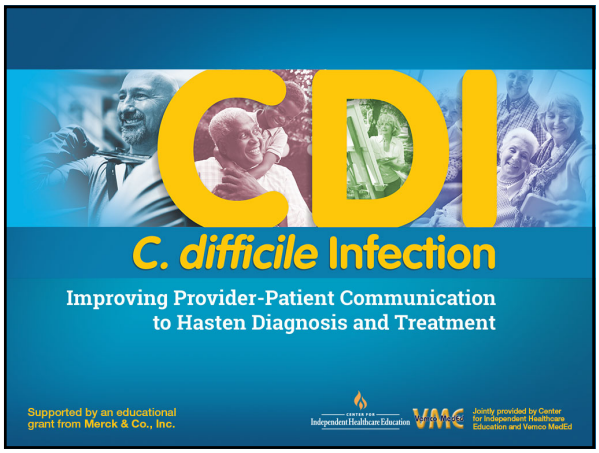


1

Agenda

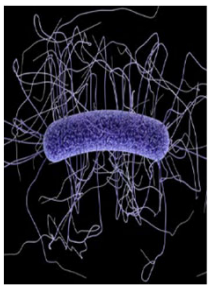
- What is *Clostridium (Clostridioides) difficile* infection?
- Pathophysiology
- Updated guidelines from IDSA/SHEA
  - Testing
  - Treatment
- Recurrence: relapse vs. reinfection?
- Management of CDI and recurrent CDI
- Prevention

2

The Impact of *Clostridium (Clostridioides) difficile* Infection

Epidemiology

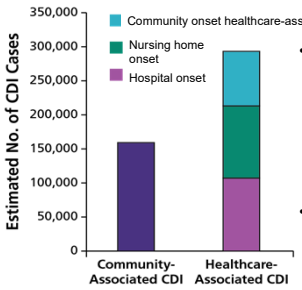
- 450,000 new cases
- 83,000+ recurrences per year in the United States
- 29,000 deaths per year (~80 per day!)



Lessa FC, et al. *N Engl J Med.* 2015;372:825-834.

3

CDI in the Community



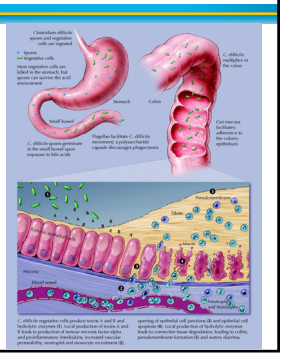
- 65% healthcare-associated
  - Only 1/3 hospital onset
  - About 1/3 nursing home onset
  - About 1/3 is community onset healthcare-associated
- 35% community-associated
  - 82% had outpatient care

Lessa FC, et al. *N Engl J Med.* 2015;372:825-834.

4

Microbiology

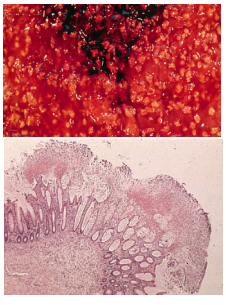
- Gram-positive spore-forming anaerobic rod
- Spores survive up to 6 months
- Vegetative forms survive up to 6 hours
- 400 strains of *C. difficile*
- Toxin A, B, +/- binary toxin



5

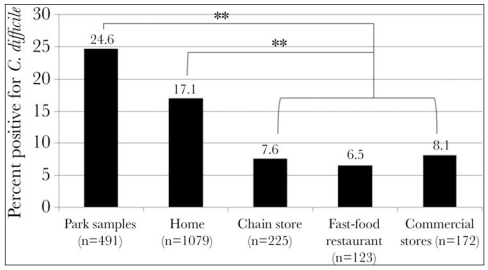
Spectrum of Disease

- Asymptomatic carriage state
  - 3%–5% in healthy adults
  - 20% in patients hospitalized for 1 week
  - 50% in patients hospitalized for 4 weeks
- *C. difficile*-associated diarrhea (simple diarrhea)
  - 20% of antibiotic-associated diarrhea
- Pseudomembranous colitis
  - 10% of CDI
- Fulminant colitis: sepsis, acute abdomen
  - 3% CDI
  - Toxic megacolon
  - Ileus/no diarrhea
  - Perforation/peritonitis



6

C. difficile is Everywhere!



**p<0.001
Alam MJ, et al. *Open Forum Infect Dis.* 2017;4(1):ofx018.

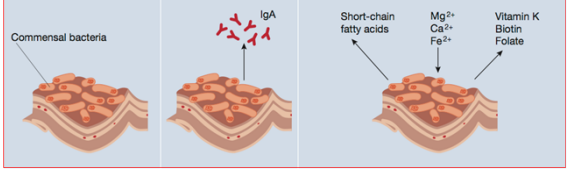
7

Pathophysiology

8

Functions of the Microbiome

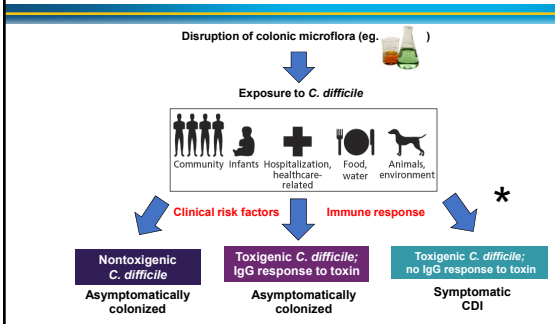
Protective functions	Structural functions	Metabolic functions
Pathogen displacement	Barrier fortification	Control IEC differentiation and proliferation
Nutrient competition	Induction of IgA	Metabolize dietary carcinogens
Receptor competition	Apical tightening of tight junctions	Synthesize vitamins e.g., biotin, folate
Production of anti-microbial factors e.g., bacteriocins, lactic acids	Immune system development	Ferment non-digestible dietary residue and endogenous epithelial-derived mucus
		Ion absorption
		Salvage of energy



O'Hara AM, Shanahan F. *EMBO Rep.* 2006;7:688-693.

9

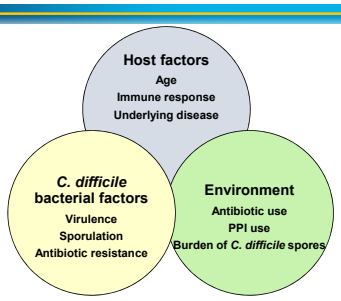
Clostridioides difficile: Steps to Infection



Rupnik M, et al. *Nat Rev Microbiol.* 2009;7:526-536.

10

CDI Risk Factors



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
Lessa FC, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S65-S70.
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

11

Differentiating CDI from Other GI Conditions Commonly Found in the Community

12

Making the Differential Diagnosis: Other Causes of Diarrhea

Infectious

- Bacterial
  - *Salmonella*
  - *Shigella*
  - *E. coli*
- Viral gastroenteritis
  - Norovirus
  - Rotavirus
- Parasites
  - *Giardia*

Non-infectious

- Inflammatory Bowel Disease (IBD)
  - Crohn's disease
  - Ulcerative colitis
  - Microscopic colitis
- Irritable bowel syndrome (IBS)
- Malabsorption syndrome
  - Celiac disease
  - Lactose intolerance
  - Gluten intolerance
  - Artificial sweeteners
- Medications
  - PPIs

13

Clinical Presentation of CDI: Recognizing the Signs and Symptoms

Common Findings

- Mild-to-moderate watery diarrhea (rarely bloody)
- Crampy abdominal pain
- Anorexia
- Malaise

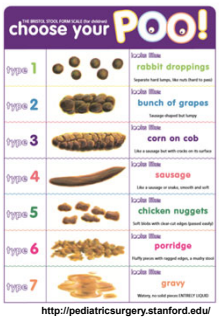
Possible Findings

- Fever
- Dehydration
- Electrolyte imbalance
- Hypoalbuminemia
- Rebound tenderness or lower abdominal tenderness

14

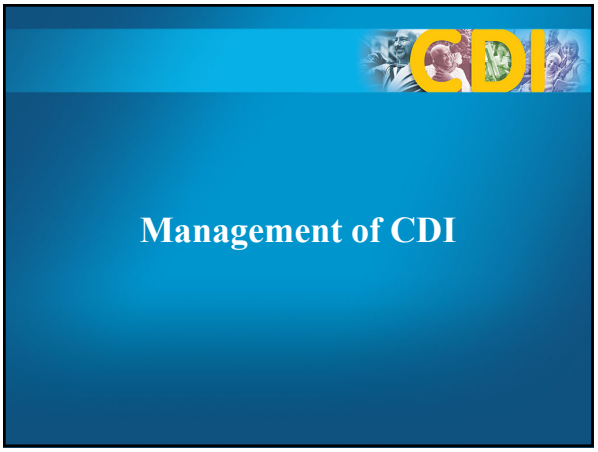
Evaluation of CDI

- **Assessment of Severity:**
  - Determine amount of diarrhea
  - Check for presence of *C. difficile* and/or cytotoxin in stool
  - CBC (elevated WBCs (>15,000 cells/mL))
  - Serum creatinine (>1.5x baseline)
  - Electrolytes (Low potassium)
  - Flexible sigmoidoscopy/ colonoscopy (not routinely recommended for diagnosis)
  - CT scan (colitis)
  - Lactate (reserved for inpatients)
  - Fever
  - Age >65 years
  - Albumin <2.5 g/dL



http://pediatricsurgery.stanford.edu/

15



16

CDI: Basic Management Principles[1-4]

- Suspect CDI on clinical grounds
  - Usually diarrhea and recent antibiotic use (within 1–3 months)

1. Discontinue all nonessential antimicrobials

1. Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-1940.
2. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455.
3. Debast SB, et al. *Clin Microbiol Infect.* 2014;20(suppl 2):1-26.
4. Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

17

Antibiotics Predisposing to CDI

Uncommonly Related	Less Commonly Related	Very Commonly Related
Aminoglycosides	Other penicillins	Clindamycin
Bacitracin	Sulfonamides	Ampicillin
Metronidazole	Trimethoprim	Amoxicillin
Teicoplanin	Co-trimoxazole	Cephalosporins (second and third generation)
Rifampin	Macrolides	Fluoroquinolones
Chloramphenicol		
Tetracyclines		
Carbapenems		
Daptomycin		
Tigecycline		

Bouza E, et al. *Med Clin North Am.* 2006;90:1141-1163.
Loo VG, et al. *N Engl J Med.* 2005;353:2442-2449.

18

Importance of Stopping Antibiotics in CDI

Outcome	No Additional Antibiotics	With Additional Antibiotics	*P*
Time to resolution of diarrhea, median	52 h	96 h	<.001
Diarrhea *not* resolved at 10 d, %	7	16	.001
Sustained response and no recurrence, %	34	25	.005

Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-447.

19

CDI: Basic Management Principles[1-4]

- Suspect CDI on clinical grounds
  - Usually diarrhea and recent antibiotic use (within 1–3 months)

1. Discontinue all nonessential antimicrobials
2. Confirm presence of toxin-producing *C. difficile* in stool

Only test patients with symptoms
Colonization seen in 60–70% neonates and children <2 years of age
Up to 50% of those in health care facilities
3% of the population not in this audience
Most labs will reject Formed Stool

1. Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-1940.
2. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455.
3. Debast SB, et al. *Clin Microbiol Infect.* 2014;20(suppl 2):1-26.
4. Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

20

Diagnostic Testing for *Clostridioides difficile*

Test	Sensitivity	Specificity	Availability	Expense[a]	Utilization
C. difficile culture	Low	Moderate	Limited	$5-10	No diagnostic use; only toxigenic organisms cause disease
Toxigenic culture	High	High	Limited	$10-30	Reference method Epidemiologic tool Limited diagnostic use
CCNA	High	High	Limited	$15-25	Reference method Limited diagnostic use
GDH	High	Low	Widely	$5-15	Diagnostically as a screening test; must be confirmed
Toxin EIA tests	Low	High	Widely	$5-15	Must detect toxins A+B; inferior sensitivity
NAATs	High	High	Widely	$20-50	Use only in acute disease; false positives of concern

[a]Cost of goods; does not reflect laboratory changes.

Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

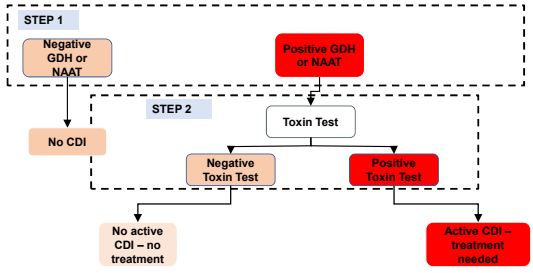
21

What Do the Main Tests Tell Us?

- GDH (glutamate dehydrogenase)
  - An enzyme produced by all *Clostridioides*, including those that do not make toxin
- Toxin Assay
  - Looks for the presence of the toxin protein itself
- PCR
  - Only detects the gene (DNA) that codes for the toxin (protein)
  - Does not tell us if the organism is currently making the toxin, hence disease
  - Not all *C. difficile* organisms can make toxin
  - Only the ones that make toxin can cause disease in the right setting

22

Multi-Step Diagnosis of *C. difficile* Infection



Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

23

CDI: Basic Management Principles[1-4]

- Suspect CDI on clinical grounds
  - Usually diarrhea and recent antibiotic use (within 1–3 months)

1. Discontinue all nonessential antimicrobials
2. Confirm presence of toxin-producing *C. difficile* in stool
3. Empiric treatment best avoided *unless*
   - Extremely high clinical index of suspicion *or*
   - Very severe illness *or*
   - Prompt stool testing not available

1. Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-1940.
2. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455.
3. Debast SB, et al. *Clin Microbiol Infect.* 2014;20(suppl 2):1-26.
4. Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

24

CDI: Basic Management Principles

- Do not test for cure
  - Toxin can be shed for up to six weeks after treatment
  - Do not panic if bowel symptoms do not return to normal right away
    - Up to 35% of patients can develop a post-infectious irritable bowel syndrome

Bagdasarian N, et al. *JAMA* 2015; 313:398-408

25

CDI: SHEA/IDSA Treatment Guidelines[1-3]

Out of Date

CDI Severity	Treatment
Mild to moderate	***Metronidazole*** *500 mg 3 times per day orally for 10-14 days*
Severe	***Vancomycin*** *125 mg 4 times per day orally for 10-14 days*
Severe, complicated (fulminant)	**Vancomycin** 500 mg 4 times per day orally or by nasogastric tube or enema plus IV **metronidazole** 500 mg every 8 hours

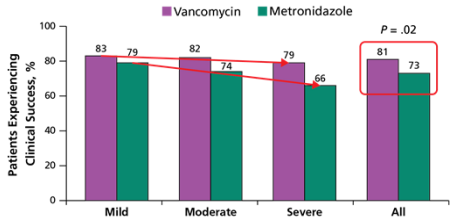
IDSA: Infectious Diseases Society of America; SHEA: Society for Healthcare Epidemiology of America.

1. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455. 2. Debast SB, et al. *Clin Microbiol Infect.* 2014;20(suppl 2):1-26. 3. Surawicz CM, et al. *Am J Gastroenterol.* 2013;108:478-498.

26

Vancomycin Compared With Metronidazole in Patients With CDI

- **Multivariate analysis**
- **Odds of clinical success with therapy**
- **Vancomycin (n = 259) vs metronidazole (n = 278)**
- **OR 1.58 (95% CI, 1.04-2.40; *P* = .034)**



Johnson S, et al. *Clin Infect Dis.* 2014;59:345-354.

27

CDI Treatment Failures With Metronidazole After 2000[1-3]

Variable	Number of Studies	Treatment Failure Number/Total Number
Metronidazole		
Year 2000 or before	4	18/718 (2.5%)
After 2000	5	275/1508 (18.2%)
Combined periods	9	293/2226 (13.2%)
Vancomycin		
Year 2000 or before	11	22/637 (3.5%)
After 2000	2	2/71 (2.8%)
Combined periods	13	24/708 (3.4%)

1. Aslam S et al. *Lancet Infect Dis.* 2005;5:549-557.
2. Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-1940.
3. Zar FA et al. *Clin Infect Dis.* 2007;45:302-307.

28

CDI: SHEA/IDSA Treatment Guidelines

Clinical Infectious Diseases
IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

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)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[3,4] Johan S. Bakken,[5] Karen C. Carroll,[6] Susan E. Coffin,[7] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[1] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

29

Management of CDI: Current Recommendations

Clinical Definition	Clinical Parameters	Recommended Treatment
Initial episode → Non-Severe	**WBC <15,000 cells/mL and Cr <1.5 mg/dL**	• **Vanc 125mg PO QID x 10 days or** • **FDX 200 mg PO BID x 10 days or** • **If above not available then metronidazole 500 mg PO/IV TID x 10 days**
Initial episode → Severe	**WBC>15,000 cells/mL or Cr>1.5 mg/dL**	• **Vanc 125mg PO QID x 10 days or** • **FDX 200 mg PO BID x 10 days**
Initial episode → Fulminant	**Hypotension/shock, ileus, megacolon** ***Consider just being in ICU***	• **Vanc 500 mg PO QID; If ileus, then add Vanc enema + metronidazole 500 mg IV TID**

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

30

What About Recurrences?

31

Recurrences: Relapses vs. Reinfections

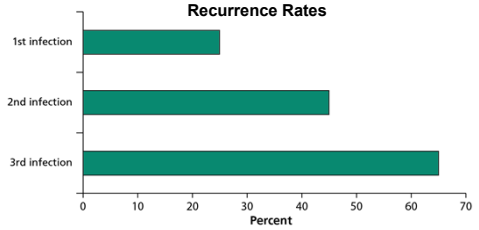
Recurrent CDI: **Complete abatement of CDI symptoms while on appropriate therapy, followed by subsequent reappearance of diarrhea and other symptoms after treatment has been stopped**

- One of the most challenging aspects of CDI
- Can result from **RELAPSE** with the same or a **REINFECTION** with a different strain of *C. difficile*[1-3]
  - Relapse and reinfection difficult to distinguish
- Both metronidazole and vancomycin have exhibited unacceptably high rates of recurrence[4-7]
- Increases mortality and morbidity, LOS, healthcare costs, and utilization of other healthcare resources; also puts additional burden on the patient's and family's QOL[8-10]

1. Walters BA, et al. *Gut.* 1983;24:206. 2. Young G, McDonald M. *Gastroenterology.* 1986;90:1098. 3. Wilcox MH, et al. *J Hosp Infect.* 1998;38:93. 4. Garey KW, et al. *J Hosp Infect.* 2008;70:298-304. 5. Louie TJ, et al. *N Engl J Med.* 2011;364:422-431. 6. Cornely OA, et al. *Lancet Infect Dis.* 2012;12:281-289. 7. Johnson S. *J Infect.* 2009;58:403-410. 8. LaBarbera FD, et al. *J Community Hosp Intern Med Perspect.* 2015;5:26-33. 9. Ghantoji SS, et al. *J Hosp Infect.* 2010;74:309-318. 10. Rohlke F, Stollman N. *Therap Adv Gastroenterol.* 2012;5:403-420.

32

Risk of Recurrent CDI Increases With Each Episode



- **Although some studies have looked at the causes, there is little consensus on causes of *C. difficile* recurrence**
  - **Persisting dysbiosis as the root cause?**

33

Pathophysiology of Recurrent CDI: Hypothesized Mechanisms and the Perfect Storm

- Persistent spores from initial infection or in environment
- Impairment of the host immune response to *C. difficile* toxins
- Altered colonic microenvironment (Para-cresol)

34

Risk Factors for rCDI

- **Clinical Factors[a]**
  - **Previous episodes of CDI or severe CDI**
  - **Immunocompromised**
  - **Decreased serum anti-toxin A IgG**
  - **Increasing peripheral leukocyte count**
  - **Presence of comorbid conditions (Inflammatory bowel disease)**
  - **Ongoing or recurrent antibiotic exposure**
  - **Prolonged hospitalization**
  - **Use of acid suppression medications**
  - **Feeding tubes**
- **Physiologic Factors[b]**
  - **Persistent impairment of colonization resistance by dysbiosis**
  - **Impaired adaptive immune response to toxins A/B or virulence factors of *C. difficile***
  - **Retained endogenous or newly acquired spores in the setting of a dysbiotic state**

a. Khanna S, et al. *Mayo Clin Proc.* 2012;87:1106-1117.
b. DuPont HL. *N Engl J Med.* 2011;364:473-474.

35

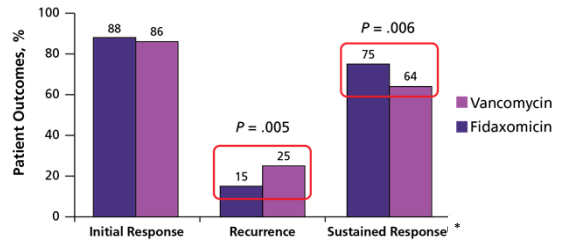
Management of Recurrent CDI: Current Recommendations

Clinical Definition	Recommended Treatment
First recurrence	• Vanc 125 mg PO QID x 10 days if metronidazole was used first or • Go straight to tapered-pulse if vanc was used for first episode or • FDX 200 mg PO BID x 10 days if vanc was used for first episode
Second or more recurrence	• Vanc tapered-pulse or • Vanc 125 mg PO QID x 10 days followed by rifaximin 400 mg po TID x 20 days or • FDX 200 mg PO BID x 10 days or • FMT (Need more than one recurrence or 3 infections or more)

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

36

Fidaxomicin vs. Vancomycin for CDI: Initial Response Rates and Recurrences



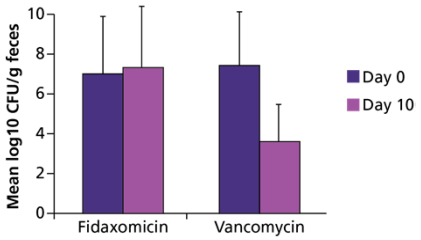
*Response without recurrence.

Louie TJ, et al. *New Engl J Med.* 2011;364:422-431.
Cornely OA, et al. *Lancet Infect Dis.* 2012;12:281-289.

37

Fidaxomicin May Cause Less Intestinal Dysbiosis Than Vancomycin

Bacteroides **group counts in feces before and after 10 days of treatment with fidaxomicin (200 mg bid) or vancomycin (125 mg qid)**



Louis TJ, et al. *Clin Infect Dis.* 2012;55(suppl 2):S132-S142.

38

Fecal Microbiota Transplant

IDSA/SHEA 2017 Guidelines:

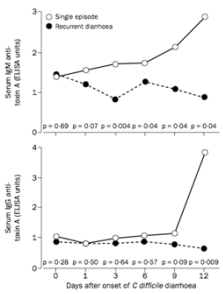
- **FMT can be considered after the third episode (≥2 recurrences)**

39

Emerging Therapies: Immunotherapy

40

Immune Therapy



Kyne L, et al. *Lancet.* 2001;357:189-193.

Immunity to *C. difficile* toxins is an important factor in recurrences

- Intravenous immunoglobulin:
  - 300–500 mg/kg given once, twice (one patient 6 times)
  - 3/5 no recurrence, 1 recurred at 6 weeks, one died of CDI
  - Inconclusive evidence given heterogeneity of infusion but consider 400 mg/kg IV QD x 3 days as salvage in the critically ill or heading towards surgery

Wilcox MH, et al *J Antimicrob Chemother.* 2004;53:882-4.
Sougioultzis S, et al. *Gastroenterology.* 2005; 128:764-70.

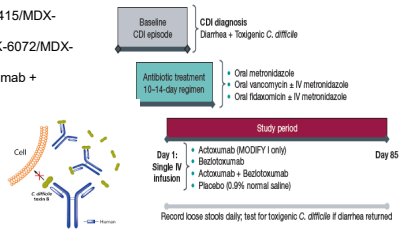
41

Bezlotoxumab for Prevention of CDI

Fully human mAbs against *C. difficile* toxins A and B[a]

- Actoxumab = MK-3415/MDX-066/CDA-1
- Bezlotoxumab = MK-6072/MDX-1388/CDB-1
- MK-3415A = actoxumab + bezlotoxumab

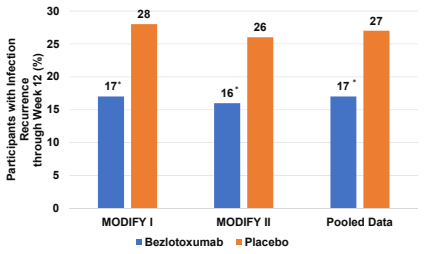
Trial Design Flow Diagram[b]



a. Lowy I, et al. *N Engl J Med.* 2010;362:197-205.
b. Gerding DN, et al. ECCMID 2016. Abstract EP0176.

42

Recurrence of CDI During the 12-wk Follow-Up Period with Bezlotoxumab



*p<0.001
Wilcox MH, et al. *N Engl J Med.* 2017;376:305-17.

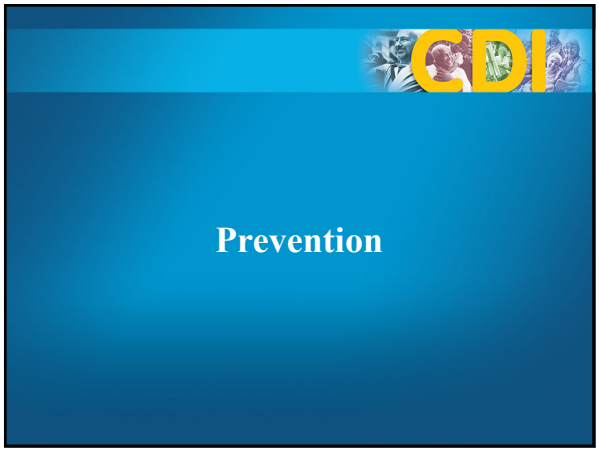
43

Bezlotoxumab in High-Risk Patients

- Greatest risk reductions observed in high-risk groups:
  - Age ≥65 y
  - >1 episode in past 6 mo
  - ≥2 prior episodes
  - Immunocompromised
- Pros
  - Different mechanism to treat those at high risk
  - Spares the gut flora
  - ? Those who will receive antibiotics in future
- Cons
  - Cost: drug + infusion
  - Convenience: where to infuse
  - Warning in patients with CHF
    - Higher rates of heart failure vs placebo: 12.7% vs 4.8%
    - Higher rates of death vs placebo: 19.5% vs 12.5%

Wilcox MH, et al. *N Engl J Med.* 2017;376:305-317.

44



45

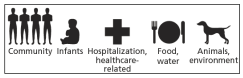
CDI: Strategies for Prevention[1,2]

1. Judicious antibiotic use
2. Education

Disruption of colonic microflora (eg. antibiotic therapy)

1. Rapid diagnosis
2. Isolation/barrier precautions for patients with CDI
3. Universal precautions including hand hygiene with soap and water
4. Environmental cleaning (chlorine)

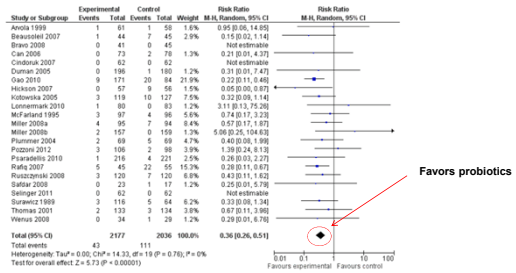
Exposure to *Clostridium difficile*



1. Rupnik M, et al. *Nat Rev Microbiol.* 2009;7:526-536.
2. Lessa FC, et al. *N Engl J Med.* 2015;372:825-834.

46

Meta-Analysis of RCT of Probiotics in the Prevention of CDI in Adults and Children



Goldenberg JZ, et al. *Cochrane Database Syst Rev.* 2013;5:CD006095.

47

Do Probiotics Really Work?

- *Saccharomyces boulardii*
  - 15/18 patients with recurrent CDI
  - Vancomycin 2 g/day × 10 days and *Saccharomyces boulardii* 1 g/day × 28 days had successful outcomes vs high-dose vancomycin and placebo (p=0.05)
- Staggered Tapered Antibiotic Withdrawal (STAW): Retrospective case series
  - 25 patients with history of multiple recurrences
  - Retrospective review
  - Kefir® 150 mL TID
  - 84% free of diarrhea for 9 months

Surawicz CM, et al. *Clin Infect Dis.* 2000;31:1012-7.
Bakken JS. *Clin Infect Dis.* 2014;59:858-61.

48

Overview of Current Management: Testing

Trust your clinical suspicion
- **Strong recommendation, moderate quality evidence**

Only test patients with diarrhea
- **Strong recommendation, high quality evidence**

Avoid repeat testing
- **Strong recommendation, moderate quality evidence**

Do not "test for cure"
- **Strong recommendation, moderate quality evidence**

49

What Patients Should Know

- Soap and water for washing hands and bathing
- Risk of spread is highest with active diarrhea and lowest with formed stools
- Separate bathrooms if one has diarrhea or clean surfaces with a 1:10 dilution of bleach (1/4 cup bleach poured into 2 1/2 cups water)
- Launder clothing and lines
  - Chlorine bleach is ideal
- Return to work/school when diarrhea has resolved

50

When Specialist Referral is Needed

- Refer to Gastroenterology or Infectious Diseases
  - Multiple recurrences (after 3rd recurrence)
    - GI or ID
  - Refractory symptoms (not improving after 3–5 days)
    - GI to rule out other etiologies for diarrhea (IBD, microscopic colitis, etc.)
- Surgical referrals usually reserved for inpatients

51

Summary

- ***Clostridioides difficile* = *Clostridium difficile***
- When you suspect CDI
  - Discontinue all nonessential antimicrobials
  - Confirm presence of toxigenic *C. difficile* in a timely fashion
  - Avoid empiric treatment if possible
  - Know when to refer
- **Vancomycin and fidaxomicin are first line unless patient can't swallow, allergic or dying, then IV metronidazole can be used**
- **Refer/consider FMT after 2nd recurrence** or advanced regimens (i.e. rifaximin, fidaxomicin, vancomycin chasers and tapers, bezlotoxumab)
- Reduce spore burden at home
- Prevention is key→ use antibiotics wisely…

52