal microbiota transplantation (FMT) is recommended for patients with multiple recurrences of CDI who have failed *appropriate* antibiotic treatments (*at least 2 recurrent CDI episodes*)

strong recommendation, moderate quality evidence ( $\oplus\oplus\oplus\ominus$ )

# Vancomycin taper and pulsed regimen (VAN-TP) and careful follow up for recurrent CDI

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- Retrospective review of consecutive patients treated for recurrent CDI with a VAN-TP regimen in our clinic over 5 years (2009-2014). Follow up for at least 90 days after completion of regimen.
- Cohort description (n, 100)
  - 64%, female; prior CDI episodes (mean):  $3.15 \pm 1.3$
  - After tapering vancomycin to once daily,
    - 36 received every other day (QOD) pulse dosing
    - 64 received QOD, then every third day (Q3D) pulse dosing
  - Mean length of treatment:  $77 \pm 29.9$  days
- Cure rate:
  - Overall: **74%** (56% if count exclusions as failures)
  - QOD dosing only: **61.1%** (22/36)
  - QOD+Q3D dosing: **81.1%** (52/64) (P = 0.03, compared to QOD)
  - Trend for higher cure rates among those with < 2 prior CDI episodes

# Enforcement policy regarding Investigational New Drug requirements for use of FMT to treat CDI not responsive to standard therapies (Draft guidance for industry)

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FDA intends to exercise enforcement discretion under limited conditions, regarding the IND requirements for the use of FMT to treat CDI not responding to standard therapies. FDA intends to exercise this discretion, provided that:

- 1) the licensed health care provider treating the patient obtains adequate consent
- 2) the **FMT product is not obtained from a stool bank\***; and
- 3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider

*\*A stool bank is defined, for the purpose of this guidance, as an establishment that collects, prepares, and stores FMT product for distribution to other establishments, health care providers, or other entities for use in patient therapy or clinical research. An establishment that collects or prepares FMT products solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance.*

# New IDSA/SHEA recommendations (pediatric):

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-Either **metronidazole or vancomycin** is recommended for the treatment of children with an initial episode or first recurrence of non-severe CDI

weak recommendation, low quality evidence (⊕⊕⊖⊖)

-For children with an initial episode of severe CDI, oral vancomycin is recommended over metronidazole

strong recommendation, moderate quality evidence (⊕⊕⊕⊖)

-For children with a second or greater episode of recurrent CDI, oral vancomycin is recommended over metronidazole

weak recommendation, low quality evidence (⊕⊕⊖⊖)

-Consider fecal microbiota transplantation (FMT) for pediatric patients with multiple recurrences of CDI following standard antibiotic treatments

weak recommendation, very low quality of evidence (⊕⊖⊖⊖)

# **New IDSA/SHEA recommendations (prophylaxis):**

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-There are insufficient data at this time to recommend extending the length of anti-*C. difficile* treatment beyond the recommended treatment course

## **OR:**

-restarting an anti-*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment

no recommendation

# Oral vancomycin prophylaxis (OVP) for patients with a prior history of CDI:

## 2 retrospective studies

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- 203 patients with prior CDI subsequently hospitalized and given systemic antibiotics (mean of 6 to 8 months after prior CDI):

*Van Hise CID 2016*

- Recurrent CDI rate: 19%
- 71 (35%) received OVP: **125 mg BID** (n, 29) or **250 mg BID** (n, 42)
- Mean duration of OVP after d/c of systemic antibiotics: 0.8 days
- Results (subsequent CDI recurrence):  
OVP, 4%; no OVP, 27% ( **$p < .001$** )

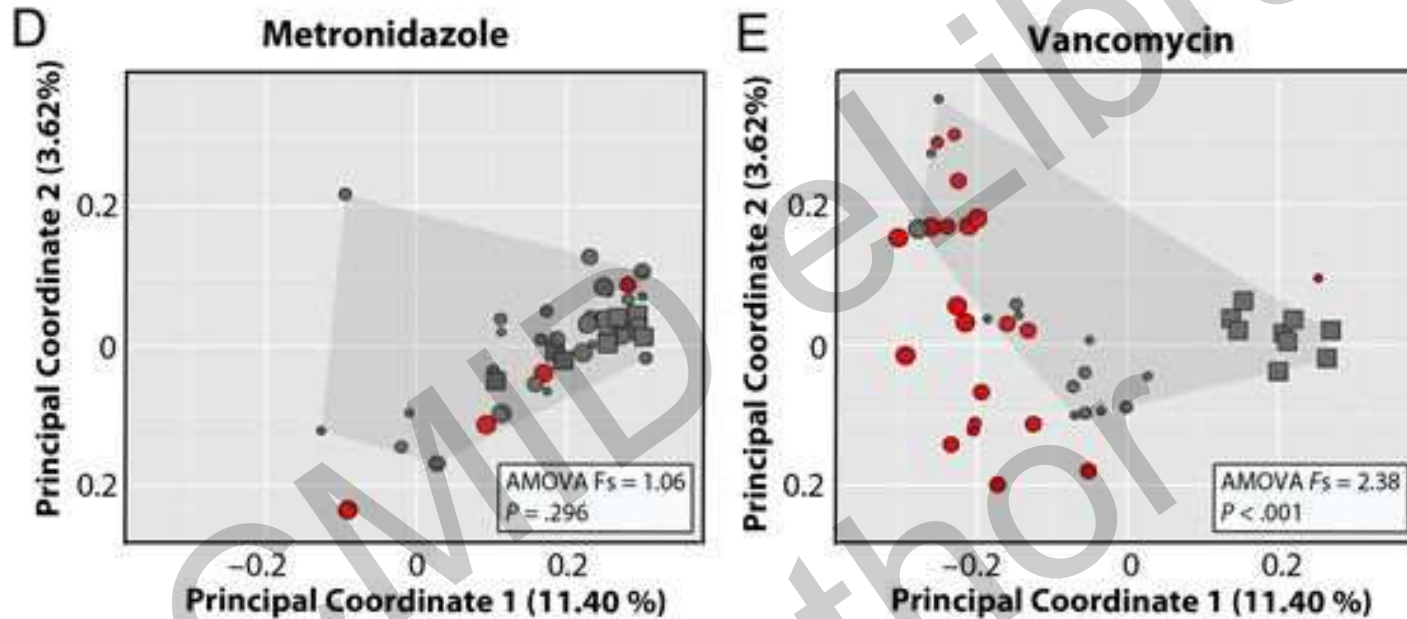
- 551 patients with prior CDI who received subsequent antibiotics (within 90 days):

*Carignan Am J Gastro 2016*

- Recurrent CDI rate: 33%
- 227 (42%) received OVP (**125 mg QID** in 84%)
- OVP given for >50% of the duration of concomitant antibiotics in 73%
- Results (subsequent CDI recurrence):  
Prior recurrent CDI (AHR, 0.47; 95%CI 0.32-0.69,  **$p < 0.0001$** )  
Previous primary CDI (AHR, 0.91; 95%CI, 0.57-1.45,  $p = 0.68$ )

# Caution against 'vancomycin prophylaxis' strategy

(Principal coordinate analysis of colon samples after infection of mice with *C. difficile*)



Squares: preantibiotic, Circles: postantibiotic treatment

Red: *C. difficile* growth supported; Grey: *C. difficile* not detected

'Oral vancomycin markedly disrupted the microbiota, leading to prolonged loss of colonization resistance to CDI and dense colonization by VRE, *K. pneumoniae*, and *E. coli*'

# Issues not address by current CDI guidelines

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- Bezlotoxumab as adjunctive therapy for patients at increased risk of recurrent CDI
- Extended, pulsed-dosing of fidaxomicin



# Summary

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- Either vancomycin or fidaxomicin is now recommended for treatment of initial CDI episode in adults (*metronidazole for mild-to-moderate, first episode CDI **only** if access to vancomycin or fidaxomicin is limited*)
- Metronidazole is still given as an option for treatment of non-severe CDI in children
- Patients with early recurrent CDI (i.e., 1st recurrence) can be managed with currently available antimicrobials, although the best regimen is not known and the current recommendations are weak and based on low or moderate quality evidence)
- FMT should be reserved for patients not responding to antibiotic management (e.g.,  $\geq 3^{\text{rd}}$  recurrence)
- ***Good clinical trials in recurrent CDI are needed!***

# CSP# 596 (OpTION Study)

## Optimal treatment of recurrent *C. difficile* infection

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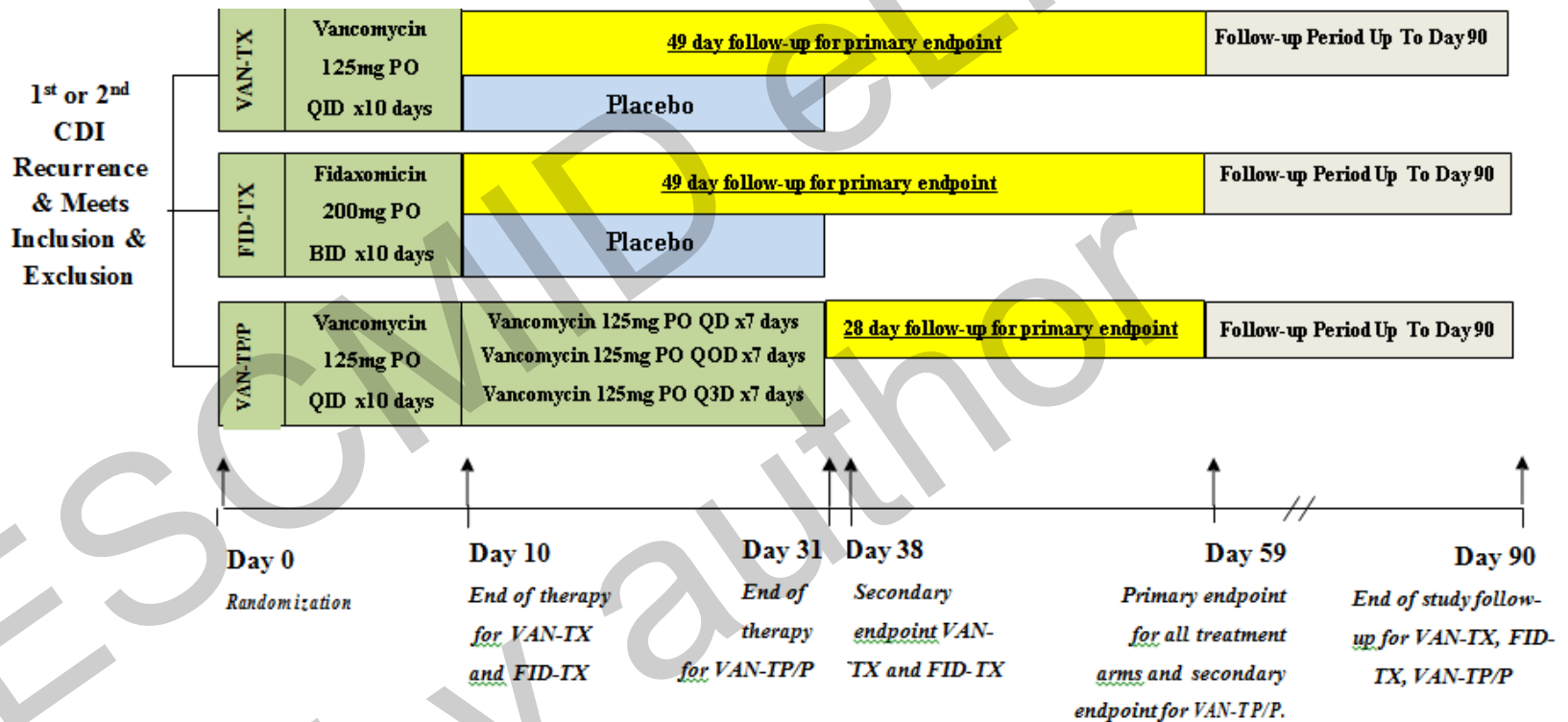
- Prospective, multicenter, double-blind, randomized controlled study
- Funded by the U.S. Veterans Affairs Cooperative Studies Programs
- Target enrollment and Sites:
  - 546 patients in 4.0 years, with 90 days f/up
  - 24 participating sites contributing 0.5 patients per month (6 per year)

# CSP 596 (OpTION) study objectives

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- Compare the efficacy of promising, but unproven, therapies for the treatment of recurrent *Clostridium difficile* infection (CDI)
- The primary objective is to determine whether:
  - 1) **fidaxomicin treatment** and
  - 2) **vancomycin treatment followed by taper/pulse** are superior for *sustained clinical response at day 59* to
  - 3) **10 days of treatment with vancomycin** 125 mg four times daily, a standard recommended treatment for a *first and second recurrence of CDI*

# CSP 596 Study design



# 2017 IDSA/SHEA CDI Guideline Panel

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