What is New with *Clostridioides difficile* Infection (CDI) and the Microbiome?

Andrea C. Scherschel, MSN, FNP PhD(c)

Senior Medical Science Liaison

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Disclosures:

I am employed by Seres Therapeutics as a Medical Science Liaison and work within the Medical Affairs Division of the company and own stock in the company.

Objectives:

- Describe the current epidemiology of *Clostridioides difficile infection* (CDI) and recurrent CDI in the United States
- Explain the role of the microbiome in human health and its importance in the pathogenesis of CDI
- Understand the role of currently available diagnostic tests in the diagnosis of *Clostridioides difficile* and recurrent CDI
- Discuss the risks and benefits of microbiota restoration therapies available for patients with recurrent *Clostridioides difficile* infection

Burden of *Clostridioides difficile* Infection (CDI)

Clostridioides difficile Infection (CDI) Overview

Clostridioides (formerly _Clostridium_) _difficile_ is a spore-forming, toxin producing, gram-positive anaerobic bacterium

Pathogenesis[1]

- The pathogenesis of *C. difficile typically* occurs as a two-hit process
  - **Microbiome disruption** usually caused by broad spectrum antibiotics
  - **Exposure to *C. difficile* spores**

Symptoms[2,3]

- Watery diarrhea (typically ≥3 but as many as 15-20 bowel movements a day)
- Fever, abdominal pain and cramping, loss of appetite, nausea, and weight loss
- Can progress to life-threatening colitis and toxic megacolon

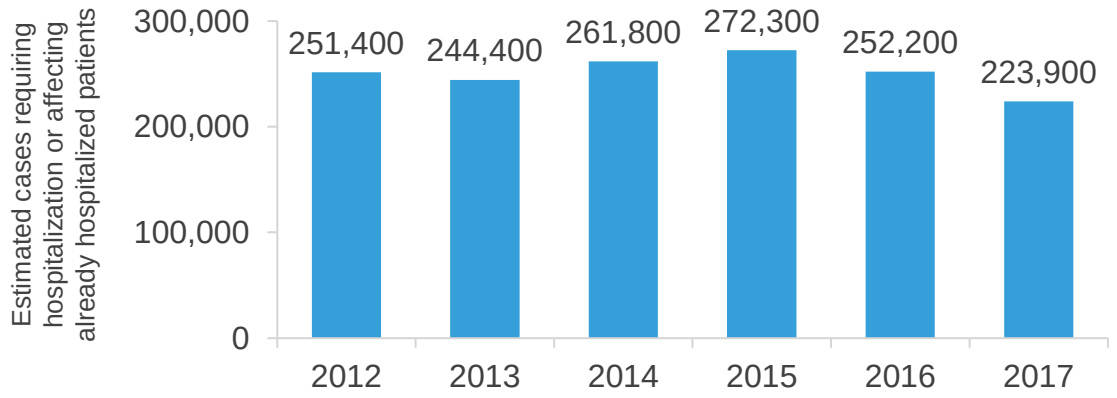
Risk Factors[2,4]

- **Use of antibiotics**, especially
  - Fluoroquinolones
  - Clindamycin
  - Broad spectrum β - lactams
- **Age ≥ 65 years**
- Immunosuppression (e.g., chemotherapy, HSCT, solid organ transplant)
- Proton pump inhibitors (PPIs)
- Prolonged hospitalization
- Inflammatory Bowel Disease (IBD)
- Gastrointestinal surgery

1) Wilcox M., et al. *Open Forum Infectious Disease* 2020;7(5):ofaa114; 2) Lamont et al. *UpToDate* (2021); 3) Ofosu, A. *Ann Gastroenterol* 2016;29(2):147-54; 4) McDonald, et al., *Clin Infect Dis* 2018;66(1):e1-e48)

CDI is Considered an Urgent Threat by the CDC

Cases Over Time[1]



- The estimated national burden of CDI was 462,100 cases in 2017[2]
- Burden of community-associated CDI in the US **did not** change with 170,000 cases in 2011 and 170,300 in 2017[2]
- Approximately 25% of patients develop a recurrence of CDI within 8 weeks of their initial episode, increasing to >40% after the first recurrence[2,3]

1) Centers for Disease Control, 2019. 2) Guh AY, et al. *N Engl, J Med*;382:1320-33; 3) Desai K, et al. *BMC Infect Dis* 2016;16:303;

Exposure to Broad Spectrum Antibiotics and Previous CDI are Risk Factors for CDI and Recurrent CDI (rCDI)

Antibiotic Use

- Increased age (≥ 65 years)
- Female
- History of hospitalization or long-term care residence
- Comorbidities (e.g., diabetes, renal insufficiency)
- Immunosuppression or immunocompromised
- Inflammatory bowel disease
- Proton pump inhibitor use
- Gastrointestinal surgery

Additional Risks for rCDI

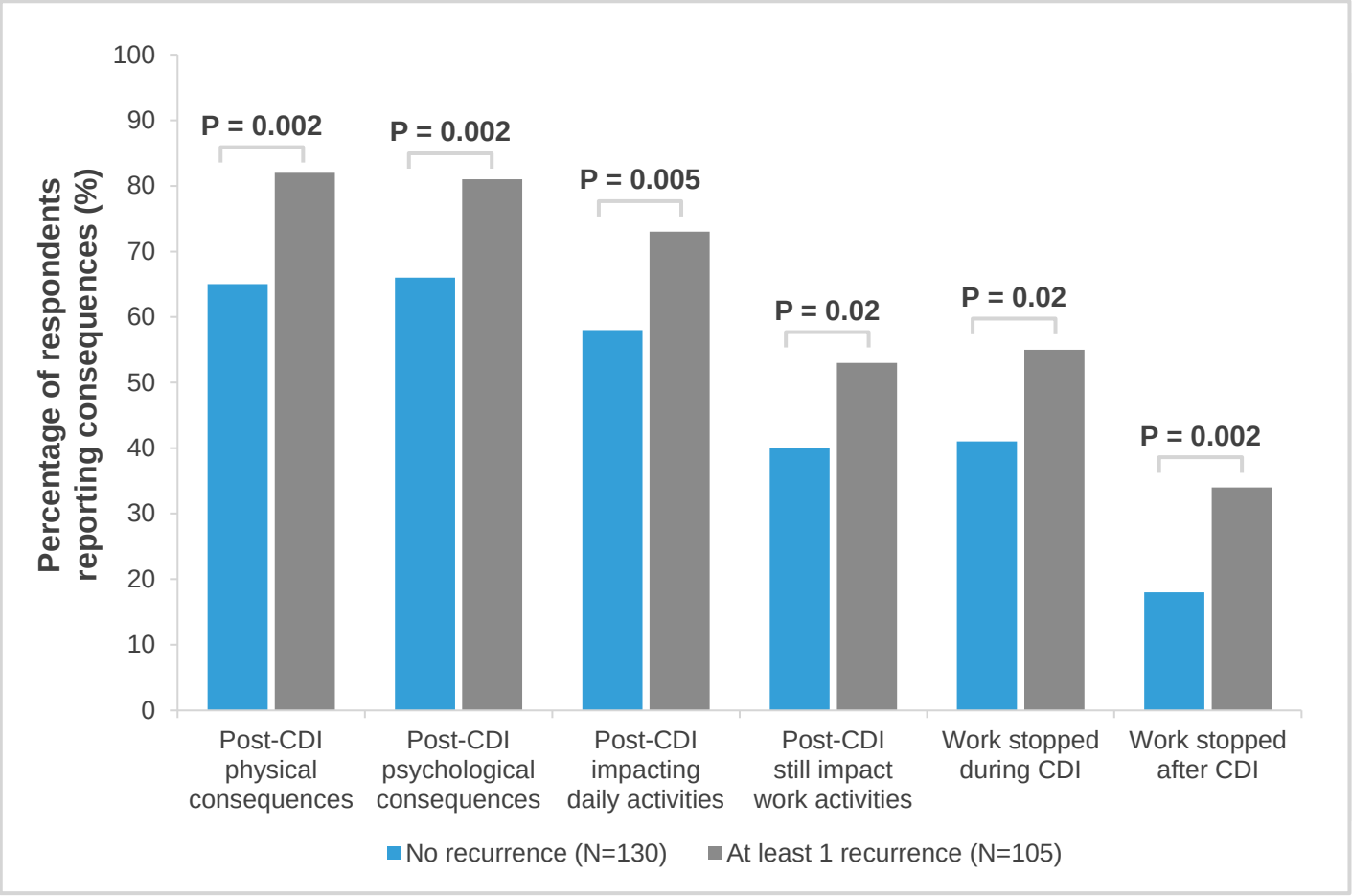
History of recurrence

C. difficile ribotype/ virulence / severity

Prolonged inpatient status

1) McDonald, et al., Clin Infect Dis 2018;66(1):e1-e48); 2) Kelly CR, et al. Ann Intern Med 2016;165:609-16; 3) Gerding DN, et al. Clin Infect Dis 2018; 67(1):649-56; 4) Hota SS, et al. Clin Infect Dis 2017; 64(3):265-71; 5) Fekety R, et al Clin Infect Dis 1997;24:324-33

Quality of Life in Patients with and without Recurrent CDI



Observational, cross-sectional study in subjects with self-reported CDI. Self-administered online survey (N=350)

- 115 subjects reported CDI at time of survey
- 44.7% of patients with past CDI reported a recurrence, of these patients, 50% had ≥3 recurrences

92% reported fear of worsening CDI; this fear remained even after clearing the infection

- In those with a history of IBS, 25% had ongoing symptoms ≥ 6 months after completion of treatment

Individuals reported that depression was three times greater than the US adult population

Almost all subjects expressed fear of having to take a future antibiotic

Lurienne L. et al. J Pat Rep Outcomes. 2020; 4:14

C. difficile Infection Pathogenesis

CDI is a Two-hit Process

Leading risk factor for CDI is exposure to broad spectrum antibiotics, which cause collateral damage to the beneficial bacteria that form the first line defense against *C. difficile*

Wilcox M, et al. Open Forum Infectious Diseases. 2020;7(5):ofaa114; Theriot CM, et al. Ann Rev Microbiol 2015;69:445-61
Crobach MJT, et al. Clin Microbiol Rev 2018;31:e00021-17

Due to the Two-phase Life Cycle of *C. difficile*, Antibiotic Therapy is Necessary but Often Insufficient for Many Patients

When the microbiome is disrupted by broad-spectrum antibiotics, *C. difficile* spores germinate into toxin-producing bacteria

→

Onset of symptomatic disease

Vegetative bacteria

Antibiotics kill vegetative bacteria that produce toxin

Spores

Antibiotics without any effect on reservoir of *C. difficile* spores

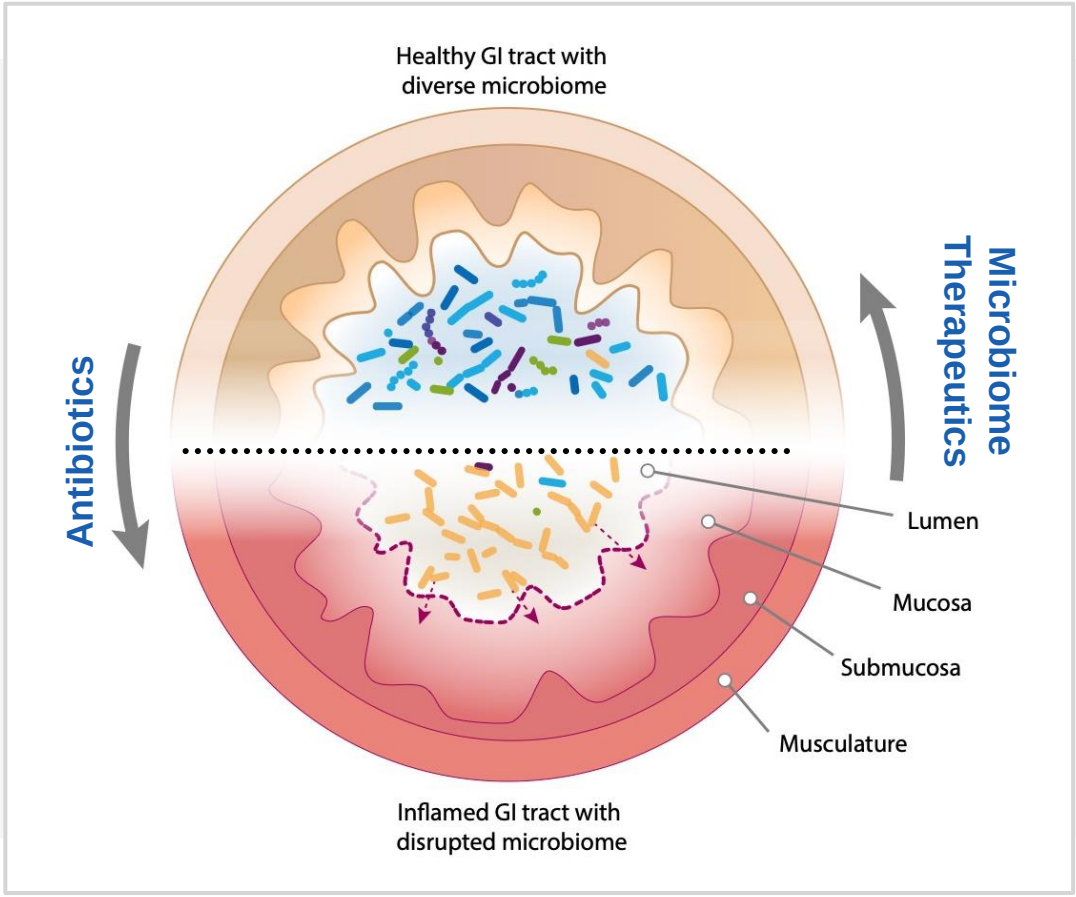
Symptoms recur because a dysfunctional microbiome facilitates spore germination

McGovern, BH et al. *Clin Infect Dis* 2020;ciaa387; Theroit CM et al. *mSphere* 2016;1(1):e00045-15

Microbiome Therapeutics Can Restore Host Defenses Against Potential Pathogens and Improve Clinical Outcomes

GI tract is a reservoir for potential bacterial invaders

- A diverse microbiome is essential to prevent colonization and infection with potential pathogens[1]
- Antibiotics drive loss of beneficial bacteria, enabling *C. difficile* and drug-resistant bacteria to expand in GI tract[2]



1. Pamer, E., Science 2016
2. Taur et al, Clin Infect Dis, 2012
3. Tamburini et al, Nat Med 2018

Diagnostic Testing Methods for CDI

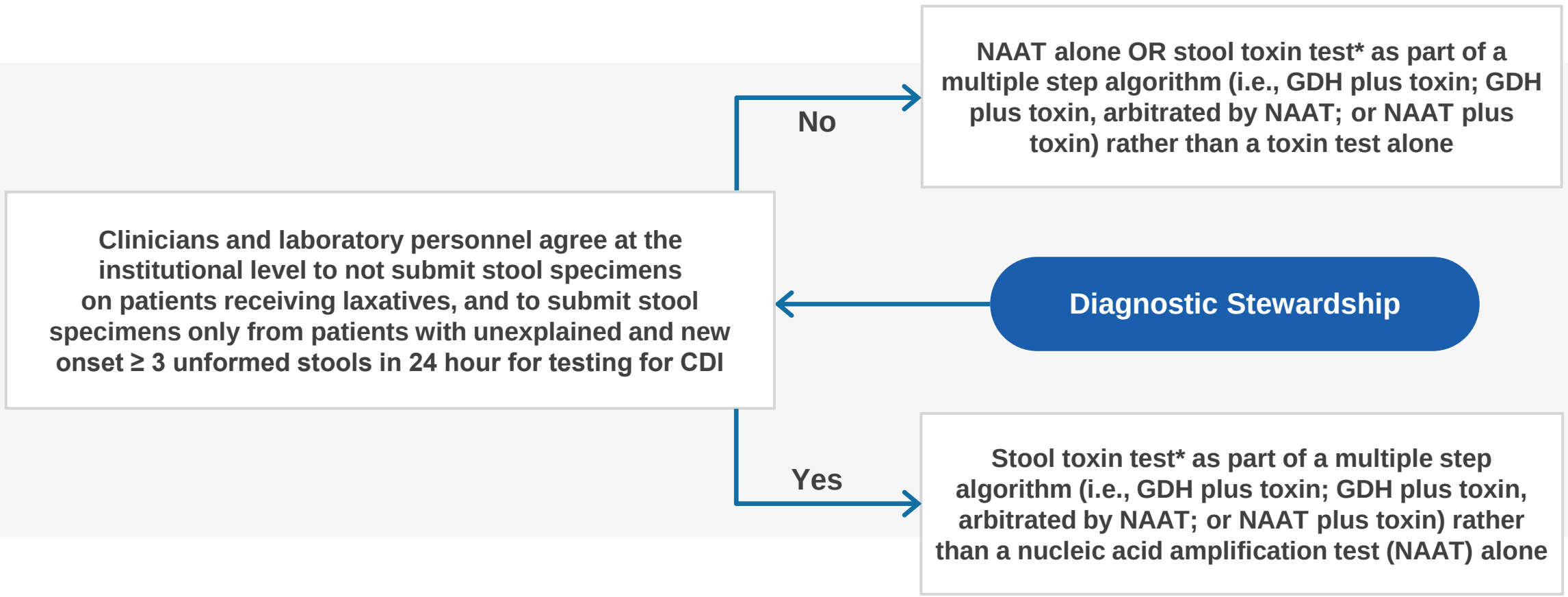
Pooled Sensitivity and Specificity of Available Tests for *C. difficile* Infection

Test	Substance Detected	Sensitivity (95% CI) Compared to Toxigenic Culture	Specificity (95% CI) Compared to Toxigenic Culture
Nucleic acid amplification test (NAAT)	*C. Difficile* (*tcdA, tcdB*, binary toxin genes) genes	0.95 (0.92-0.97)	0.98 (0.97-0.99)
Glutamate dehydrogenase (GDH) enzyme immunoassay	*C. Difficile* common antigen	0.96 (0.86-0.99)	0.96 (0.91-0.98)
Toxin A and Toxin B enzyme immunoassays (EIA)	Free toxin A and B	0.57 (0.51-0.63)	0.99 (0.98-0.99)

Use of a 2-step testing algorithm is the preferred testing method for optimal diagnostic accuracy – American College of Gastroenterology

Kelly, CR et al. Am J Gastroenterol 2021: 1124-47 | Crobach MJT, et al. CMI 2016;22:S63

SHEA/IDSA Diagnostic Guidelines 2018



*Approved stool EIA toxin tests vary widely in sensitivity. Laboratories should choose a toxin test sensitivity in the upper range of sensitivity as reported in the literature

McDonald LC et al. Clin Infect Dis 2018;66(7):e1-e48

2021 Focused Update IDSA/SHEA Guidelines on Management of CDI in Adults

Clinical Definition	Supportive Clinical Data	Recommended and Alternative Treatment	Strength of Recommendation / Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤ 15,000 cells/mL and serum creatinine level <1.5 mg/dL	**Preferred**: FDX 200 mg given 2x daily for 10 days	Conditional / moderate
		Alternative: VAN 125 mg given 4x daily by mouth for 10 days	
		Alternate if above agents are unavailable, metronidazole 500 mg 3x daily by mouth for 10 days	Weak / high
Initial episode, severe	Leukocytosis with a white blood cell count of ≥ 15,000 cells/mL or a serum creatinine level >1.5 mg/dL	**Preferred**: FDX 200 mg given 2x daily for 10 days	Conditional / moderate
		Alternative: VAN 125 mg given 4x daily by mouth for 10 days	
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN 500 mg 4x daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. IV administrated metronidazole should be administered together with oral or rectal VAN, particularly if ileus is present	Strong / moderate (oral VAN)
			Weak / low (rectal VAN)
			Strong / moderate (IV metronidazole)

Johnson S, et al. Clin Infect Dis 2021;June 24:ciab549

2021 Focused Update IDSA/SHEA Guidelines on Management of CDI in Adults

Clinical Definition	Recommended and Alternative Treatment	Strength of Recommendation / Quality of Evidence
First recurrence	**Preferred**: FDX 200 mg given 2x daily for 10 days OR 2x daily for 5 days followed by once every other day for 20 days	Conditional / low
	Alternative: Prolonged tapered and pulsed VAN (e.g., 125 mg 4x daily for 10-14 days, 2x daily for 7 days, 1x daily for 1 week, and then every 2 or 3 days for 2-8 weeks)	
	Alternative: VAN 125 mg given 4x daily by mouth for 10 days	
	Adjunctive treatment: Bezlotoxumab 10 mg/kg intravenously once during administration of standard of care antibiotics**	Conditional / very low ***Data when combined with FDX are limited. Caution for use in patient with congestive heart failure (CHF)
Second or subsequent recurrence	VAN in a tapered and pulse regimen	Weak / low
	VAN 125 mg given 4x daily by mouth for 10 days followed by rifaximin 400 mg 3x daily for 20 days	Weak / low
	FDX 200 mg given 2x daily for 10 days OR twice daily for 5 days followed by 1x every other day for 20 days	Weak / low
	FMT	Strong / moderate
	Adjunctive treatment: Bezlotoxumab 10 mg/kg intravenously once during administration of standard of care antibiotics**	See above comments***

** Bezlotoxumab may be considered for patients at risk for CDI recurrence including age >65 years, immunocompromised host, and severe CDI on presentation; *** FDA warns " in patients with CHF, bezlotoxumab should be reserved for use when benefits outweighs risk.
Johnson S, et al. Clin Infect Dis 2021;June 24:ciab549

Therapeutic Options Remain Limited for Recurrent CDI

Current treatments target *C. difficile* toxin production but do not repair the disrupted microbiome, which facilitates recurrent infection and recurrent debilitating symptoms

Antibiotics shut down toxin-producing bacteria

Monoclonal antibodies bind toxin B

Sustained clinical response rates remain low since no approved treatments eradicate *C. difficile spores*, which rapidly germinate into toxin-producing bacteria within a disrupted microbiome

1) Louie TJ, et al. Clin Infect Dis. 2012;55 (suppl 2):S132-42; 2) McDonald LC, et al. Clin Infect Dis 2018; 66(7):e1-e48

Recovery of Firmicutes are Key to Sustained Clinical Response

Fecal Transplant as Proof-of-concept

Within days of stool transplant

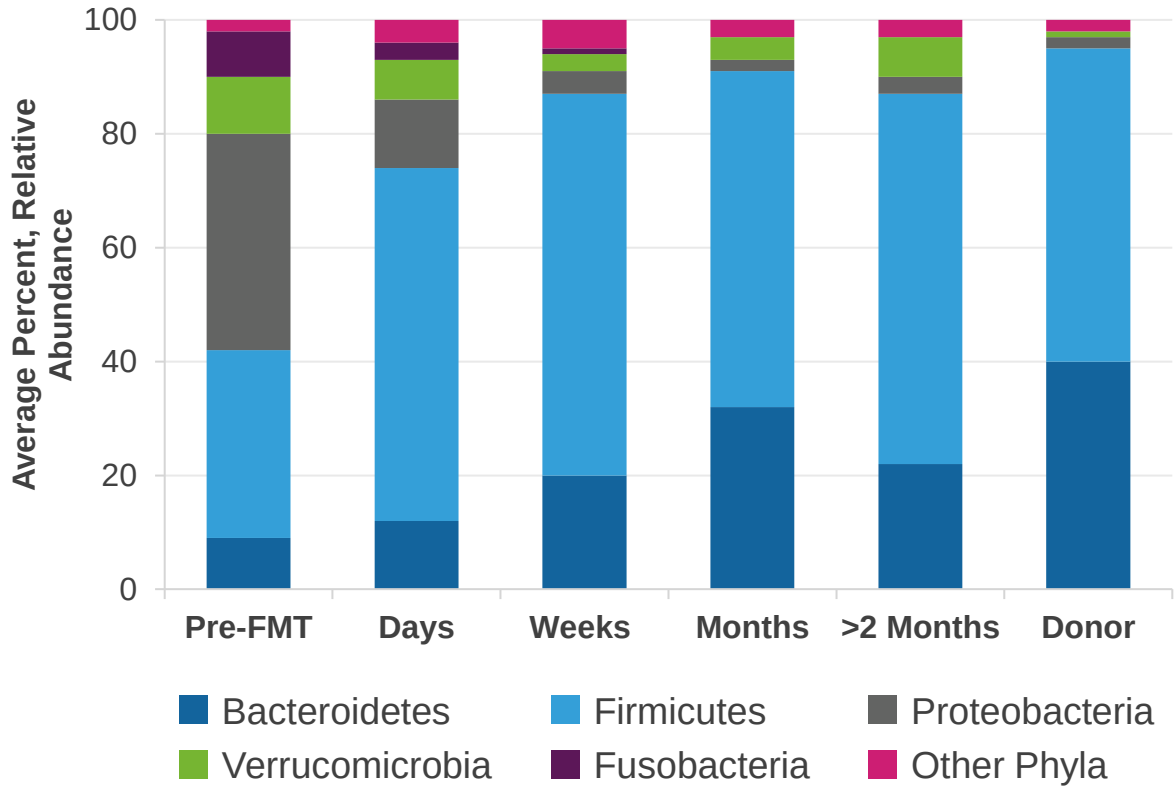
- Spore-forming Firmicutes bacteria are gained
- Pro-inflammatory Proteobacteria are lost

By 30-60 days

- Changes in Bacteroidetes

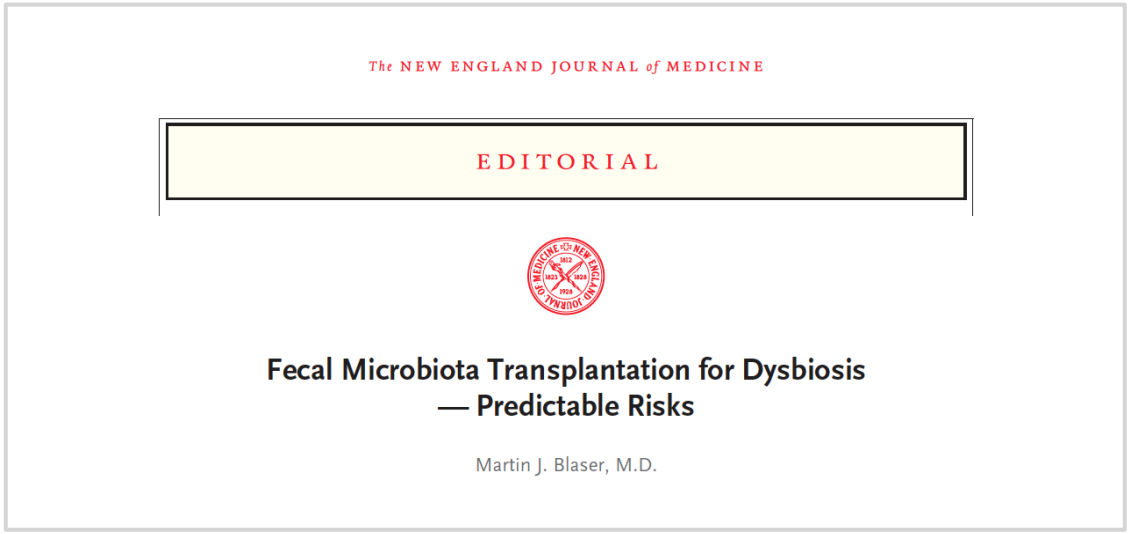
Timing of changes suggest that Firmicutes are a key driver to clinical outcomes

- Critical for generating important metabolites (e.g., metabolism of bile acids)



Staley C, et al. Amer J Gastro 2017; 112:940-947; Jiang Z, PLoS One 2018; e0205064; Blount K Open Forum Infect Dis 2019;6 ofz095

FMT and Investigational FMT Drug Products are Vulnerable to Emerging infections



Concerns About Transmission[4] of SARS-CoV-2

Using complete communities of bacteria may be associated with risk when new infections are not detected[3]

1) DeFillip Z, et al. N Eng J Med 2019; 381:2043-2050; 2) Blaser M, et al. N Eng J Med 2019; 381:2064-2066; 3) Wilcox M et al. Open Forum Infect Dis 2020; 7: ofaa114; 4) Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Additional Safety Protections Pertaining to SARS-CoV-2 and COVID-19 | FDA (accessed July 15, 2021)

Therapeutics for Recurrent *C. difficile* in Late-stage Development Pipeline

	Material Source	Composition	Delivery	Dosing	Clinical Trial
Rebiotix *RBX-2660*	Donor-derived	Full-spectrum	Enema	—	PUNCH-CD3 Phase 3 NCT03244644 BLA filing completed November 2021
Seres *SER-109*	Donor-derived	Enriched Firmicutes Spores	Capsule	4 capsules daily for 3 days	ECOSPOR III Phase 3 NCT03183128
Vedanta *VE 303*	Fermented Strain	8 clonal human commensal bacterial strains	Capsules	2 -10 capsules daily for 14 days	Phase 2 NCT03788434
Finch *CP101*	Donor-derived	Full-spectrum	Capsule	10 capsules single dose	PRISM 4 Phase 3 NCT05153499
Destiny Pharma NTCD M3	Fermented Strain	Non-toxigenic *C. difficile*	Oral Liquid	10 mL daily for 7 to 14 days	Phase 2 NCT01259726

Disease State Summary of *Clostridioides difficile* Infection (CDI)

CDI Disease State Overview Key Takeaways

C. difficile is an urgent threat pathogen and CDI is a leading healthcare associated infection causing debilitating diarrhea, life-threatening complications, and significant societal and economic burden

Recurrent CDI prevalence estimates are around 20-25%, increasing to >40% after first recurrence

CDI occurs as a "two-hit" process requiring both microbiome disruption and exposure to _C. difficile_ spores that reside in the GI tract prior to antibiotic insult

CDI recurrence is rapid and indicates that the host microbiome is not resilient enough to recover spontaneously

There are currently few options available for the treatment of recurrent CDI

Treatment of recurrent CDI merits a two-pronged approach including antibiotics to treat toxin-producing _C. difficile_ and microbiome restoration to achieve a sustained clinical response

Patient and Prescriber Resources for Education, Assistance with Medications, Home Care, Advocacy and Available Clinical Trials for CDI

- Infectious Disease Society of America : www.idsociety.org
- American College of Gastroenterology : https://gi.org/guideline/
- C Diff Foundation : www.cdifffoundation.org
- National Transitions of Care Coalition : www.NTOCC.org
- Everything *C. diff* : www.everythingcdifficile.com
- C. Diff Survivors Network : www.cdiffsurvivors.org
- Centers for Disease Control and Prevention : www.cdc.gov/cdiff/prevent.html
- Peggy Lillis Foundation : www.peggyfoundation.org

Thank you!

Questions?