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April 30, 2024

Clostridioides Difficile: A Recurring Problem

Darra Drucker, PharmD

Project ECHO

Patient Case

CD is an 82-year-old female with past medical history of chronic kidney disease, hypertension, and **recurrent CDI (x2 prior episodes 7 and 4 weeks ago)** previously treated with PO vancomycin and PO fidaxomicin.

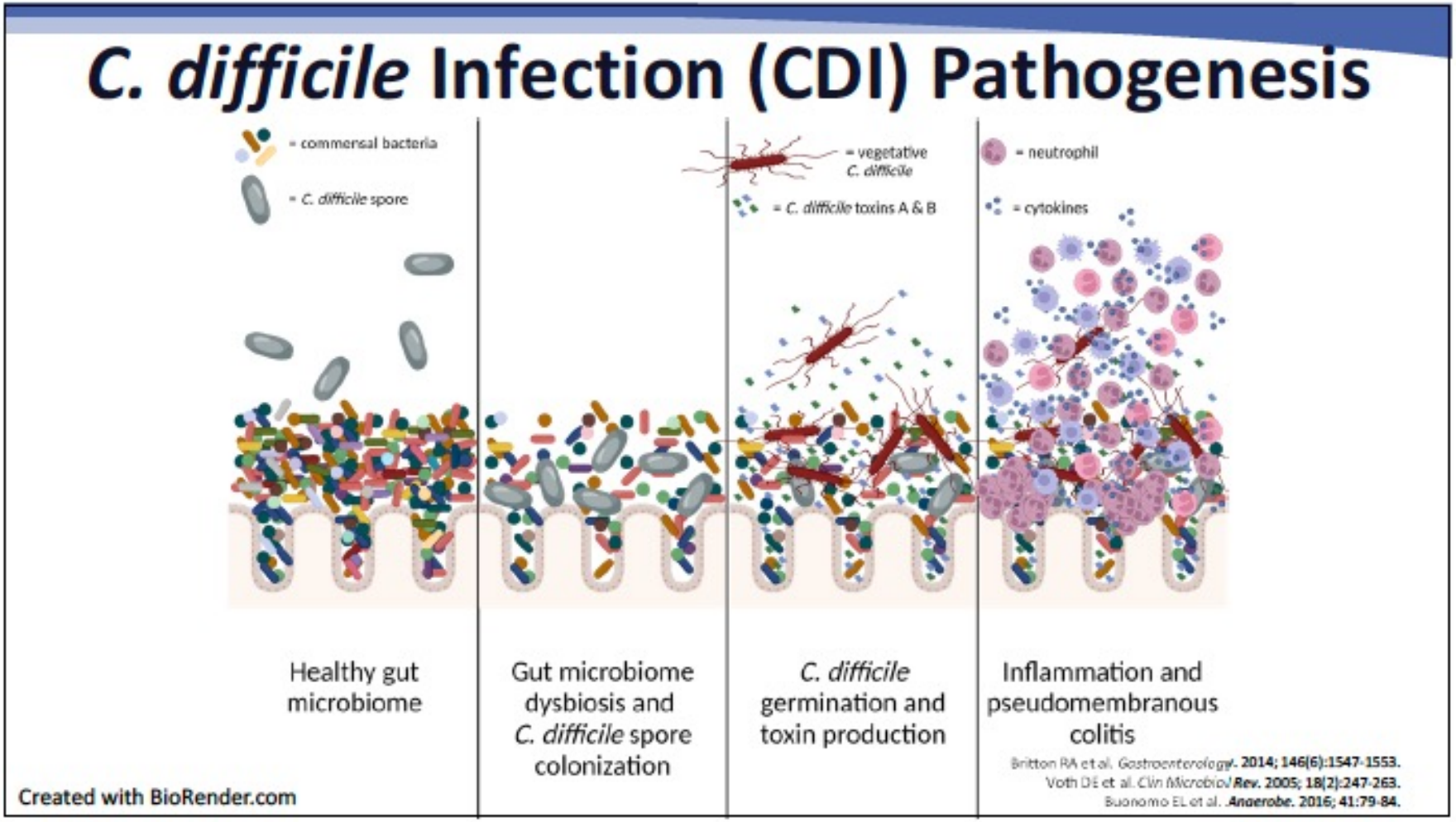
Patient presents to the ED from their nursing home again with complaints of new-onset diarrhea (10 episodes in 24 hours), abdominal cramping, and fever. Patient is not currently receiving a bowel regimen. *C. difficile* PCR stool test is positive. ED physician asks you your thoughts regarding **whether patient is a candidate for fecal microbiota transplantation.**

Audience Response

Do you have access to fecal microbiota transplantation (FMT) at your institution?

- Traditional FMT
- Rebyota
- Vowst
- None of the above
- I'm not sure

What is *Clostridiodes difficile*?



Slide from Dr. Travis J. Carlson, PharmD, BCIDP

Risk Factors for Recurrent CDI

Prior CDI episode in past 6 months

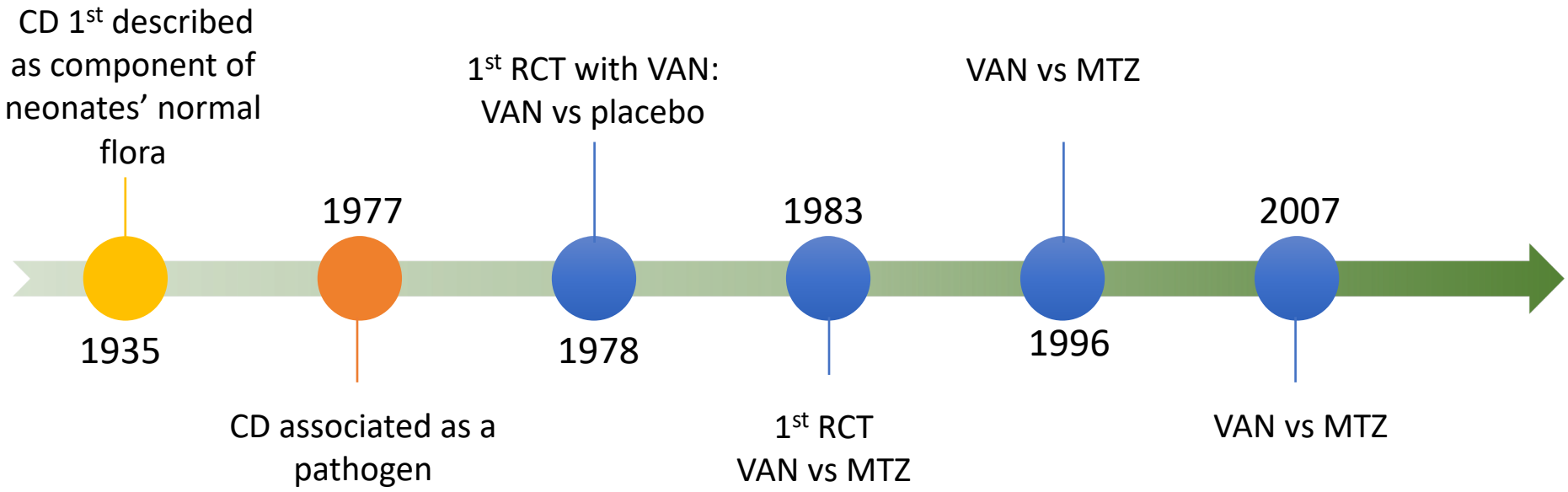
Immunocompromised

Severe CDI

Age ≥ 65 years

Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Kelly CR et al. *Am J Gastroenterol*. 2021; 116(6):1124-1147.
Van Prehn J et al. *Clin Microbiol Infect*. 2021; 27(Suppl 2):S1-S21.
Johnson S et al. *Clin Infect Dis*. 2021; 73(5):e1029-e1044.

History of CDI Treatment

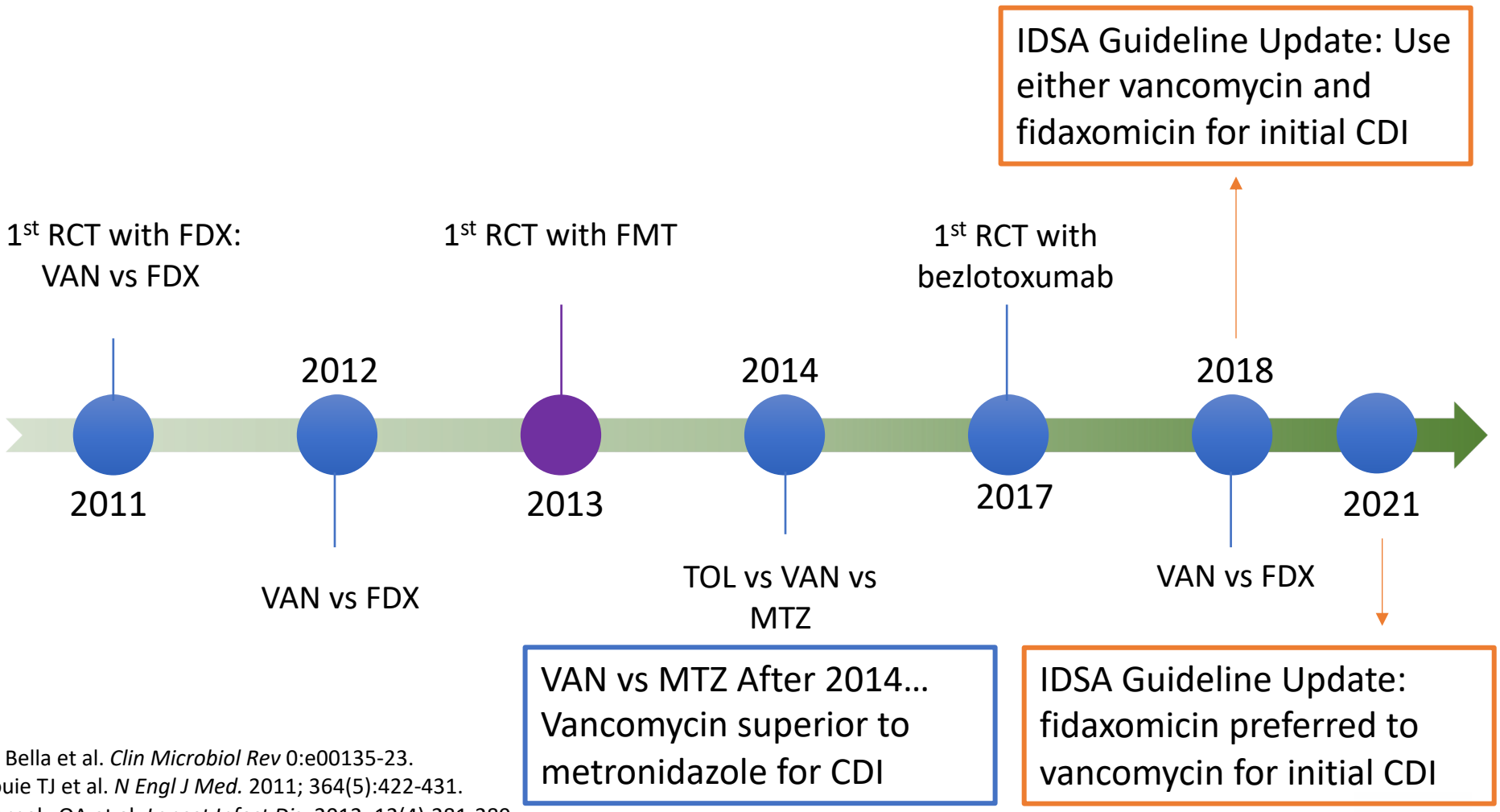


Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Keighley et al. *Br Med J.* 1978; 2(6153):1667-1669.
Teasley et al. *Lancet.* 1983; 2(8358):1043-1046.
Wenisch et al. *Clin Infect Dis.* 1996; 22(5):813-818.
Zar et al. *Clin Infect Dis.* 2007; 45(3):302-307.

Slide adapted from Dr. Travis J. Carlson, PharmD, BCIDP

VAN vs MTZ Before 2014…
Both acceptable treatment for 1st mild CDI episode

History of CDI Treatment



Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Louie TJ et al. *N Engl J Med.* 2011; 364(5):422-431.
Cornely OA et al. *Lancet Infect Dis*. 2012; 12(4):281-289.
Johnson S et al. *Clin Infect Dis*. 2014; 59(3):345-354.
Guery B et al. *Lancet Infect Dis*. 2018; 18(3):296-307.
Mikamo H et al. *J Infect Chemother*. 2018; 24(9):744-752.

Slide adapted from Dr. Travis J. Carlson, PharmD, BCIDP

CDI Guideline Recommendations

Updated 2021

JOURNAL ARTICLE GUIDELINES

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults

FREE

Stuart Johnson ✉, Valéry Lavergne, Andrew M Skinner, Anne J Gonzales-Luna, Kevin W Garey, Ciaran P Kelly, Mark H Wilcox

Clinical Infectious Diseases, Volume 73, Issue 5, 1 September 2021, Pages e1029–e1044, https://doi.org/10.1093/cid/ciab549

Published: 14 June 2021 **Article history** ▾

IDSA/SHEA

GUIDELINES | VOLUME 27, SUPPLEMENT 2, S1-S21, DECEMBER 2021 Download Full Issue

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults

Download Full Issue

Joffrey van Prehn • Elena Reigadas • Erik H. Vogelzang • ... Fidelma Fitzpatrick • Ed J. Kuijper ✉ •

The Guideline Committee of the European Study Group on *Clostridioides difficile* • Show all authors

Open Access • Published: October 19, 2021 • DOI: https://doi.org/10.1016/j.cmi.2021.09.038

ESCMID

CLINICAL GUIDELINES

ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections

Kelly, Colleen R. MD, AGAF, FACG[1]; Fischer, Monika MD, MSc, AGAF, FACG[2]; Allegretti, Jessica R. MD, MPH, FACG[3]; LaPlante, Kerry PharmD, FCCP, FIDSA[4]; Stewart, David B. MD, FACS, FASCRS[5]; Limketkai, Berkeley N. MD, PhD, FACG (GRADE Methodologist)[6]; Stollman, Neil H. MD, FACG[7]

Author Information

The American Journal of Gastroenterology 116(6):p 1124-1147, June 2021. | **DOI:** 10.14309/ajg.0000000000001278

ACG

Kelly CR et al. *Am J Gastroenterol*. 2021; 116(6):1124-1147.
Van Prehn J et al. *Clin Microbiol Infect*. 2021; 27(Suppl 2):S1-S21.
Johnson S et al. *Clin Infect Dis*. 2021; 73(5):e1029-e1044.

CDI Guideline Recommendations

Kelly CR et al. *Am J Gastroenterol*. 2021; 116(6):1124-1147.
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Johnson S et al. *Clin Infect Dis*. 2021; 73(5):e1029-e1044.

IDSA/SHEA CDI Guideline Recommendations

1st Recurrence

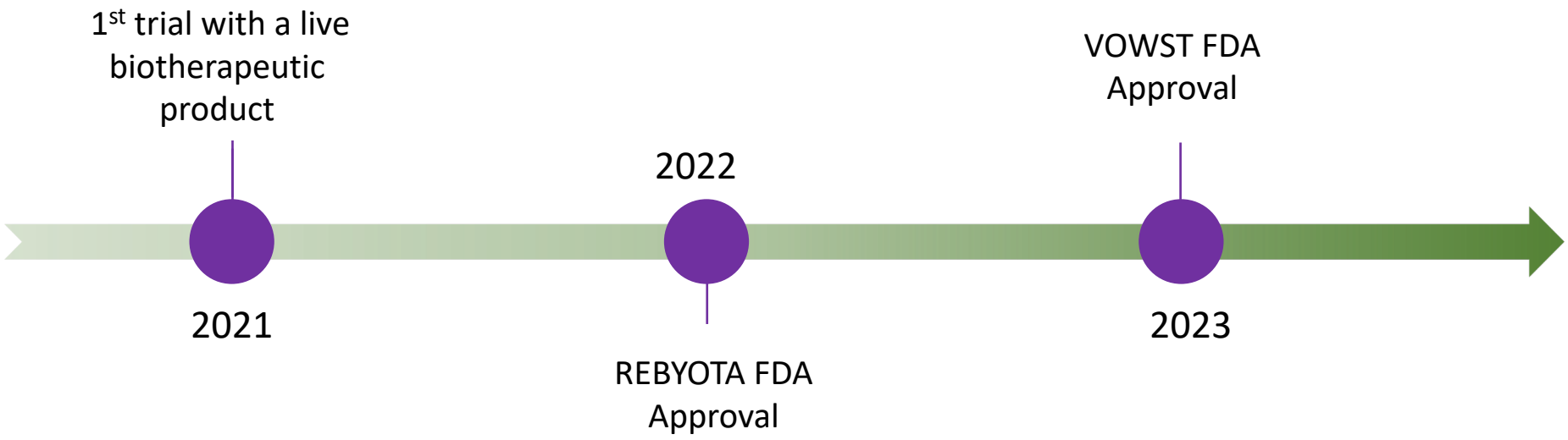
- Preferred: fidaxomicin 200 mg PO BID x 10 days OR BID x 5 days followed by once every other day x 20 days
- Vancomycin PO tapered/pulsed regimen
- Vancomycin 125 mg PO QID x 10 days
- Add: bezlotoxumab 10 mg/kg IV once during administration of PO antibiotics

2nd or Subsequent Recurrence

- Preferred: fidaxomicin 200 mg PO BID x 10 days OR BID x 5 days followed by once every other day x 20 days
- Vancomycin PO tapered/pulsed regimen
- Vancomycin 125 mg PO QID x 10 days followed by rifaximin 400 mg PO TID x 20 days
- Add: bezlotoxumab 10 mg/kg IV once during administration of PO antibiotics
- Fecal microbiota transplantation (FMT)

Johnson S et al. *Clin Infect Dis*. 2021; 73(5):e1029-e1044.

Evolving CDI Treatment



What role do the new microbiota-based therapeutics have in CDI treatment?

Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Rebyota [package insert]. 2022.
Vowst [package insert]. 2023.

2013 Landmark FMT Trial

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

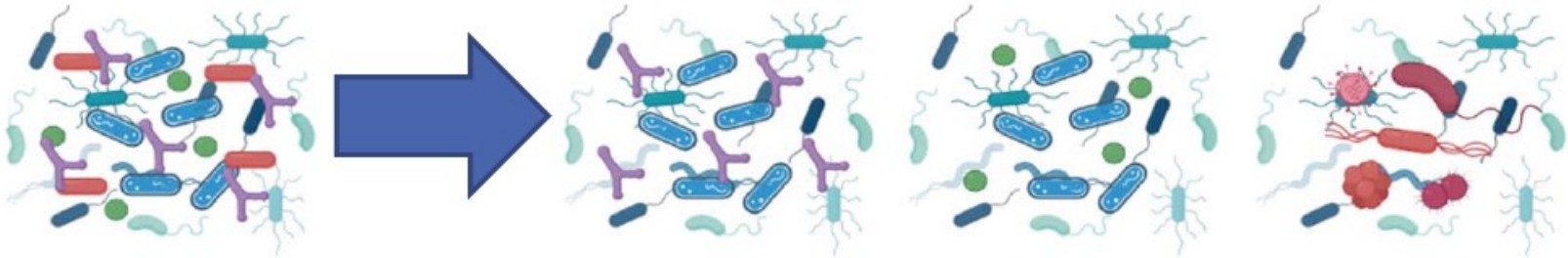
Vancomycin 500 mg PO QID x 4 days → bowel lavage and FMT	Vancomycin 500 mg PO QID x 14 days	Vancomycin 500 mg PO QID x 14 days with bowel lavage

- Study stopped after interim analysis
- FMT significantly more effective for treatment of recurrent CDI vs vancomycin
- After FMT, patients showed increased bacterial diversity

Va Nood et al. *N Engl J Med.* 2013;368(5):407-415.

New Fecal Microbiota Therapeutics

Microbiome Disruption Can Result in Dysbiosis



Petersen C, et al. *Cell Microbiol*. 2014;6(7):1024-33
Iebba V, et al. *New Microbiol*. 2016;39(1):1-12

Created with BioRender.com

Slide from Dr. Kelly R. Reveles, PharmD, PhD, BCPS

New Fecal Microbiota Therapeutics

Indication = prevent recurrent CDI in individuals ≥ 18 years following antibiotic treatment for recurrent CDI

- Biologically source from human fecal matter from qualified donors
- Goal = change recipient's microbial composition and confer a health benefit

REBYOTA® (fecal microbiota, live-jslm) suspension, for rectal use

NEW VOWST™ (fecal microbiota spores, live-brpk) capsules

Rebyota [package insert]. 2022. Image: https://www.rebyota.com/
Vowst [package insert]. 2023. Image: https://www.vowst.com/about-vowst

Rebyota (RBX2660)

- Fecal microbiota **suspension** containing live microorganisms – each dose contains between $1x10^8$ and $5x10^{10}$ colony forming units (CFU) per mL of fecal microbes including > $1x10^5$ CFU/mL of *Bacteroides*.
- 1-time dose = 150 mL rectal enema given 24-72 hours after last dose of antibiotics for CDI treatment.
- Requires clinic administration and storage in an ultra-cold freezer.
- May be beneficial in patients unable to take oral medication or when concerned for adherence.
- Studied in the PUNCH CD3 Phase 3 trial in adults with at least 1 recurrent CDI episode (2^{nd} episode)

Rebyota [package insert]. 2022.

Vowst (SER-109)

- **Capsules** of bacterial spores – each contains between $1x10^6$ and $3x10^7$ Firmicutes spore colony forming units.
- Dose = 4 capsules PO once daily x 3 days given 2-4 days after last dose of antibiotics for CDI treatment.
- Can be administered at home and stored at room temperature.
- Studied in the ECOSPOR III Phase 3 trial in adults with at least 2 recurrent CDI episodes (3rd episode)

Vowst [package insert]. 2023.

New Fecal Microbiota Therapeutics

No Head-to-Head Studies

Safety

- No serious adverse effects considered related to either therapeutic agent in clinical studies.
- GI adverse effects = most common for both agents
- No reported transmission of pathogenic bacteria – excluded immunocompromised patients in trials

	Rebyota	Vowst
Cardiovascular	-	-
Gastrointestinal	Abdominal pain (8.9%) Diarrhea (7.2%) Abdominal distension (3.9%) Flatulence (3.3%) Nausea (3.3%)	Abdominal distension (31.1%) Constipation (14.4%) Diarrhea (10%) Flatulence (4.2%) Nausea (3.0%)
Other	-	Fatigue (22.2%) Chills (11.1%)

Rebyota [package insert]. 2022.
Vowst [package insert]. 2023.

New Fecal Microbiota Therapeutics

No Head-to-Head Studies

Efficacy

- Both therapeutic agents demonstrated to be superior to placebo in phase III clinical trials.

	Rebyota	Vowst
Primary Outcome	Absence of CDI diarrhea within 8 weeks of study treatment	CDI recurrence within 8 weeks of study treatment
Results	Rebyota: 70.4% Placebo: 58.1% NNT = 9	Vowst: 12% Placebo: 40% NNT = 4

Rebyota [package insert]. 2022.
Vowst [package insert]. 2023.

New Fecal Microbiota Therapeutics

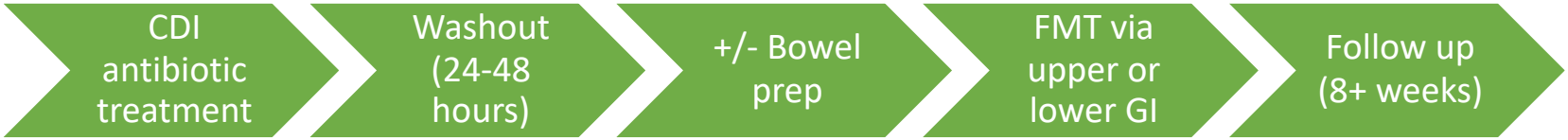
Distinguishing Characteristics

	Rebyota	Vowst
Number Needed to Treat *No direct comparison trials*	9	4
Dosage Formulation	Rectal enema that contains live organisms	Oral capsule that contains bacterial spores
Dosing	1-time dose	4 pills daily x 3 days
Administration	Clinic administration	Home
Storage	Ultra-cold freezer	Room temperature
Antibiotic Restrictions	Avoid for 8 weeks after administration	None
Acquisition Cost at Our Institution	$6,921	$17,500

Rebyota [package insert]. 2022.
Vowst [package insert]. 2023.

Implementation Considerations

Traditional FMT



- No FDA-approved products
- Safety: primarily GI adverse effects
- Colonoscopy or enema or NG/NJ/G-tube
- Costs: donor testing + colonoscopy + outpatient visit + FMT instillation +/- oral antibiotic for CDI

Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Cammarota et al. *Gut.* 2017;66:569-80.

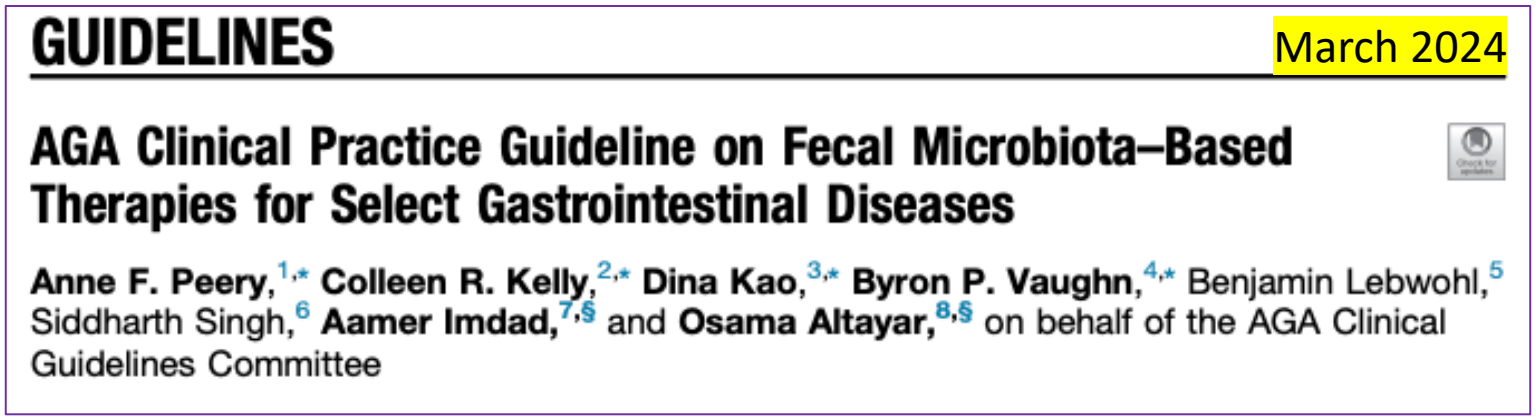
Implementation Considerations

Rebyota and Vowst

- FDA-approved products
- Safety: primarily GI adverse effects
- Rebyota: storage and clinic administration
- Costs: oral antibiotic for CDI + fecal microbiota agent + bowel prep (Vowst) + administration (Rebyota)

Di Bella et al. *Clin Microbiol Rev* 0:e00135-23.
Rebyota [package insert]. 2022.
Vowst [package insert]. 2023.

What's New(er)?



GUIDELINES

March 2024

AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases

Anne F. Peery,[1,*] **Colleen R. Kelly,**[2,*] **Dina Kao,**[3,*] **Byron P. Vaughn,**[4,*] Benjamin Lebwohl,[5] Siddharth Singh,[6] **Aamer Imdad,**[7,§] and **Osama Altayar,**[8,§] on behalf of the AGA Clinical Guidelines Committee

- Consider fecal microbiota-based therapies (FMT, Rebyota, Vowst)
  - After 2nd recurrence (3rd episode) of CDI
  - Select patients at high risk of recurrent CDI or a morbid CDI recurrence
- Careful consideration if patients will require frequent antibiotics or long-term antibiotic prophylaxis
  - Ongoing antibiotics can decrease efficacy of fecal microbiota-based therapies

Peery et al. *Gastroenterology.* 2024;166(3):409-434.

Take-Aways

- Unlike PO antibiotics, new FMT therapeutics address root cause of CDI = dysbiosis
- FMT and new fecal microbiota therapeutics can be considered for patients with 2 or more recurrences
- New therapeutic agents may overcome some limitations of traditional FMT but are associated with unique costs and implementation challenges
- The new FMT therapeutic agents are indicated for secondary prophylaxis, NOT CDI treatment vs traditional FMT can be used for treatment or secondary prophylaxis

Thank You!

Questions?

Darrad@uw.edu