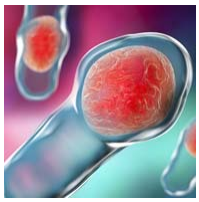

Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

Presented as a Live Webinar

Monday, November 9, 2020
12:00 p.m. - 1:00 p.m. ET

On-demand Activity

Recording of live webinar
Available after January 15, 2021

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- Webinar registration link
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Provided by ASHP
Supported by an educational grant from Merck

Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

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Disclosure of Relevant Financial Relationships

All planners, presenters, reviewers, ASHP staff, and others with an opportunity to control content report no financial relationships relevant to this activity.

Learning Objectives

- Discuss the epidemiology of recurrent *Clostridioides difficile* infection (CDI).
- Identify special populations at risk for recurrent CDI in practice.
- Summarize current and emerging pharmacologic and non-pharmacologic therapies for the prevention and treatment of recurrent CDI.
- Develop an interprofessional treatment plan for recurrent CDI for special populations.

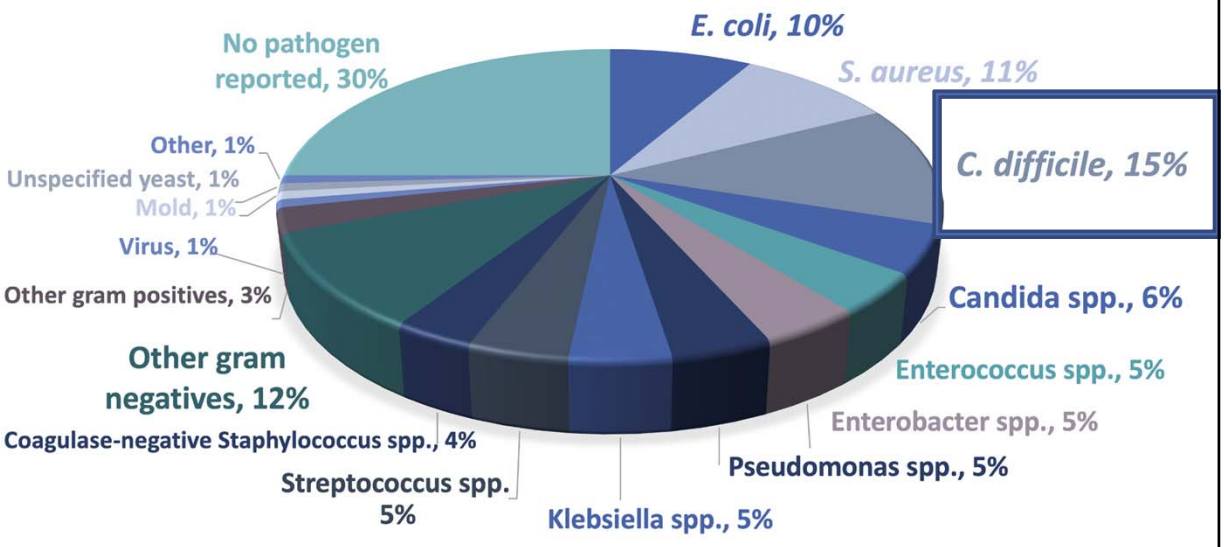
Abbreviations

- AML- acute myeloid leukemia
- BID- twice daily
- CDC- Centers for Disease Control and Prevention
- EIA- enzyme-linked immunosorbent assay
- FDX- fidaxomicin
- FMT- fecal microbiota transplant
- GERD- gastroesophageal reflux disease
- GDH- glutamate dehydrogenase
- HSCT- hematopoietic stem cell transplantation
- IBD- inflammatory bowel disease
- IV - intravenous
- MTZ- metronidazole
- NAAT- nucleic acid amplification test
- PMH- past medical history
- QID- four times daily
- RCT- randomized controlled trial
- rCDI- recurrent CDI
- SCr- serum creatinine
- SOC- standard of care
- UTI- urinary tract infection
- VAN- vancomycin
- WBC- white blood cell count

The Epidemiology of Recurrent *Clostridioides difficile* Infections

Andrew Skinner, M.D.
Clinical Instructor
Loyola University Medical Center
Maywood, Illinois

Etiology of Healthcare-Associated Infection



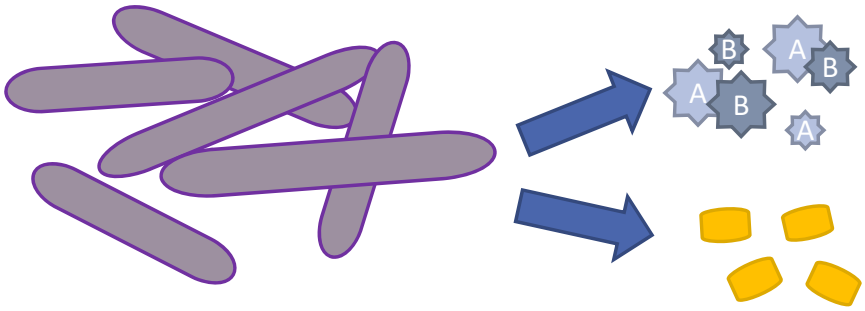
Magill SS et al. *N Engl J Med.* 2018; 379:1732-44.

Clostridioides difficile: A history

- 1893 • Pseudomembranous colitis described
- 1935 • First described as *Bacillus difficilis by* Hall and O'Toole
- 1978 • *C. difficile associated with antibiotic-associated diarrhea*
- 2002 • *C. difficile* incidence, morbidity, and mortality increase
- *2013* • CDC labels *C. difficile* as threat level Urgent
- 2019 • CDC reaffirms *C. difficile* as threat level Urgent

What is *Clostridioides difficile*?

- Formerly known as *Clostridium difficile*
  - Nomenclature changed in 2018



Gram-positive, anaerobic bacilli

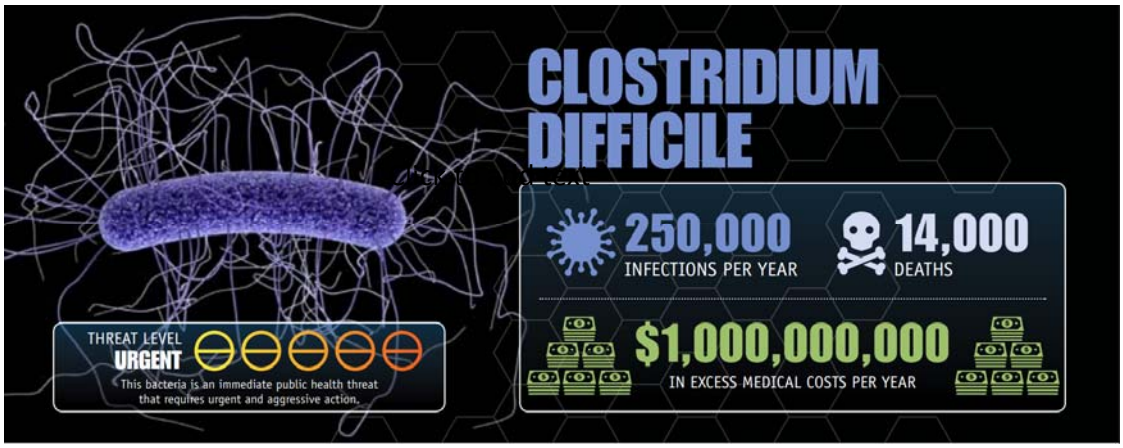
Toxin-producing

- Toxin A (TcdA)
- Toxin B (TcdB)
- Binary Toxin (CDT)

Spore-forming

Abt MC et al. *Nat Rev Microbiol.* 2016; 14:609-20.

CDC 2013
C. difficile, Threat Level Urgent



Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

CDC 2019
C. difficile, Threat Level Urgent

Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

C. difficile Infection

- CDI symptoms range from asymptomatic carriage to mild diarrhea to fulminant colitis and death
- CDI is defined as the presence of symptoms plus:
  - A positive stool test for *C. difficile* toxin B or detection of toxigenic *C. difficile* by PCR

    OR
  - Colonoscopy or histopathologic findings revealing pseudomembranous colitis

Kelly CP et al. *N Engl J Med.* 1994; 330:257–62.
McDonald LC et al. *Clin Infect Dis.* 2018; 66:e1–e48.

Diagnosis of CDI

- Symptoms
  - Diarrhea: Defined as three or more unformed stools over 24 hours
- Diagnostic tests
  - Toxin A/B EIA
  - GDH
  - NAAT
  - Multistep algorithms
    - GDH/Toxin EIA Plus NAAT
    - NAAT Plus Toxin EIA

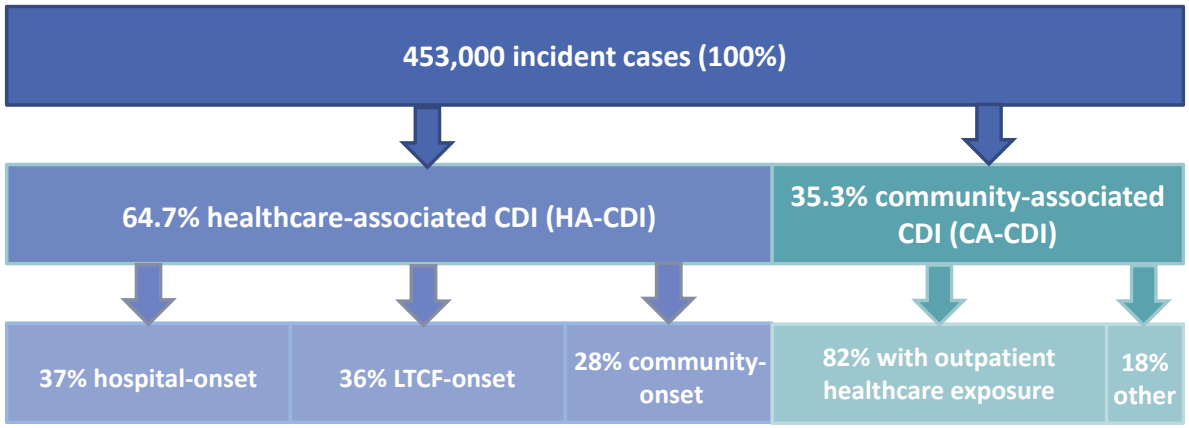
McDonald LC et al. *Clin Infect Dis.* 2018; 66:e1–e48.

Current *C. difficile* Testing Methods

Diagnostic Test	Testing Target	NPV	PPV	Comments
GDH/Toxin EIA + NAAT (MST)	1)Glutamate dehydrogenase 2)Presence of Toxin A or B 3)Genes that code for toxin production	99%	90%	1)Test for GDH and Toxin EIA. -If both positive, confirms CDI. 2)Complete NAAT if GDH and Toxin EIA results are discordant -If NAAT positive, confirms likely CDI
NAAT	1)Genes that code for toxin production	99%	92%	1)Does not discriminate between infection and colonization. 2)Overdiagnosis of CDI
NAAT + Toxin EIA	1)Genes that code for Toxin production 2)Presence of Toxin	99%	90%	1)Test for *C. difficile* NAAT 2)If NAAT positive, Toxin EIA test completed 3)Positive Toxin EIA confirms likely CDI -Negative Toxin EIA, does not exclude CDI and requires clinical assessment

Chapin KC et al. *J Mol Diagn.* 2011; 13:395-400.
Planche TD et al. *Lancet Infect Dis*. 2013; 13:936-945.

CDI Epidemiologic Categories

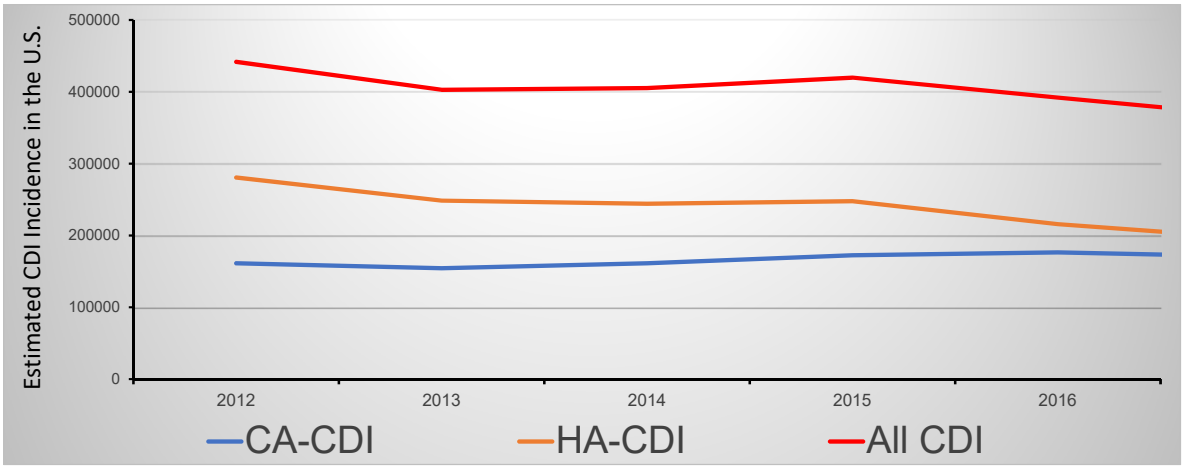


- 94% of all CDI cases had a recent healthcare exposure

LTCF=long-term care facilities

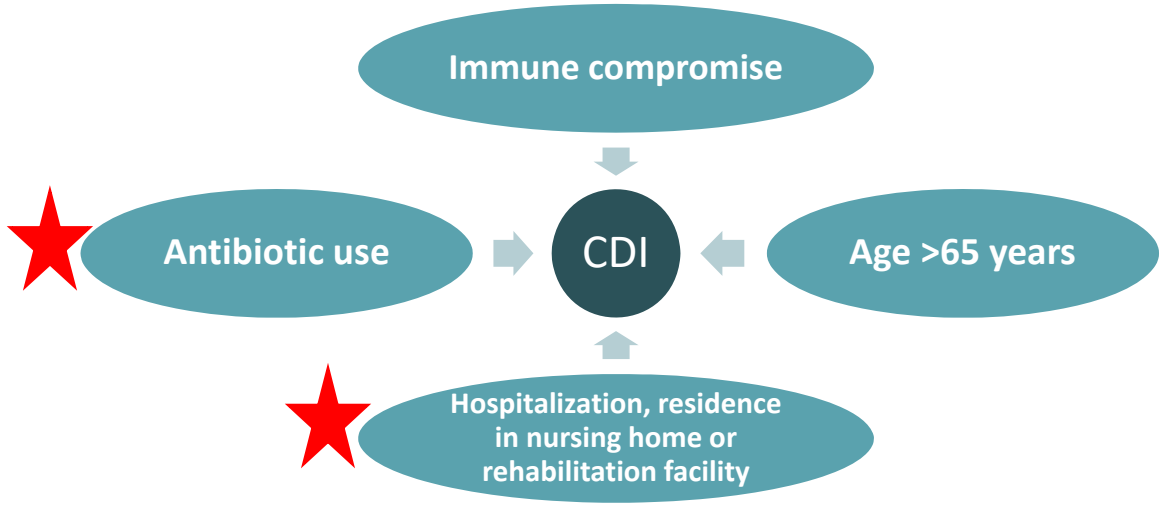
Lessa FC et al. *N Engl J Med.* 2015; 372:825-34.

CDI Epidemiology



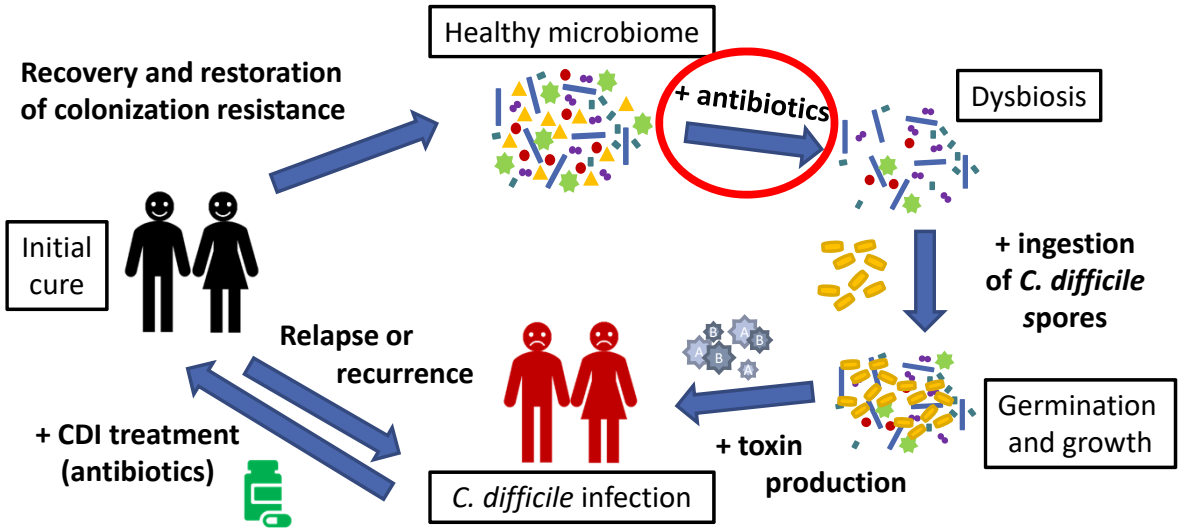
Guh AY et al. *N Engl J Med.* 2020; 382:1320-30.

Risk Factors for CDI



Pepin J et al. *CMAJ.* 2005; 173:1037–42. Stevens V et al. *Clin Infect Dis.* 2011; 53:42-8.

CDI Pathogenesis



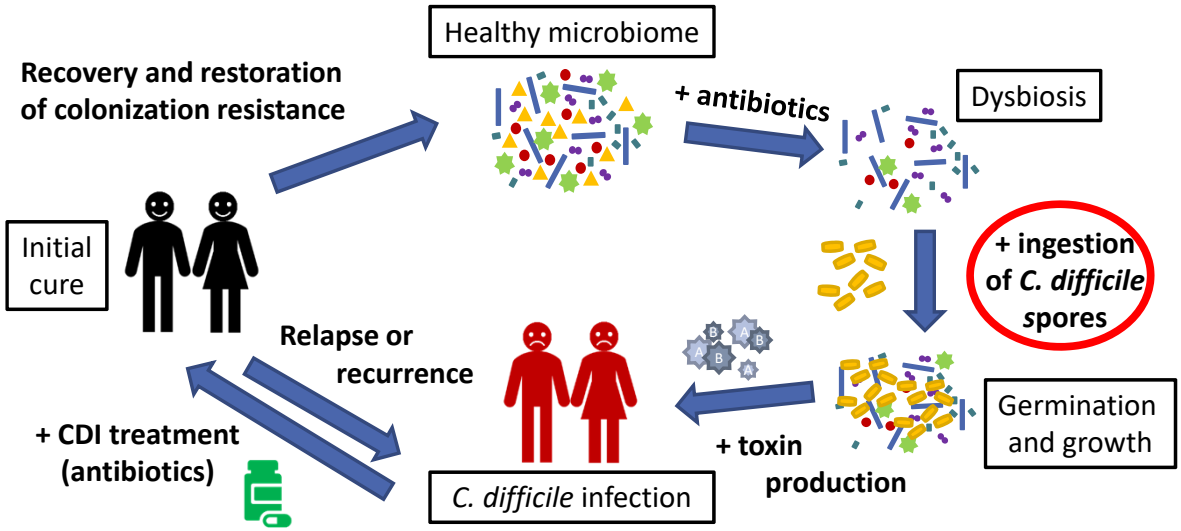
Britton RA et al. *Gastroenterology.* 2014; 146:1547–53.

Antibiotics as a Risk Factor for CDI

- Highest risk of CDI (7- to 10-fold increase) during and in the first month following antibiotic exposure
  - Increased risk seen **up to 3 months** after cessation of antibiotic therapy
- Dose-dependent increases in CDI risk associated with:
  - Increasing cumulative antibiotic dose
  - Increasing number of antibiotics
  - Increasing number of days of antibiotic exposure

Hensgens MP et al. *J Antimicrob Chemother.* 2012; 67:742–8.
Stevens V et al. *Clin Infect Dis.* 2011; 53:42-8.

CDI Pathogenesis



Britton RA et al. *Gastroenterology.* 2014; 146:1547–53.

Route of Transmission

- Ingestion of *C. difficile* spores via fecal-oral route:
  - Person-to-person transmission (hands of healthcare personnel)
  - Environmental contamination with *C. difficile* spores
- Healthcare facility transmission
  - Being placed in a hospital room where the previous occupant had CDI increases risk
    - Only accounts for 10% of CDI
  - Asymptomatic carriers can transmit spores leading to infection within a hospital
    - 29% of CDI related to asymptomatic carriers, and 30% related to symptomatic patients

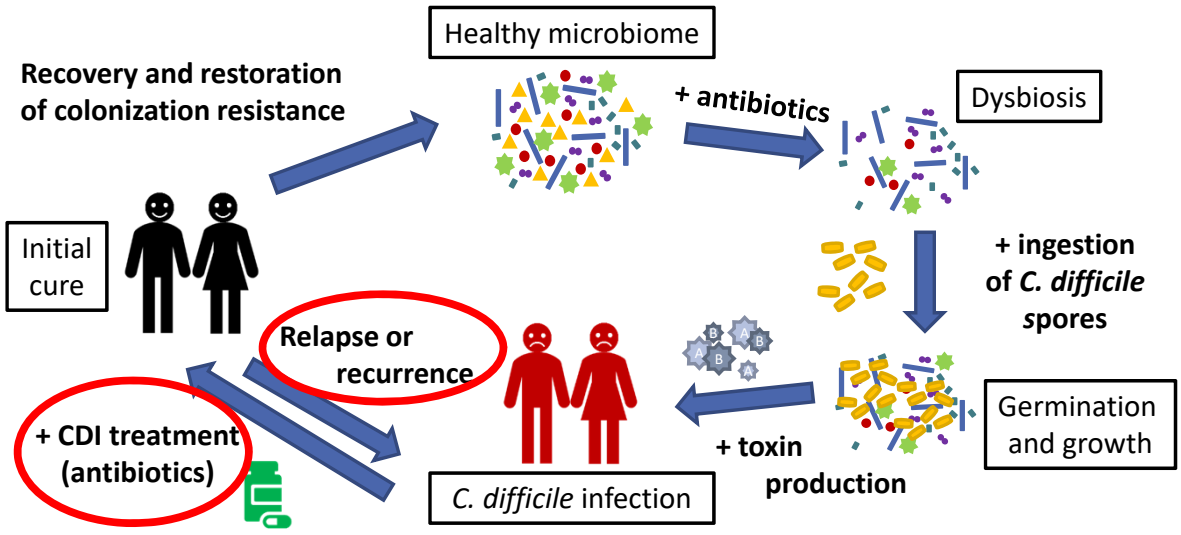
Curry SR et al. *Clin Infect Dis.* 2013; 57:1094–102.
Shaughnessy MK et al. *Infect Control Hosp Epidemiol.* 2011; 32:201–6.
Bobulsky GS et al. *J Antimicrob Clin Infect Dis.* 2008; 46:447–50.

Healthcare association with CDI

- The prevalence of asymptomatic colonization with *C. difficile* is 3 – 26% in hospitalized adults
  - In elderly patients in LTCFs the asymptomatic colonization is 5-7%
- The prevalence of asymptomatic *C. difficile* carriage in adults without recent healthcare facility exposure is <2%
- A meta-analysis pooling 19 studies revealed the colonization rate at hospital admission was 8.1% with the main risk factor being previous hospitalization

Zacharioudakis IM et al. *Am J Gastroenterol.* 2015; 110:381–90.
Viscidi R et al. *Gastroenterology.* 1981; 81:5–9.
Curry SR et al. *Clin Infect Dis.* 2013; 57:1094–102.

CDI Pathogenesis



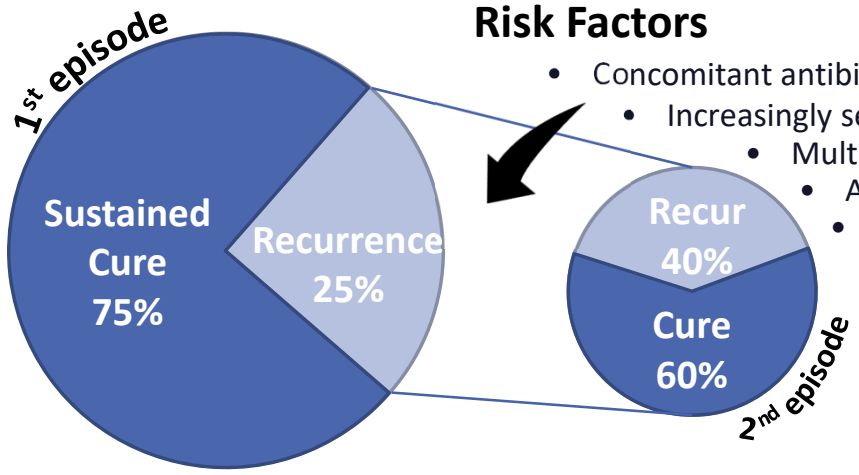
Britton RA et al. *Gastroenterology.* 2014; 146:1547–53.

Recurrent CDI

- New CDI symptoms after resolution of symptoms with a positive test for *C. difficile* within 2-8 weeks
  - 10 – 30% of all patients with first episode CDI diagnosis suffer from recurrent disease
  - Risk increases with each successive recurrence
- Recurrence rate in CA-CDI is 9.7 cases per 100,000 people
- Recurrence rate in HA-CDI is 12 cases per 100,000 people
- Risk of mortality increases by 33% with recurrent CDI at 180 days

Fekety R et al. *Clin Infect Dis.* 1997; 24:324–33.
Guh AY et al. *N Engl J Med.* 2020; 382:1320-1330.
Olsen MA et al. *Clin Microbiol Infect.* 2015; 21:164–70.

Cycle of Recurrence



Risk Factors

- Concomitant antibiotic administration
- Increasingly severe underlying disease
- Multiple recurrences
- Advancing age
- Hematologic malignancy

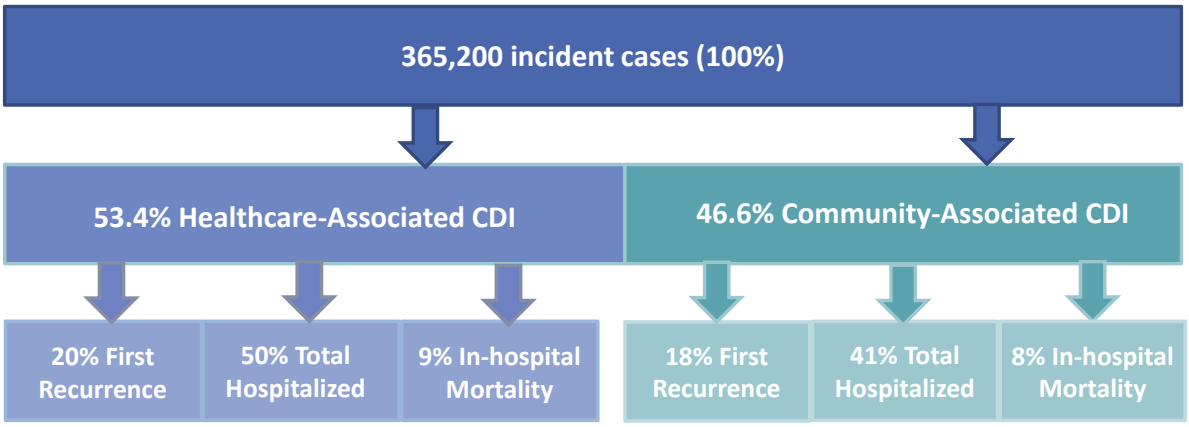
Cornely OA et al. *Clin Infect Dis.* 2012; 55(Suppl 2):S154-61.
McFarland LV et al. *Am J Gastroenterol.* 2002; 97:1769-75. Nair S et al. *Am J Gastroenterol.* 1998; 93:1873-6.

Burden of CDI in the U.S.

- *C. difficile* responsible for **~500,000 infections** annually
  - 83,000 1st recurrences
- Associated with **20,500** in-hospital CDI-associated deaths annually
- Associated with **29,000** 30-day CDI-associated deaths annually
- Overall annual costs estimated at **$5.4 billion** in U.S.
  - $4.7 billion (86.7%) incurred in healthcare settings
    - CDI-attributable costs $3,427–$9,960/episode for acute care hospitals
  - $725 million (13.3%) incurred in the community

Lessa FC et al. *N Engl J Med.* 2015; 372:825-34. Desai K et al. *BMC Infect Dis.* 2016; 16:303. Kwon JH. *Infect Dis Clin North Am.* 2015; 29:123–34. Guh AY et al. *N Engl J Med.* 2020; 382:1320-30.

CDI Burden



Guh AY et al. *N Engl J Med.* 2020; 382:1320-30.

Selected Special Populations

Andrew Skinner, M.D.

Inflammatory Bowel Disease (IBD)

- Ulcerative colitis (UC)
  - Underlying dysbiosis
  - 3.4% risk of CDI within 5 years
  - 33% more likely to suffer recurrent CDI when compared to persons without IBD
  - Combination of UC and CDI increase the risk of colectomy compared to persons without UC

Negrón ME et al. *Am J Gastroenterol.* 2016; 111:691–704.
Razik R et al. *Am J Gastroenterol.* 2016; 111:1141–6.
Peng JC et al. *Saudi J Gastroenterol.* 2015; 21:208–12.

Immunocompromised Status

- Solid organ transplant
  - 5-fold increased rate of CDI
    - Higher risk with multi-organ transplant
  - Risk of recurrence is **~20%** in solid organ transplant patients
- Hematopoietic stem cell transplant
  - Risk is 9-fold higher compared with general hospitalized patient
  - **1 in 10** allogeneic HSCT patients will have CDI

Paudel S et al. *PLoS One.* 2015; 10:e0124483.
Zacharioudakis IM et al. *Biol Blood Marrow Transplant.* 2014; 20:1641–65.

Pediatric *C. difficile*

- Infants
  - Up to 60% colonized with *C. difficile* within the first year of life.
    - CDI is rare
  - 50% of newborns are colonized with toxigenic *C. difficile*
  - By age 3 years, children are colonized by *C. difficile* at rates similar to those in adults, 1 – 3%
    - Exceptions: Pediatric IBD and pediatric malignancies

McFarland LV et al. *J Pediatr Gastroenterol Nutr.* 2000; 31:220–231. McDonald LC et al. *Clin Infect Dis.* 2018; 66:e1–e48.
Dominguez SR et al. *Clin Infect Dis.* 2014; 59:401–3. Pascarella F et al. *J. Pediatr.* 2009; 154:854–858.

Pediatric CDI

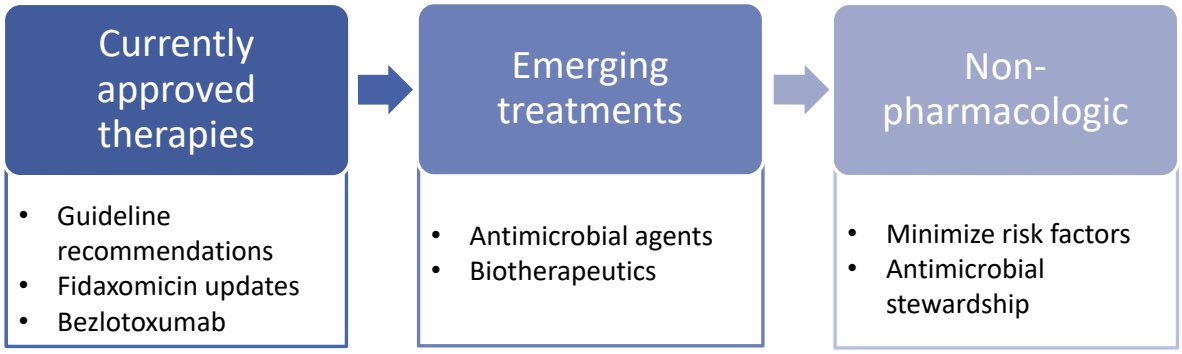
- Pediatric CDI has doubled over the past 2 decades
  - The incidence of pediatric CDI increased from 7.2 to 12.8 per 10,000 hospitalization
- From 2012 to 2016 pediatric CDI incidence increased from 24 to 35 per 100,000 patients
  - The majority are CA-CDI
- Paucity of treatment data until recently

Zilberberg MD et al. *Emerg Infect Dis.* 2010; 16:604–9.
Centers for Disease Control and Prevention. https://www.cdc.gov/hai/eip/cdiff-tracking.html

Current and Emerging Pharmacologic and Non-Pharmacologic Therapies

Anne Gonzales-Luna, PharmD, BCIDP
Research Assistant Professor
The University of Houston College of Pharmacy
Houston, Texas

Treatment Overview

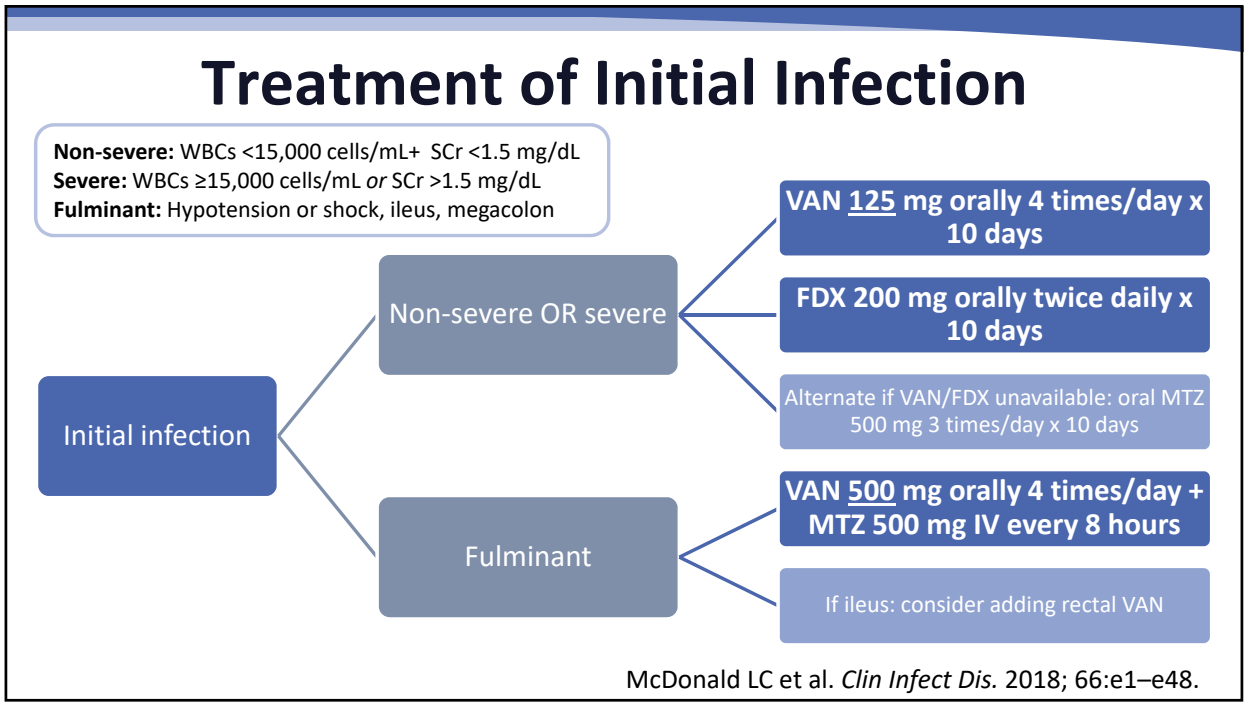


CDI Treatment Guidelines

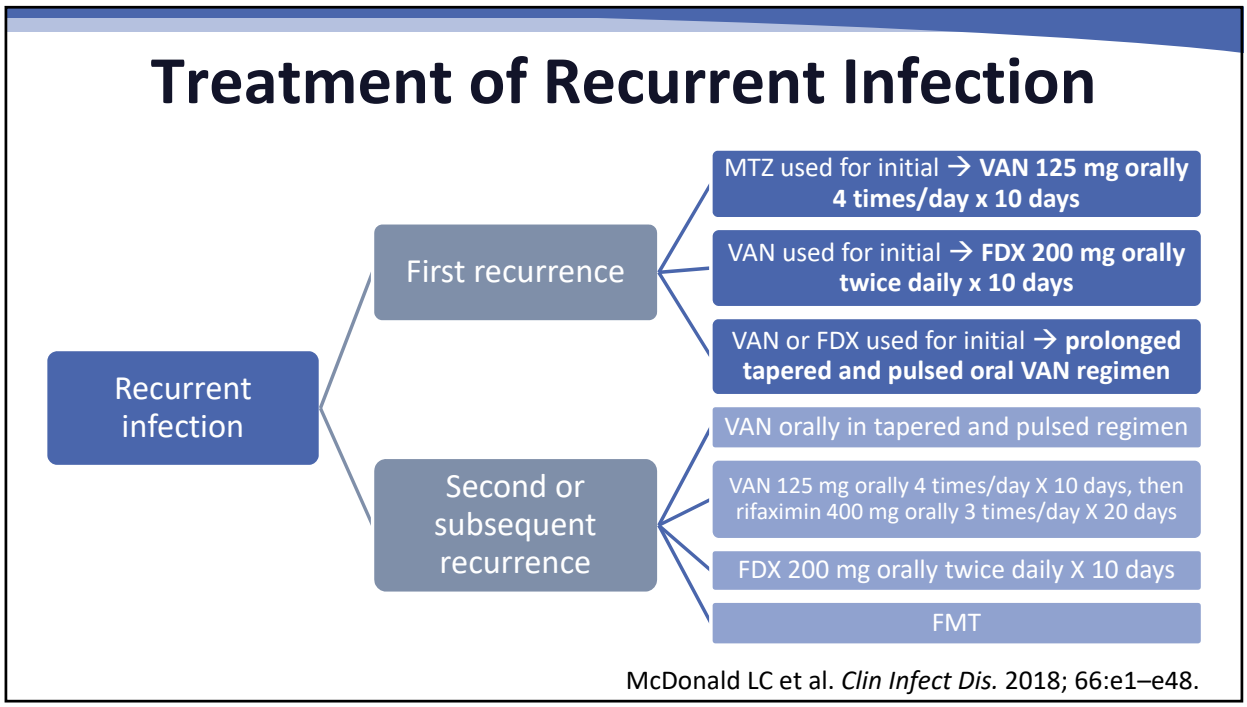
- Clinical Practice Guidelines for *Clostridioides difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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

Prevention and Treatment of Recurrent *Clostridioides difficile* Infection



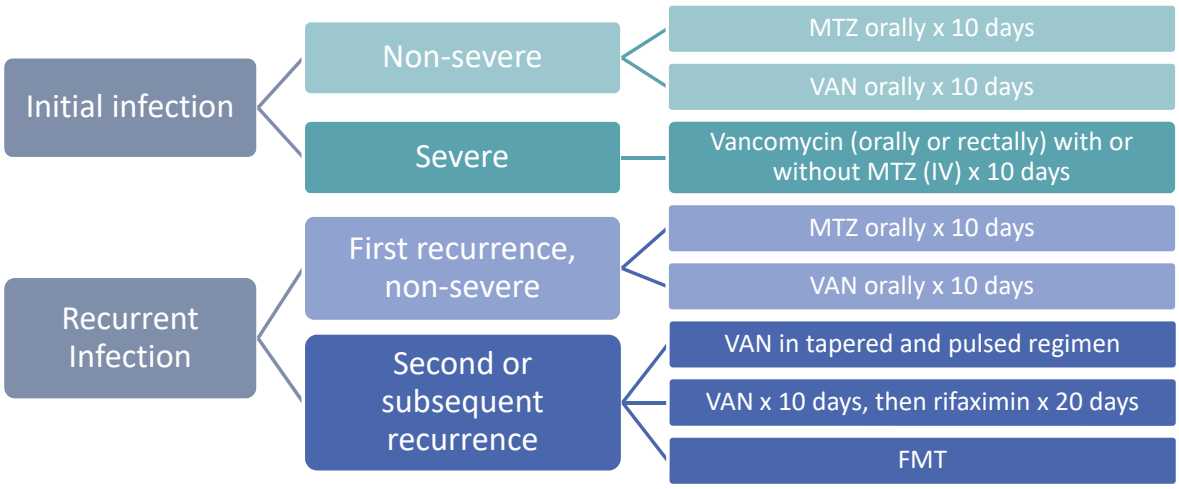
McDonald LC et al. *Clin Infect Dis.* 2018; 66:e1–e48.



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

Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

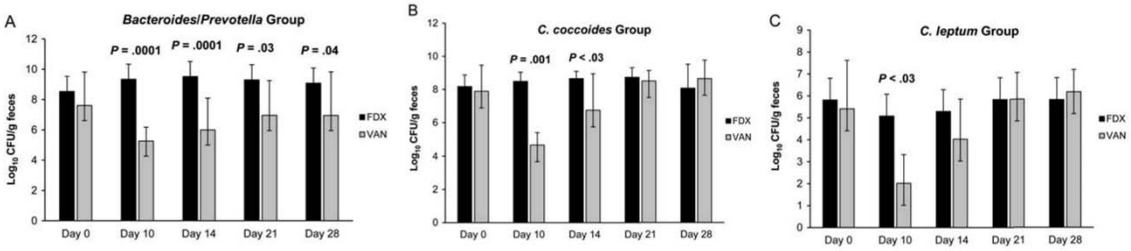
Pediatric CDI Recommendations



MTZ: 7.5 mg/kg/dose (max 500 mg) three or four times/day
VAN: 10 mg/kg/dose (max 500 mg) four times/day

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

Benefits of Fidaxomicin

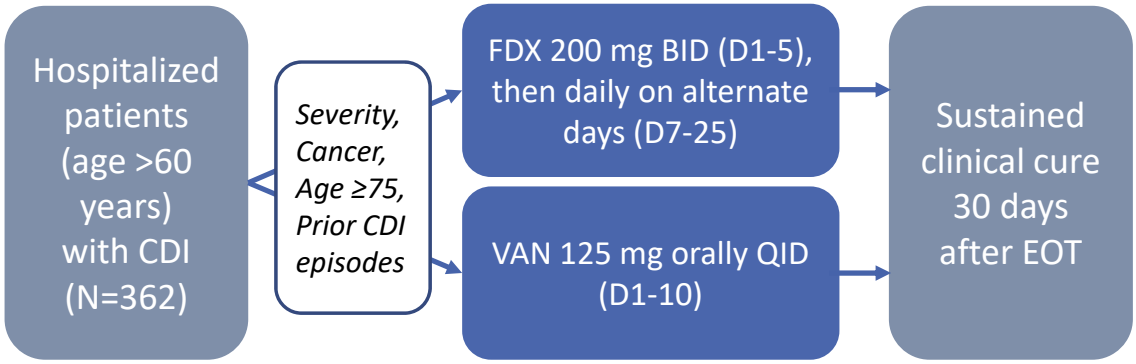


- Preservation of the intestinal microbiome during and after CDI treatment
- Prevents reappearance of stool toxin
  - Seen in 28% (26/94) of VAN-treated patients compared with 14% (13/91) of FDX-treated patients (P = 0.03)
- Adheres to *C. difficile* spores to inhibit germination and growth

Louie TJ et al. *Clin Infect Dis.* 2012; 55(Suppl 2):S132–42. Chilton CH et al. *PLoS One.* 2016; 11:e0161200.

Extended-pulsed Fidaxomicin (EPFX)

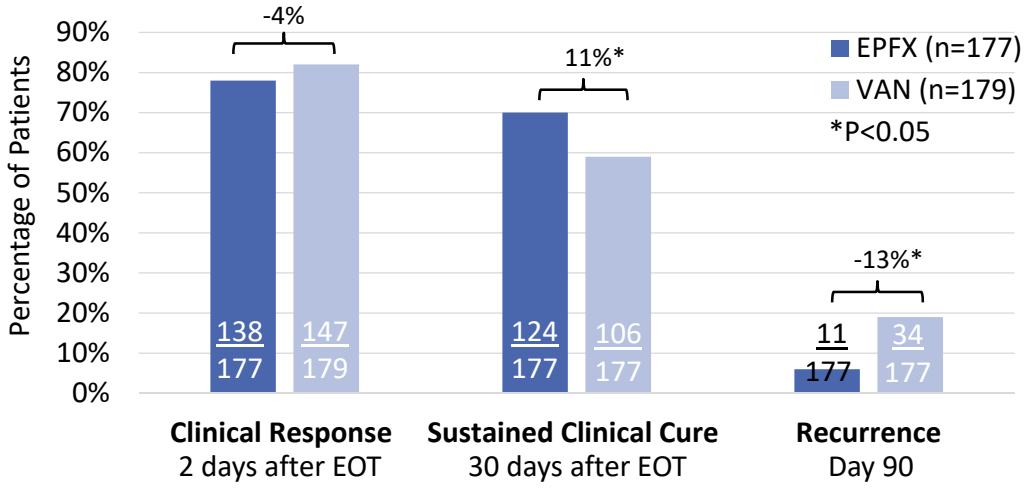
- EXTEND trial: randomized, controlled, open-label, superiority study



D = day; EOT = end of treatment

Guery B et al. *Lancet Infect Dis.* 2018; 18:296-307.

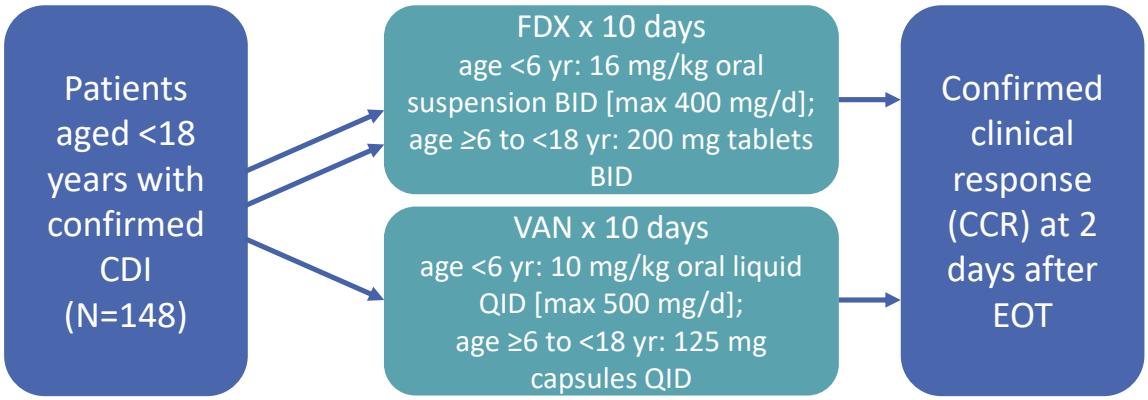
EXTEND Trial Outcomes



Guery B et al. *Lancet Infect Dis.* 2018; 18:296-307.

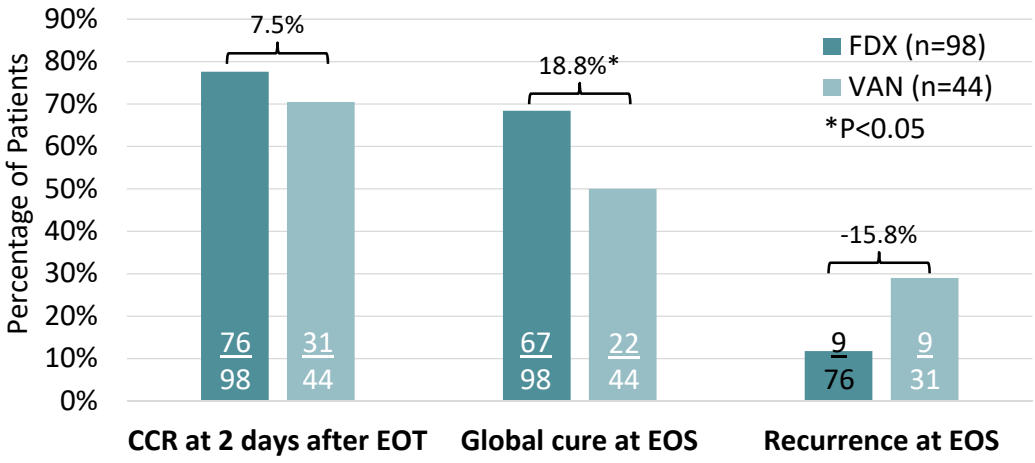
Fidaxomicin SUNSHINE Trial

- Randomized, investigator-blinded, non-inferiority study of fidaxomicin in children and adolescents



Wolf et al. *Clin Infect Dis*. 2019; ciz1149.

SUNSHINE Trial Outcomes



EOS = end of study, 30 days after EOT

Wolf et al. *Clin Infect Dis*. 2019; ciz1149.

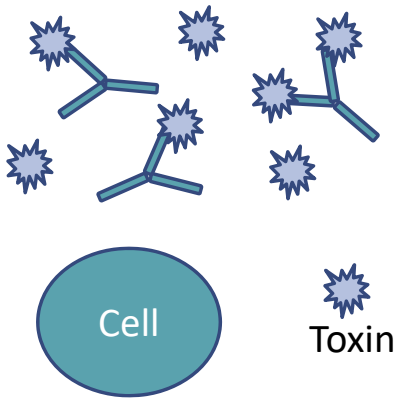
Fidaxomicin for Pediatric Patients

- New FDA-approved formulation: oral suspension
- New FDA-approved indication: treatment of CDI in children aged ≥6 months
  - Oral tablets (weight ≥12.5 kg and able to swallow tablets): 200 mg tablet BID x 10 days
  - Oral suspension (weight ≥4 kg): Weight-based dosing* BID x 10 days

*See package insert for full dosing recommendations.
Dificid (fidaxomicin) prescribing information. Merck & Co., Inc. 2020 Apr.

Bezlotoxumab

- Human monoclonal antibody that binds *C. difficile* toxin B
- Approved by FDA in June 2016
  - Secondary prevention of patients at high risk of rCDI who are receiving CDI treatment



MODIFY trials

- Two double-blind, randomized, placebo-controlled phase 3 trials (MODIFY I & II)

Adults receiving oral SOC antibiotic therapy for CDI (N=2,655)

+

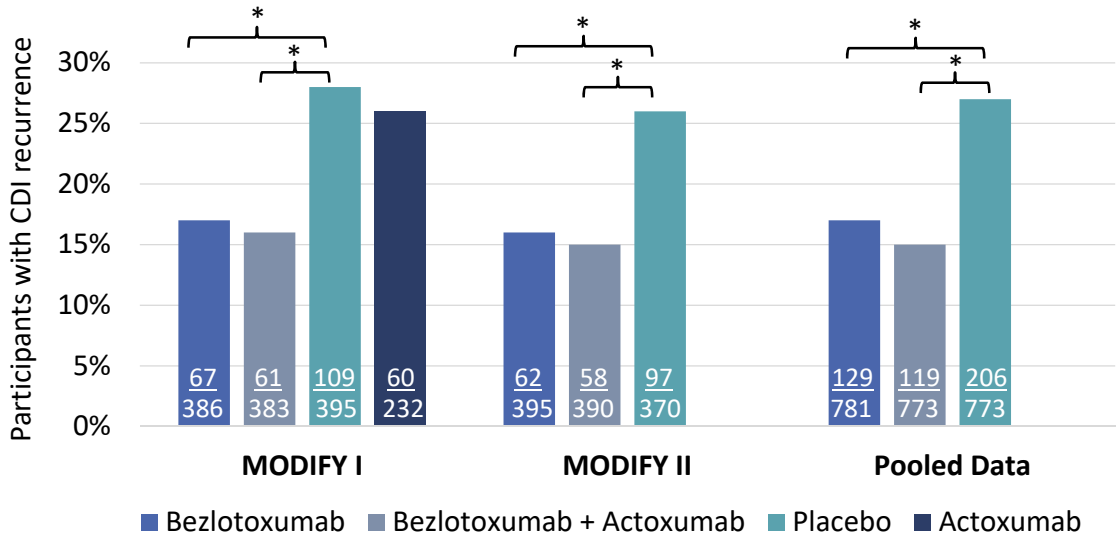
- bezlotoxumab 10 mg/kg
- actoxumab* 10 mg/kg
- bezlotoxumab + actoxumab 10 mg/kg each
- placebo

→ CDI Recurrence at 12 weeks

*Actoxumab alone in MODIFY I only

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

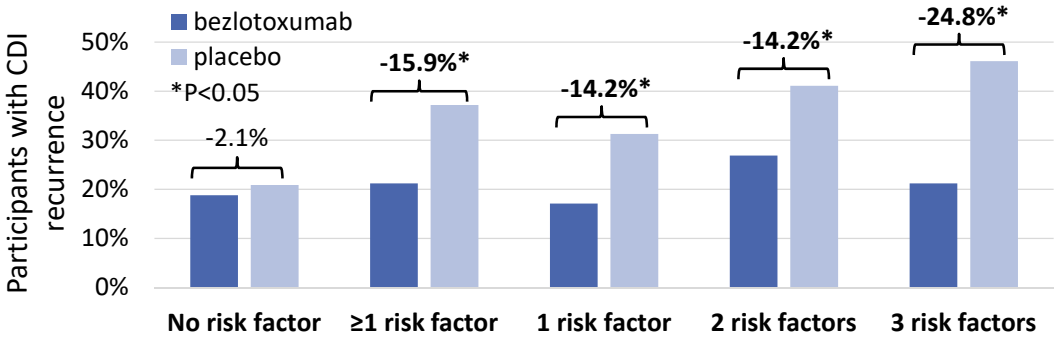
MODIFY Trials: 12-week Recurrence



*P<0.001

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

Bezlotoxumab in High-Risk Patients



Risk factors:

- Age ≥65 years
- History of CDI in prior 6 months
- Immunocompromised
- Severe CDI
- Infection with CDI ribotype 027, 078, or 244

Gerding DN et al. *Clin Infect Dis*. 2018; 67(5):649-56.

Bezlotoxumab Considerations

- Bezlotoxumab was associated with significantly lower rates of rCDI versus placebo
  - Patients with ≥3 risk factors had the greatest reduction of rCDI, but those with 1 or 2 risk factors also benefited
- Adverse reactions
  - Patients with heart failure experienced more adverse events & death with bezlotoxumab compared with placebo

Wilcox MH et al. *N Engl J Med*. 2017; 376:305-17. Gerding DN et al. *Clin Infect Dis.* 2018; 67:649-56.

CDI Antimicrobial Pipeline

Antibiotic	Mechanism of action	Formulation	Dose(s) under study	Clinical trials
Ridinilazole	Unknown	Oral capsule	200 mg twice daily x 10 days	Complete: Phase I, CoDIFy phase II Ongoing: Ri-CoDIFy phase III
LFF571	Elongation factor Tu (EF-Tu) inhibitor	Oral capsule	200 mg four times daily x 10 days	Complete: Phase I, Phase II
Ramoplanin	Peptidoglycan synthesis inhibitor	Oral	400 mg twice daily x 10 days	Complete: Phase I, Phase II
MGB-BP-3	Unknown	Oral	Unknown dose x 10 days	Complete: Phase I Ongoing: Phase II
DNV3837/DNV3681	Protein synthesis inhibitor (oxazolidinone-quinolone hybrid)	Intravenous solution	6 mg/kg infused at a rate of 0.5 mg/kg/hr over 12 hours x 10 days	Complete: Phase I Ongoing: Phase II
Ibezapolstat	DNA polymerase IIIC (pol IIIC) inhibitor	Oral capsule	450 mg twice daily x 10 days	Complete: Phase I Ongoing: Phase II

Carlson TJ, Gonzales-Luna AJ. *Curr Infect Dis Rep*. 2020; 22:20.

CDI Biotherapeutic Pipeline

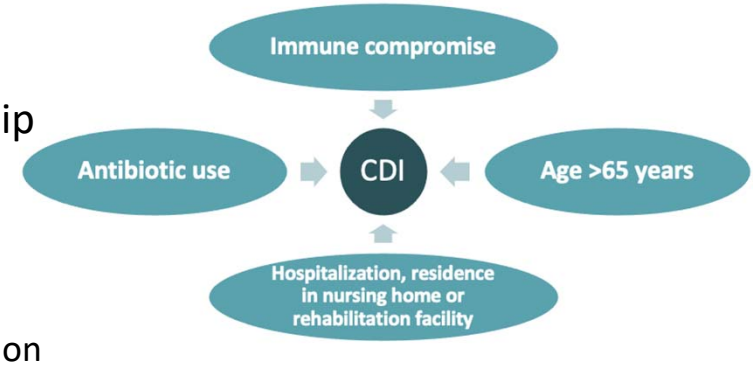
Agent	Composition	Formulation	Dose(s) under study*	Clinical trials
CP101	Lyophilized microbiota from human fecal donors	Oral capsule	1 capsule given one time	Complete: PRISM3 phase II Ongoing: PRISM-EXT phase II
RBX2660 & RBX7455	RBX2660: Live bacterial suspension derived and standardized from human fecal donors RBX7455: Lyophilized oral formulation of RBX2660; stable at room temperature	Retention enema Oral capsule	Unknown Multiple doses for 2-4 days	RBX2660: Complete: PUNCH CD phase II, PUNCH CD 2 phase II, PUNCH Open Label phase II Ongoing: PUNCH CD3 phase III, PUNCH CD3-OLS phase III *RBX7455:* Complete: Phase I
SER-109	Firmicutes spores from healthy donor stool specimens (undefined consortium)	Oral capsule	4 capsules once daily for 3 days (phase III)	Complete: Phase Ib study, ECOSPOR phase II Ongoing: ECOSPORIII phase III, ECOSPORIV phase III
VE303	Clonal human commensal bacteria strains manufactured from clonal cell banks	Oral capsule	Multiple doses for 14 days	Complete: Phase I Ongoing: CONSORTIUM Phase II

*Following ≥10-14 days of SOC antibiotics

Gonzales-Luna AJ, Carlson TJ. *Curr Infect Dis Rep.* 2020; 22:22.

Non-Pharmacologic Therapies

- Minimize modifiable host risk factors
- Diagnostic stewardship
- Infection prevention and control
  - Hand hygiene
  - Appropriate sterilization of healthcare facilities



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

The Role of Antimicrobial Stewardship

Implement antimicrobial stewardship programs (ASPs)

ASP implementation has been associated with a 52% risk reduction in CDI rate

Discontinue inciting antibiotic agent(s) as soon as possible

Continued antibiotic use is associated with decreases in clinical response rates and increases in CDI recurrence rates

Treat CDI for 10-day duration

May consider 14 days in patients with continued symptoms after 10 days of treatment

Feazel LM et al. *J Antimicrob Chemother.* 2014; 69:1748-54. Barlam TF et al. *Clin Infect Dis.* 2016; 62:e51–e77. Moehring RW et al. *Clin Infect Dis.* 2016; 64:377-83. Mullane KM et al. *Clin Infect Dis.* 2011; 53:440–7. McDonald LC et al. *Clin Infect Dis.* 2018; 66:e1–e48.

Key Takeaways

- CDI is a microbiome-mediated disease
  - Treatment approaches should take impact on microbiome into consideration
- Pharmacists can help in the prevention of initial CDI and rCDI
  - Appropriate diagnostic testing and antimicrobial stewardship play key roles
- Future rCDI treatment and prevention strategies may look very different
  - Fidaxomicin results from EXTEND and SUNSHINE trials demonstrate benefit with novel dosing and in pediatric populations
  - Robust pipeline of antimicrobials and biotherapeutics in development

Selected Resources

- **CDC *C. difficile* Guidelines and Prevention Resources:** https://www.cdc.gov/cdiff/clinicians/resources.html
- **EXTEND Trial:** Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis.* 2018; 18(3): 296-307.
- Guh AY, Mu Y, Winston LG et al. Trends in U.S. Burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med.* 2020; 382(14), 1320 – 1330.
- Lessa FC, Mu Y, Bamberg WM et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med.* 2015; 372(9), 825–834.
- ***C. difficile* Treatment Guidelines:** McDonald CL, Gerding DN, Johnson S, et al. 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). *Clin Infect Dis*. 2018; 66:e1–e48.
- **MODIFY I/II Trial:** Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection. *N Engl J Med.* 2017; 376(4): 305-17.
- **SUNSHINE Trial:** Wolf J, Kalocsai K, Fortuny C, et al. Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with *Clostridioides (Clostridium) difficile* Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE). *Clin Infect Dis.* 2019; ciz1149.

Consider these practice changes. Which will you make?

- Educate team members on factors that place patients at risk of recurrent CDI
- Educate team members on the emerging and current treatment options for managing patients with recurrent CDI
- Incorporate current evidence-based guidelines into practice when treating patients with recurrent CDI
- Collaborate with other healthcare professionals to formulate care plans for treating patients with recurrent CDI
- Collaborate with other healthcare professionals to develop strategies to prevent recurrent CDI