Clostridioides difficile: Epidemiologic Risks and Decolonization Strategies

Alice Guh, MD, MPH
Centers for Disease Control and Prevention

Drug Development Considerations for the Prevention of HealthCare-Associated Infections—Virtual Public Workshop

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What We Need

- **Decolonization strategy for *Clostridioides difficile***
  - Prevent transmission from infected patients and asymptomatic carriers
  - Prevent primary and recurrent infection

- **Approved microbiome-based therapeutic for *C. difficile* infection**
  - Several biotherapeutics currently in clinical trials

THE PROBLEM

Clostridioides difficile background

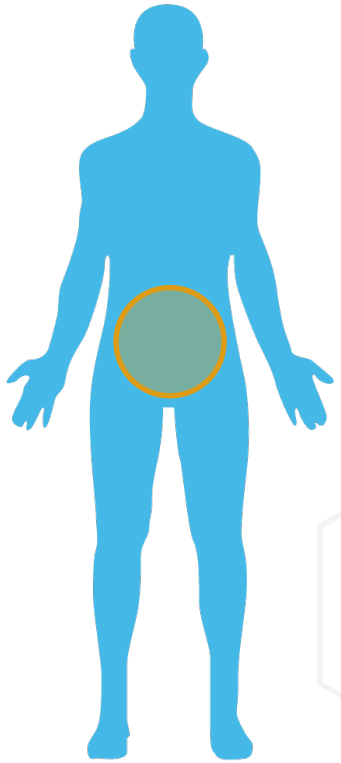
- Anaerobic, gram-positive, spore-forming gastrointestinal pathogen
- Transmission via oral-fecal route
- Clinical spectrum ranges from asymptomatic colonization to severe disease with fulminant colitis and death
- Leading cause of healthcare-associated diarrhea and increasingly reported in the community
  - Estimated 462,100 incident *C. difficile* infections (CDI) in the United States in 2017, with an estimated 223,922 cases and 12,764 associated deaths among hospitalized patients

CDC 2019 AR Threats Report

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

Asymptomatic colonization of *C. difficile* occurs in healthcare & community settings

- **Asymptomatic colonization**
  - Ranges from 7%–18% among hospitalized patients
  - 15% of long-term care facility (LTCF) residents
    - 51% colonized in outbreak setting
  - Ranges from 2%–10% among persons in the community
- **Transient carriage usually seen with intact microbiota, but some with persistent colonization lasting months**



Donskey CJ et al. Infect Dis Clin North Am. 2015;29:13–28.
Ziakas PD et al. PLoS One. 2015;10(2):e0117195.
Riggs MM et al. Clin Infect Dis. 2007;45:992–8.
Ozaki E et al. J Med Microbiol. 2004;53(Pt 2):167-172.

WHAT WE KNOW

Risk factors for *C. difficile* colonization

- **Meta-analysis of hospitalized patients**
  - Previous CDI
  - Hospitalization in the previous 6 months
  - Tube feeding
  - Gastric acid suppression
  - Corticosteroid use in the previous 8 weeks
- **Meta-analysis of LTCF residents**
  - Prior CDI outbreaks in the facility
  - Previous CDI
  - Prior hospitalization
  - Prior antimicrobial use

Anjewierden S et al. Infect Control Hosp Epidemiol. 2021;42:565-72.
Ziakas PD et al. PLoS One. 2015;10(2):e0117195.

Colonization with toxigenic *C. difficile* can result in symptomatic illness

- 10%-60% of hospitalized patients colonized with toxigenic *C. difficile* may develop CDI
  - Gut microbiome disruption and immunosuppression increase CDI risk: antibiotic use, proton pump inhibitor use, advanced age, chemotherapy
- Certain strains may be more likely to cause disease
  - Ribotype 027 found in 25% of CDI cases vs 3% of asymptomatic carriers

Donskey CJ et al. Infect Dis Clin North Am. 2015;29:13–28.
Alasmari F et al. Clin Infect Dis. 2014;59:216–22

Potential for *C. difficile* transmission by asymptomatic patients

- **Asymptomatic carriers can also shed *C. difficile* on skin and environment**
- **Subsets of colonized patients might be higher transmission risk**
  - Patients with recent CDI accounted for 22% of hospitalized asymptomatic carriers
  - Patients with higher burden of *C. difficile* colonization found to have greater skin and/or environmental shedding

Guerrero DM et al. J Hosp Infect. 2013;85:155–8.
Donskey CJ et al. J Clin Microbiol. 2014;52:315–18.

Studies demonstrating transmission of *C. difficile* by asymptomatic patients

Use of Multilocus Variable Number of Tandem Repeats Analysis Genotyping to Determine the Role of Asymptomatic Carriers in *Clostridium difficile* Transmission

Scott R. Curry,[1,2] Carlene A. Muto,[1,2,3] Jessica L. Schlackman,[2] A. William Pasculle,[4] Kathleen A. Shutt,[1,2] Jane W. Marsh,[1,2] and Lee H. Harrison[1,2]

[1]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh School of Medicine; [2]Infectious Diseases Epidemiology Research Unit, University of Pittsburgh School of Medicine and Graduate School of Public Health; [3]Division of Hospital Epidemiology and Infection Control, University of Pittsburgh Medical Center, Presbyterian Campus; and [4]Division of Microbiology, Department of Pathology, University of Pittsburgh School of Medicine, Pennsylvania

(See the Editorial Commentary by McDonald on pages 1103–5.)

- Incident CDI cases in hospital as frequently linked to transmission from asymptomatic carriers (29%) as symptomatic patients (30%)
- 4 transmission events from prior room occupants who had CDI (n=2) or were asymptomatic carriers (n=2)

Transmission of *Clostridium difficile* from asymptomatically colonized or infected long-term care facility residents

Curtis J. Donskey MD[1], Venkata C. K. Sunkesula MD[2], Nimalie D. Stone MD[3], Carolyn V. Gould MD[3], L. Clifford McDonald MD[3], Matthew Samore MD[4], JeanMarie Mayer MD[5], Susan M. Pacheco MD[5], Annette L. Jencson CIC[2], Susan P. Sambol BS[5], Laurica A. Petrella BS[6], Christopher A. Gulvik PhD[3] and Dale N. Gerding[6,7]

[1]Geriatric Research Education and Clinical Center, Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio, [2]Research Service, Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio, [3]Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion, Atlanta, Georgia, [4]University of Utah School of Medicine, Division of Epidemiology, Salt Lake City, Utah, [5]University of Utah School of Medicine, Salt Lake City, Utah, [6]Edward Hines, Jr Veterans Affairs Hospital, Hines, Illinois and [7]Loyola University, Chicago Stritch School of Medicine, Maywood, Illinois

- Using WGS, 19% of healthcare-associated CDI cases linked to LTCF residents with CDI (n=2) or asymptomatic carriage (n=5)
- 72% of asymptomatic carriers had positive cultures of groin, skin, and/or environment for toxigenic *C. difficile*
  - High burden of *C. difficile* among carriers linked to transmission (>25 colonies per perirectal swab)

Role of gut microbiota in CDI development

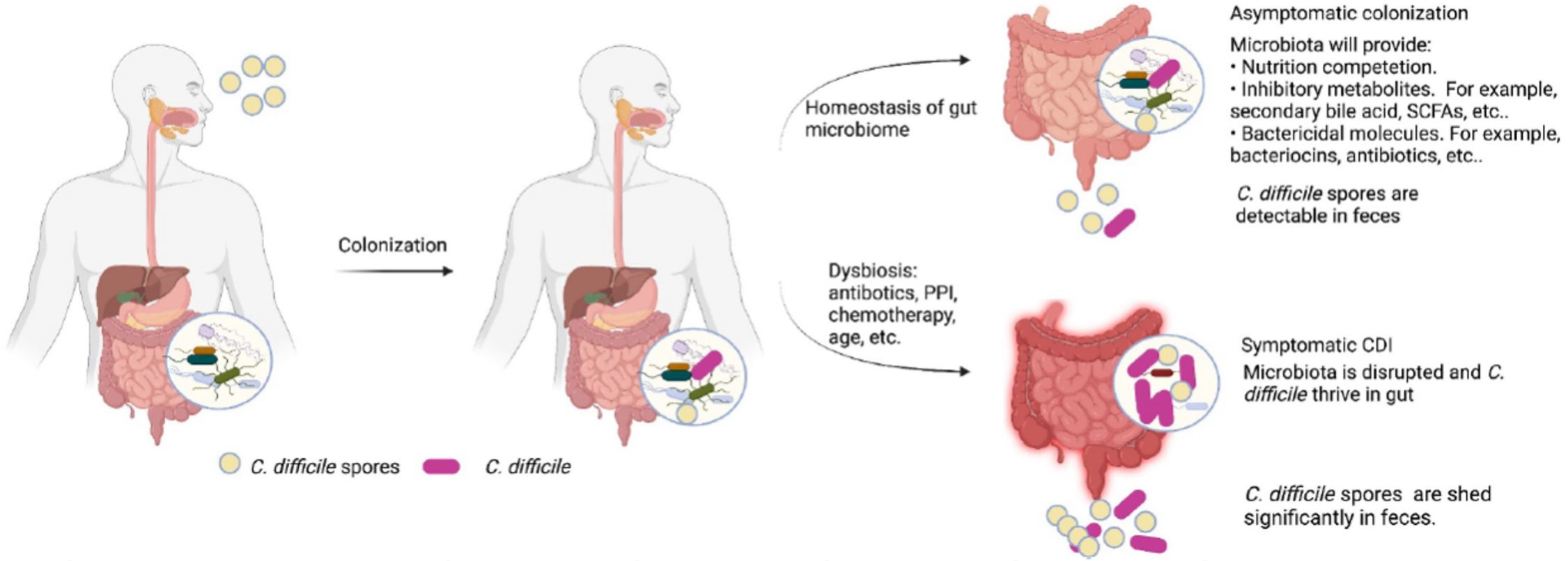


Figure obtained from Zhang Y et al. Gut Microbes 2022;14:2052698.

WHAT WE HAVE

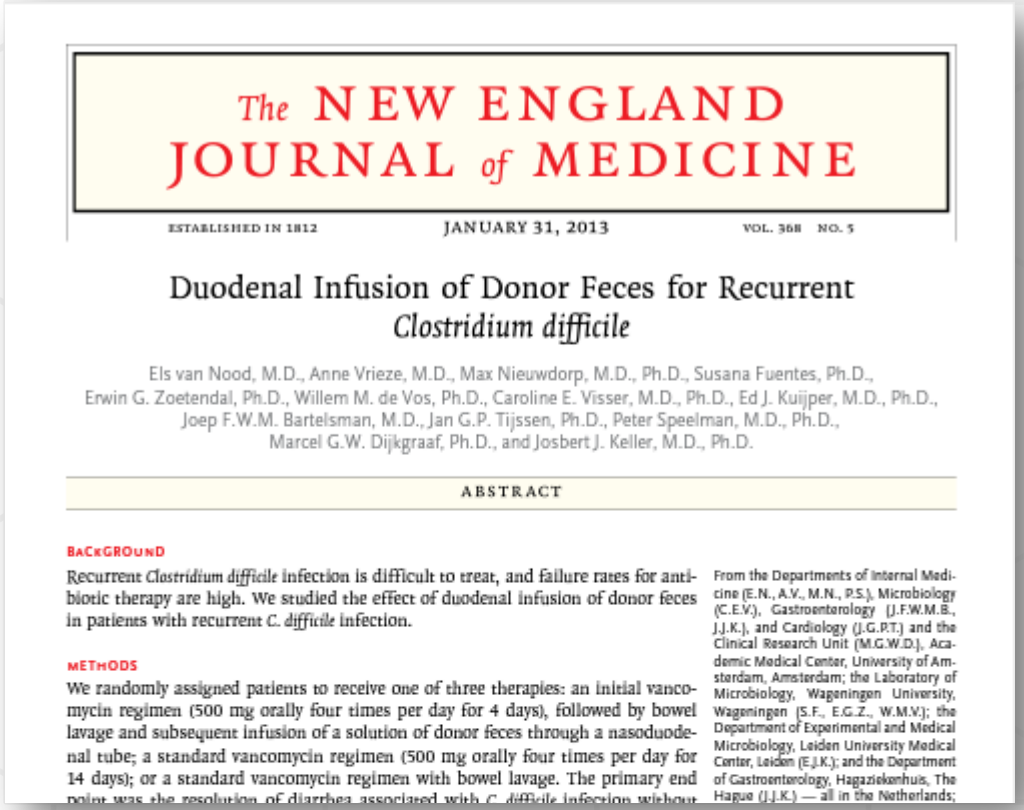
Current Tools, Studies, and Data Gaps

Current state of affairs for *C. difficile*

- Microbiome-based therapy is primarily focused on treatment of recurrent CDI
  - Fecal microbiota transplantation (FMT), novel biotherapeutics
- Lack of studies evaluating microbiome-based therapy for the prevention and treatment of primary CDI
- No effective decolonization strategy of asymptomatic carriers

Use of FMT to treat recurrent CDI

- Transplantation of the gut microbiota from a healthy donor to a patient to restore normal diversity and function
- Several randomized controlled trials (RCT) and meta-analyses have demonstrated the efficacy of FMT for recurrent CDI



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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.

ABSTRACT

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without

From the Departments of Internal Medicine (E.N., A.V., M.N., P.S.), Microbiology (C.E.V.), Gastroenterology (J.F.W.M.B., J.J.K.), and Cardiology (J.G.P.T.) and the Clinical Research Unit (M.G.W.D.), Academic Medical Center, University of Amsterdam, Amsterdam; the Laboratory of Microbiology, Wageningen University, Wageningen (S.F., E.G.Z., W.M.V.); the Department of Experimental and Medical Microbiology, Leiden University Medical Center, Leiden (E.J.K.); and the Department of Gastroenterology, Hagaziekenhuis, The Hague (J.J.K.) — all in the Netherlands;

- Assigned 43 patients:
  - Standard course of oral vancomycin
  - Oral vancomycin with bowel lavage
  - 4-day course of oral vancomycin followed by bowel lavage and FMT
- Resolution of CDI in 81% who received FMT vs 31% who received vancomycin alone vs 23% who received vancomycin with bowel lavage (P<0.001)

Challenges with traditional FMT

- **Procedural risks and short-term data on safety**
  - Associated adverse events are generally self-limited
  - Reported infectious complications are rare
    - 2 immunocompromised patients developed bacteremia from extended-spectrum beta-lactamase-producing *Escherichia coli*
    - 4 patients developed diarrheal illness from Shiga toxin-producing *E. coli*
- **Heterogeneity in FMT practice**
  - Variability in donor screening and stool preparation methods

Gupta S et al. Am J Gastroenterol 2021;116:647–56
DeFilipp Z et al. N Engl J Med 2019;381:2043-50
Zellmer C et al. Clin Infect Dis. 2021;72:e876-80.
Khanna S. J Intern Med 2021;290:294–309.

Need for standardized microbiome restoration therapies: Development of capsule- and enema-based products

- **Ease of administration, aesthetically pleasing, less invasive**
- **Clinical trials**
  - Whole-stool or defined FMT (e.g., CP101, VE303, RBX7455, RBX2660)
  - Product containing fecal bacterial spores (SER-109): purified *Firmicutes* spores
    - Phase 3, double-blinded, RCT (n=182 patients): 12% of SER-109 group vs 40% of placebo group developed recurrent CDI (relative risk, 0.32; 95% confidence interval [CI], 0.18-0.58)
- **Meta-analysis comparing different routes of administration**
  - Capsule-based FMT (4 studies): cure rate 92.1% (95% CI, 88.6-95.0%)
  - FMT using colonoscopy (16 studies): cure rate 94.8% (95% CI, 92.4-96.8%)

Zhang Y et al. Gut Microbes 2022;14:2052698.
Feuerstadt P et al. N Engl J Med 2022; 386:220–29.
Ramai D et al. Dig Dis Sci. 2021;66:369–80.

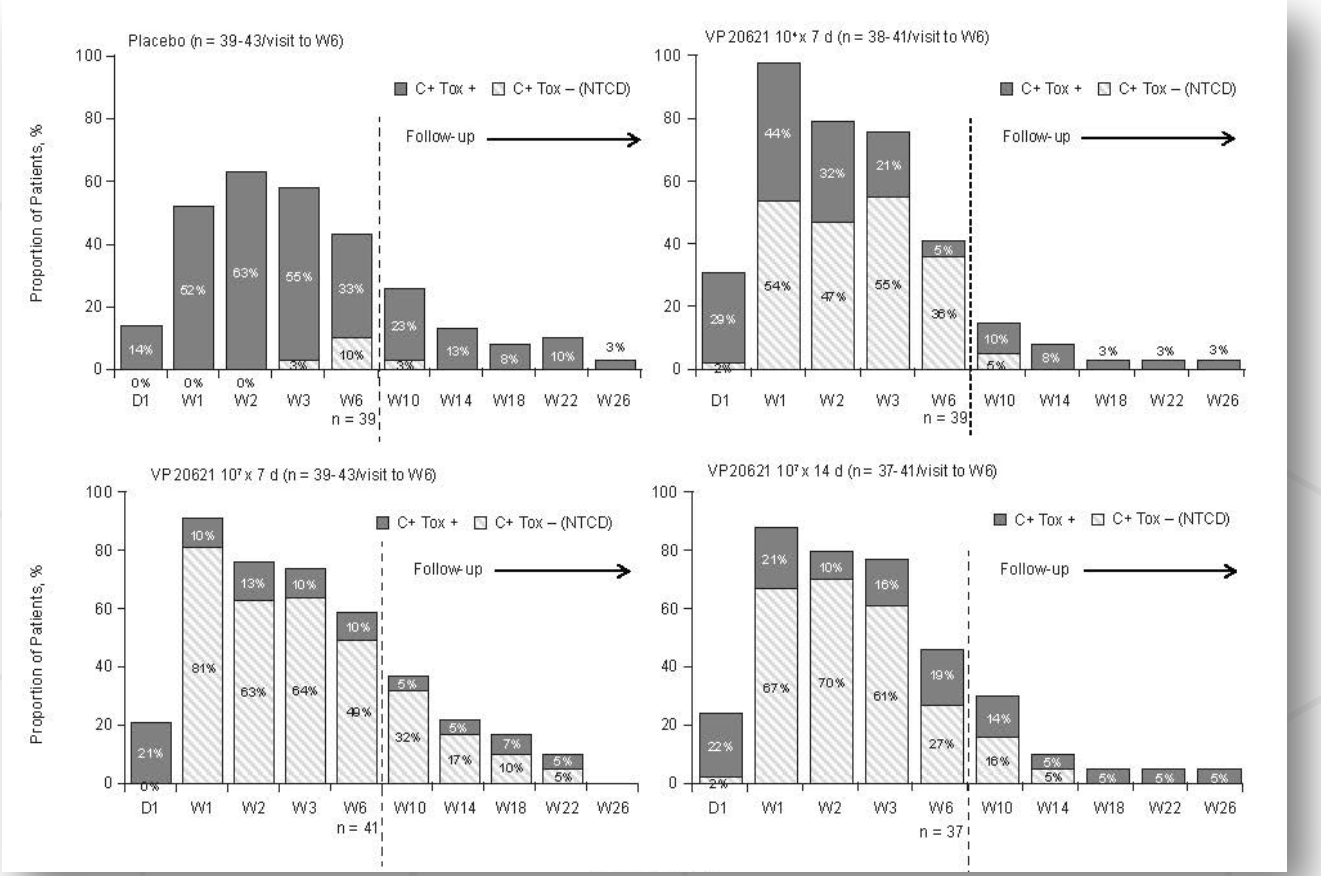
Knowledge gaps and future of FMT

- **Potential for an approved FMT product**
  - Prevent further recurrence and transmission to other patients
- **Need longitudinal follow-up data**
  - More insight on long-term safety
  - Durability of microbiome restoration therapies
- **Continued advancements in developing defined microbial consortia**
- **Explore role of FMT for management of primary CDI**
  - Proof-of-concept clinical trial (n=20 patients): full clinical response in 78% (95% CI, 40-97%) of FMT group vs 45% (95% CI, 17-77%) of metronidazole group (P=0.20)
  - Phase 3 clinical trial is underway

Juul FE et al. N Engl J Med. 2018;378:2535-6.

Use of non-toxigenic *C. difficile* (NTCD) strains to prevent recurrent CDI shows promise

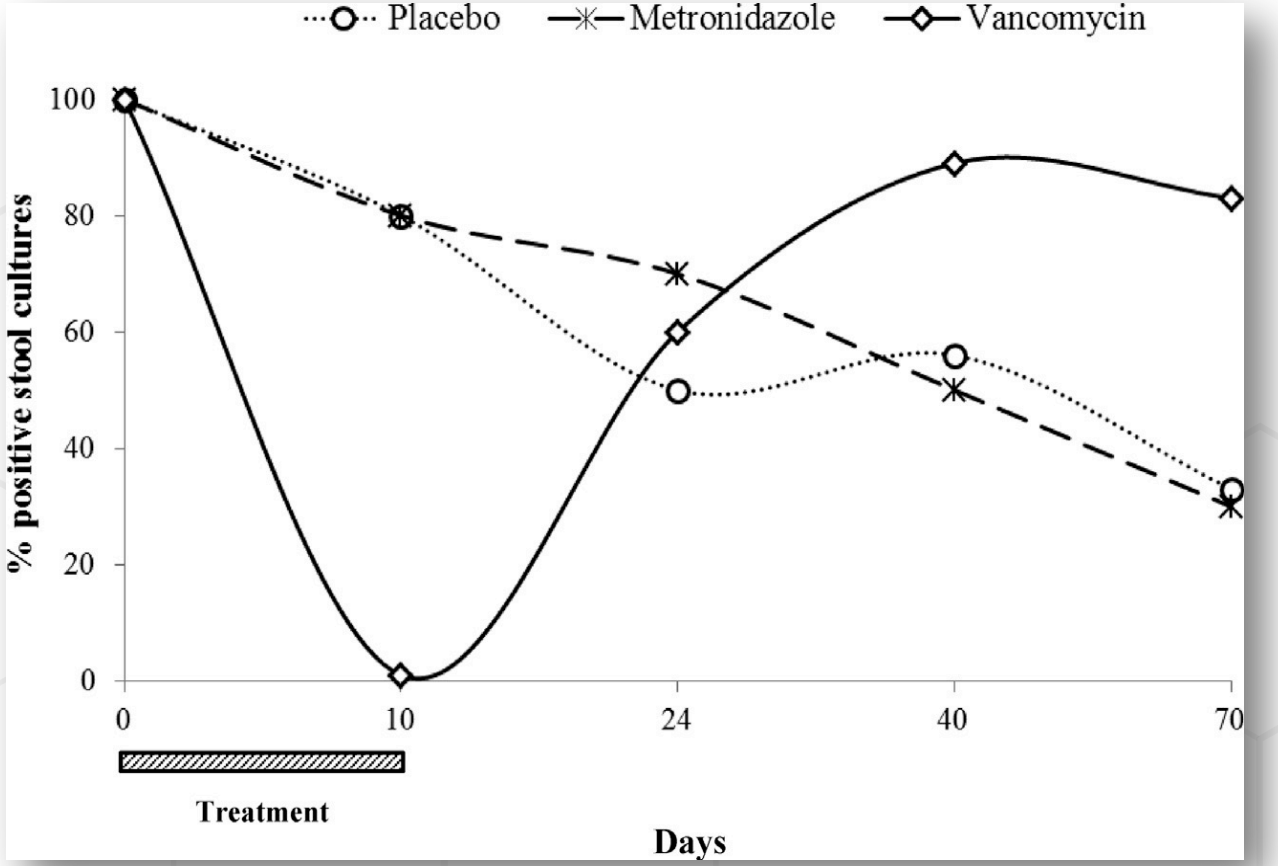
- **NTCD-M3 spores**
  - Phase 2 double-blinded RCT (n=173): assigned to receive 10^{4-7}spores/day for 7 days, 10^{7} spores/day for 14 days, or placebo for 14 days
  - CDI recurrence in 11% of NTCD-M3 patients vs 30% of placebo patients (P=0.006)
  - Decolonizing toxigenic *C. difficile* from microbiome with colonization of NTCD-M3 spore
    - NTCD-M3 colonization undetectable after week 22 of follow-up, possibly due to restoration of normal microbiota



Gerding DN et al. JAMA. 2015;313:1719-27.

Need effective strategy for decolonization of asymptomatic carriers

- **RCT (n=30 asymptomatic carriers): 10 days of oral vancomycin vs. metronidazole vs. placebo**
  - Metronidazole and placebo did not suppress *C. difficile* colonization
  - Oral vancomycin suppressed colonization during treatment but subsequently associated with increased carriage rate



Johnson S et al. Ann Intern Med. 1992;117:297-302.
Donskey CJ et al. Infect Dis Clin North Am. 2015;29:13-28.

Oral vancomycin prophylaxis (OVP) for primary and secondary CDI prevention shows promise

- Potent activity against *C. difficile*, but may result in reduced colonization resistance to *C. difficile* that can persist for weeks
- RCT (n=100): 0% in the OVP group (once-daily low dose) vs 12% in the no-prophylaxis group developed healthcare-facility onset CDI (P=0.03)
  - No new VRE colonization detected among OVP group
- Recent meta-analysis assessing efficacy of OVP for primary and secondary CDI prevention in patients treated with systemic antibiotics
  - 11 studies, including 1 RCT and studies of immunocompromised patients
  - OVP was protective against CDI (OR, 0.13; 95% 0.04-0.38)
  - Use of OVP not associated with higher risk of VRE
- More RCTs needed

Johnson SW et al. Clin Infect Dis. 2020;71:1133-9.
Maraolo AE et al. Antibiotics;2022;11:183.


WHAT WE NEED

C. difficile future directions

Decolonization strategy for *Clostridioides difficile*

- Prevent transmission from infected patients and asymptomatic carriers
- Prevent primary and recurrent infection

Approved microbiome-based therapeutic for *C. difficile* infection

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Thank you

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