Difficile Decisions: Diagnosis and Treatment of *C. difficile* Infection in Children

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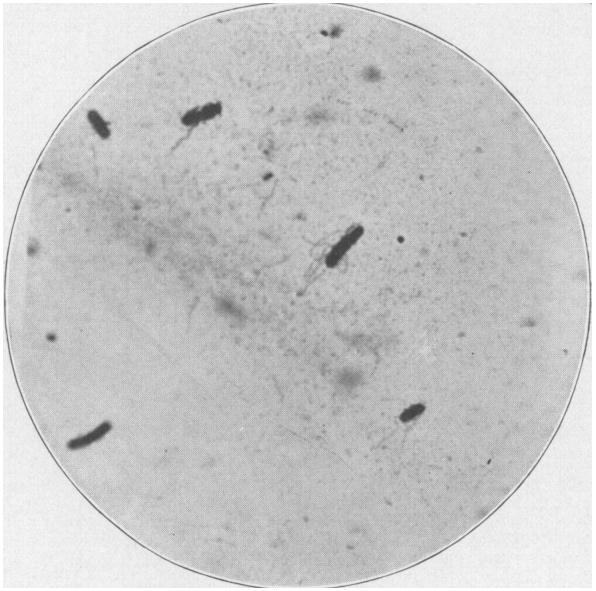
Disclosures

- I am a member of the Vowst Commercial Speaker Bureau

How It Started…

INTESTINAL FLORA IN NEW-BORN INFANTS

WITH A DESCRIPTION OF A NEW PATHOGENIC ANAEROBE,
BACILLUS DIFFICILIS



IVAN C. HALL, PH.D.
AND
ELIZABETH O'TOOLE
DENVER

Hall IC & O'Toole E. *Am J Dis Child*. 1935;49(2):390-402.

A Brief History: 1935-1983

- **1935** *Bacillus difficilis* isolated from the stool of 4/10 neonates within the first 10 days of life
- **1973** "Clindamycin-associated colitis" termed
- **1977** Pseudomembranous colitis (PMC) in a 12-year-old attributed to a toxigenic bacteria
- **1977** *Clostridium* BVA 17 HF 1-9 identified as the etiologic agent of PMC in hamsters
- **1977** PO vancomycin (500 mg QID x10 days) used to treat a 13-year-old w/ PMC
- **1978** Four cytotoxic bacterial isolates phenotypically resembled *Clostridium difficile*
- **1978** RCT (n = 44) comparing PO vancomycin (125 mg QID x5 days) vs. placebo

Hall IC & O'Toole E. *Am J Dis Child*. 1935;49(2):390-402.
Cohen LE, et al. *JAMA*. 1973;223(12):1379-1380.
Larson HE, et al. *Br Med J*. 1977;1(6071):1246-1248.
Bartlett JG, et al. *J Infect Dis*. 1977;136(5):701-705.
Rifkin GD, et al. *Lancet*. 1977;2(8048):1103-1106.
Bartlett JG, et al. *N Engl J Med*. 1978;298(10):531-534.
Keighley MRB, et al. *Br Med J*. 1978;2(6153):1667-1669.

A Brief History: 1935-1983

1978 PO metronidazole (500 mg TID x7 days) used to treat a 27-year-old w/ PMC

1983 First FMT performed in a 65-year-old with multiply recurrent CDI

1983 RCT (n = 101) comparing PO vancomycin (500 mg QID x10 days) vs. PO metronidazole (250 mg QID x10 days)

Dinh HT, et al. *Lancet*. 1978;1(8059):338-339.
Schwan A, et al. *Lancet*. 1983;2(8354):845.
Teasley DG, et al. *Lancet*. 1983;2(8358):1043-1046.

Notable Quotations

- Hall & O'Toole 1935 - "Superficially the spasms [in guinea pigs infected with *B. difficilis*] resembled those of tetanus…"
- Cohen 1973 - "… clindamycin should be reserved for specific indications and should not be used for trivial illnesses."
- Bartlett 1977 - "… *Clostridium* BVA 17 HF 1-9 is similar in many respects to *Clostridium difficile*."
- Bartlett 1978 - "… it is apparent that only a minority of patients with antibiotic-associated diarrhea [have] a positive [*C. difficile*] assay, suggesting that a clostridial toxin cannot be incriminated in the majority of patients with uncomplicated diarrhea ascribed to antibiotic administration."
- Keighley 1978 - "All [*C. difficile*] strains are sensitive to metronidazole, but this agent is unlikely to be of value in PMC because it is rapidly absorbed from the small bowel and fails to reach therapeutic concentrations in the colon."
- Teasley 1983 - "… no single test seems to be totally reliable in the diagnosis of *C. difficile* [infection]…"

Hall IC & O'Toole E. *Am J Dis Child*. 1935;49(2):390-402.
Cohen LE, et al. *JAMA*. 1973;223(12):1379-1380.
Bartlett JG, et al. *J Infect Dis*. 1977;136(5):701-705.
Bartlett JG, et al. *N Engl J Med*. 1978;298(10):531-534.
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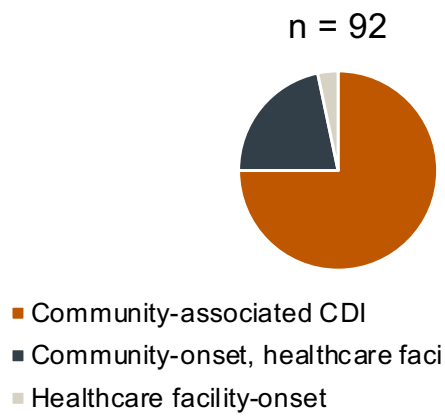
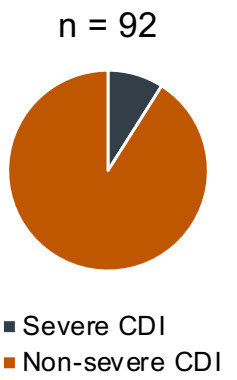
Teasley DG, et al. *Lancet*. 1983;2(8358):1043-1046.

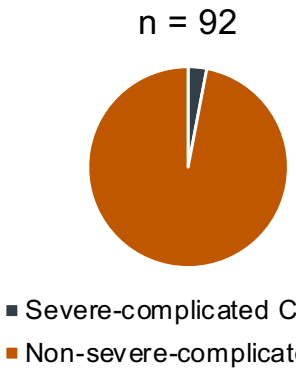
A Lay of the Land

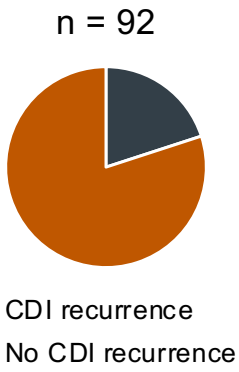
C. difficile colonization in healthy infants[1], the majority of which is toxigenic[4, 6], far exceeds the rate in "healthy" adults

"True" CDI in infants is thought to be extremely rare[2, 3, 5]



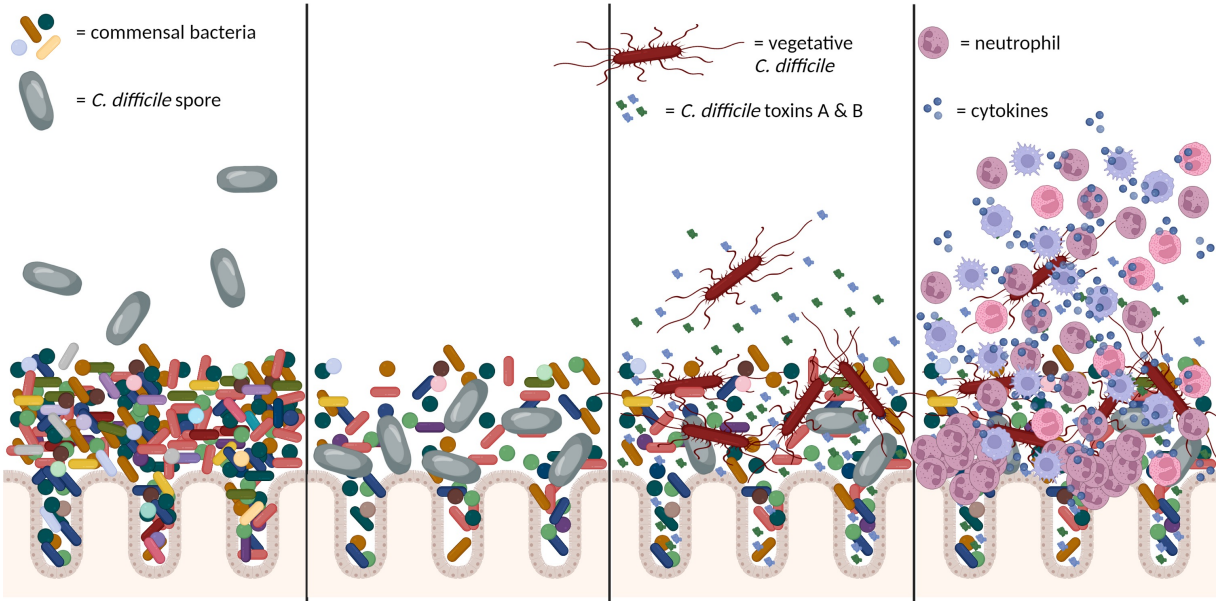






1. Cooperstock M, et al. *J Clin Microbiol*. 1983;17(5):830-833.
2. Kim J, et al. *Pediatrics.* 2008;122(6):1266-1270.
3. Khanna S, et al. *Clin Infect Dis*. 2013;56(10):1401-1406.
4. Adlerberth I, et al. *J Clin Microbiol*. 2014;52(1):173-179.
5. Lo Vecchio A, et al. *Eur J Clin Microbiol Infect Dis*. 2017;36(1):177-185.
6. Lees EA, et al. *Pediatr Infect Dis J*. 2020;39(3):221-228.

Little Ones Don’t Seem to Give A Crap



- Lack of toxin receptors[4]
- Inability of toxin to bind receptors[3, 5, 6]
- Imprinting of the immune system by the gut microbiota[7]
- Circulating toxin-neutralizing antibodies (passive[1, 2, 5, 6] vs. active[8] immunity)

1. Wada N, et al. *Infect Immunol*. 1980;29(2):545-550.
2. **Kim K, et al. *J Infect Dis*. 1984;150(1):57-62.**
3. Rolfe RD. *Infect Immunol*. 1991;59(4):1223-1230.
4. Eglow R, et al. *J Clin Invest*. 1992;90(3):822-829.
5. Rolfe RD, et al. *J Med Microbiol*. 1995;42(1):10-19.
6. **Dallas SD, et al. *J Med Microbiol*. 1998;47(10):879-888.**
7. Al Nabhani Z, et al. *Mucosal Immunol*. 2020;13(2):183-189.
8. **Kociolek LK, et al. *Clin Infect Dis*. 2020;70(10):2095-2102.**

Difficile Decision #1

To treat or not to treat?

Is this real life?

Diagnostic Test[1]	Assay Analyte	Assay Performance
Toxigenic culture	*C. difficile* is grown on selective media and a NAAT or toxin EIA is performed	High sensitivity Low specificity
Nucleic acid amplification test (NAAT)	A NAAT tests for the *C. difficile* toxin gene(s)	High sensitivity Low/moderate specificity
Glutamate dehydrogenase (GDH) enzyme immunoassay (EIA)	GDH is an antigen present on toxigenic and non-toxigenic strains of *C. difficile*	High sensitivity Low specificity
Toxin A/B EIA	A toxin EIA tests for the *C. difficile* toxin protein(s)	Low sensitivity Moderate specificity
Cell cytotoxicity neutralization assay (CCNA)	Two sets of Vero or human fibroblast cells are inoculated w/ stool filtrate (one set is co-incubated with *C. difficile* or *C. sordellii* antitoxin) and observed for cytopathic effect	High sensitivity High specificity

- Between 10-70% of infants are colonized with *C. difficile*[2, 3]
- Approximately 50% of colonizing strains are toxigenic[3]
- The incidence of parent-defined diarrhea is approximately 2 episodes per person-year among children aged 6-36 months[4]
- Approximately 25% of children <5 years of age with diarrhea seek medical care[5]

1. McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-48.
2. Jangi S, et al. *J Pediatr Gastroenterol Nutr*. 2010;51(1):2-7.
3. Kociolek LK, et al. *Clin Infect Dis*. 2020;70(10):2095-102.
4. Vernacchio L, et al. *Pediatr Infect Dis J*. 2006;25(1):2-7.
5. Scallan E, et al. *Foodborne Pathog Dis*. 2006;3(4):432-438.

Diagnostic Testing Recommendations for Children

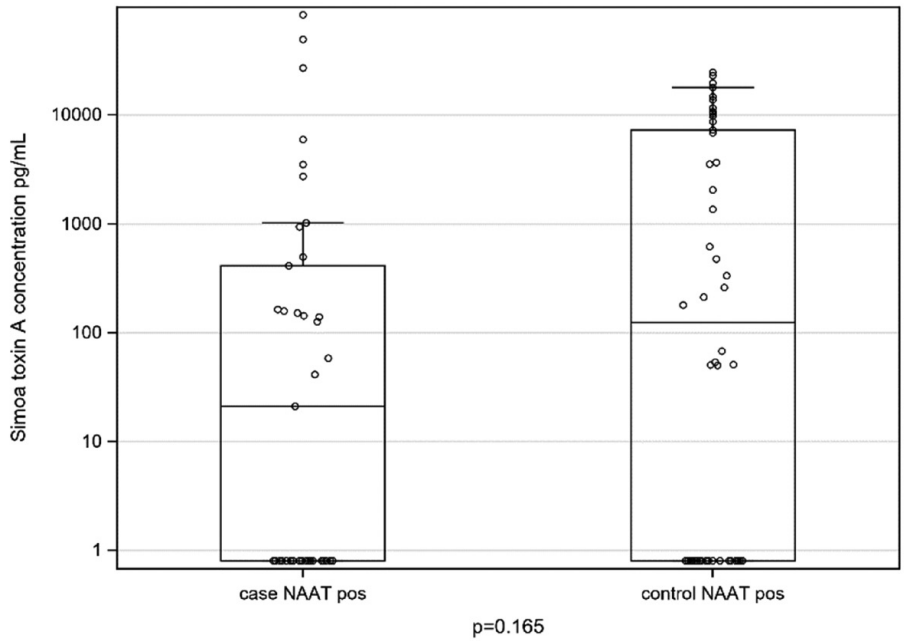
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-48.

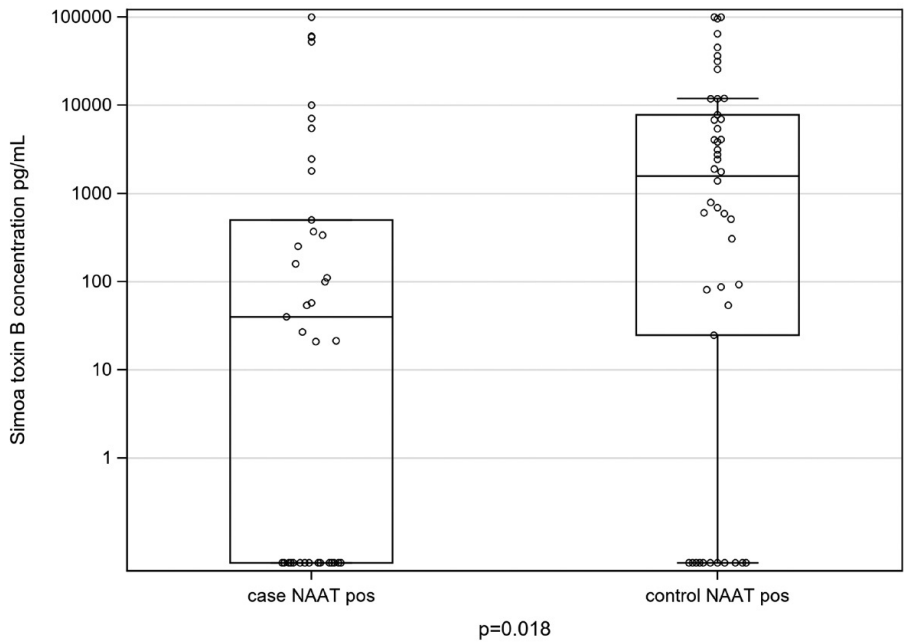
Ultrasensitive Digital Enzyme-linked Immunosorbent Assays (ELISAs)

- The C. Diff Quik Chek Complete (TechLab, Inc., Blacksburg, VA) has a lower limit of detection (LOD) at 630 and 160 pg/mL for TcdA and TcdB, respectively
- The single-molecule array, “Simoa” (bioMerieux, Marcy L’Etoile, France) has a LOD at 0.5 and 1.5 pg/mL for TcdA and TcdB, respectively (concentrations <20 pg/mL are converted to zero)
- Prospectively enrolled children <3 years old into either a “diarrhea” (n = 37) or a “no diarrhea” (n = 46) group
  - “Diarrhea” in children ≥1 year of age was defined as ≥3 unformed bowel movements or persistent diarrhea during any 24-hour period in the 48 hours before or 24 hours after stool collection
  - In children <1 year of age, it was defined as a sustained change in consistency (less formed) or frequency (increased) of stool in the same timeframe

C. Diff Quik Chek Complete. Package insert. TechLab, Inc.; 2021. Accessed January 15, 2025. https://www.techlab.com/diagnostics/c-difficile/c-diff-quik-chek-complete/
Song L, et al. *J Clin Microbiol*. 2015;53(10):3204-3212.
Sandora TJ, et al. *J Pediatr Infect Dis Soc*. 2022;11(10):454-458.

Simoa Ultrasensitive Digital ELISA: Distinguishing CDI from Colonization



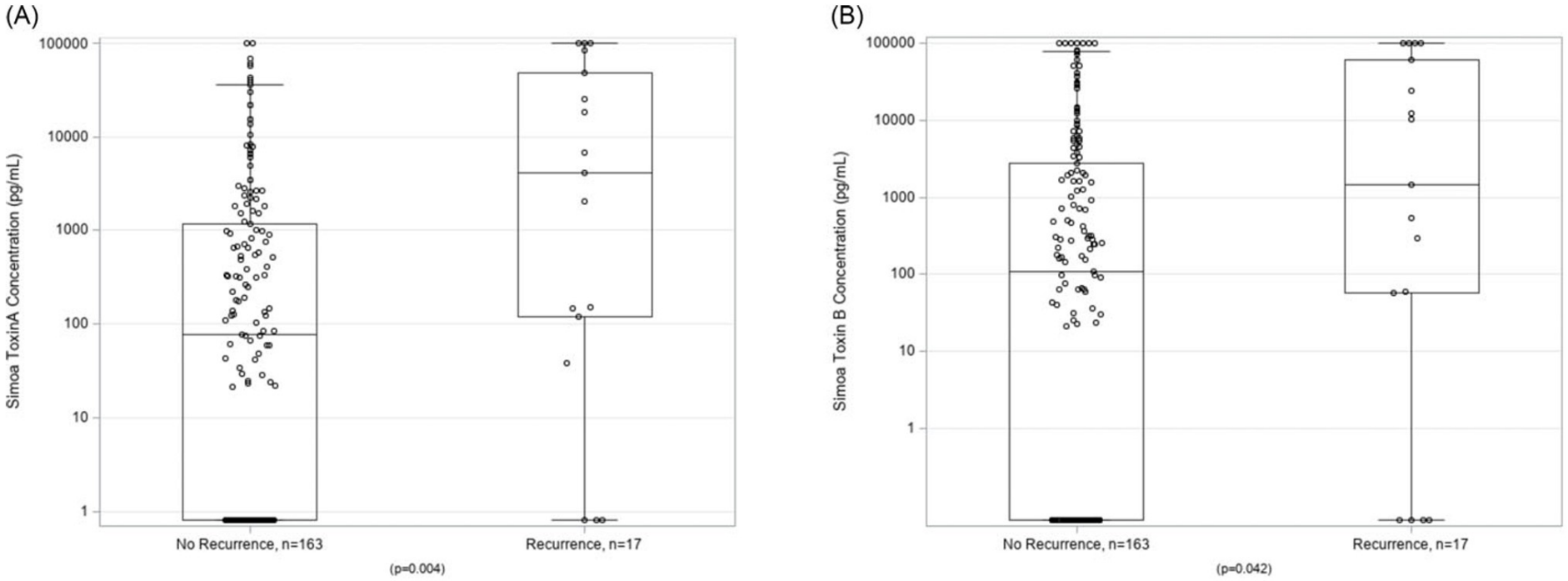


Sandora TJ, et al. *J Pediatr Infect Dis Soc*. 2022;11(10):454-458.

Simoa Ultrasensitive Digital ELISA: Distinguishing CDI from Colonization

Sandora TJ, et al. *J Pediatr Infect Dis Soc*. 2022;11(10):454-458.

Simoa Ultrasensitive Digital ELISA: Predicting CDI Recurrence



Sandora TJ, et al. *Infect Control Hosp Epidemiol*. 2023;44(9):1403-1409.

Difficile Decision #2

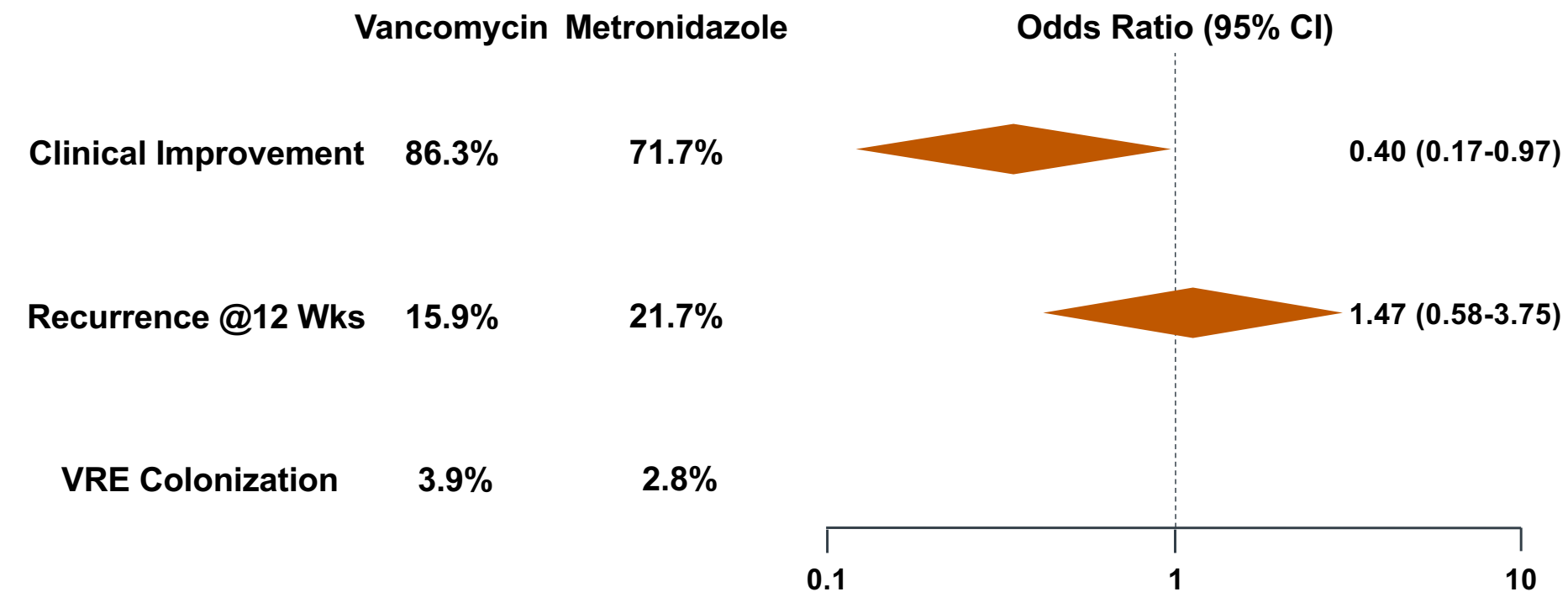
What do I treat with?

CDI Treatment Recommendations in Children

Clinical Scenario	IDSA/SHEA Treatment Recommendations
Primary CDI	Metronidazole 7.5 mg/kg/dose TID or QID for 10 days —OR— Vancomycin 10 mg/kg/dose QID for 10 days
First recurrence	Metronidazole 7.5 mg/kg/dose TID or QID for 10 days —OR— Vancomycin 10 mg/kg/dose QID for 10 days
Second or subsequent recurrence	Vancomycin 10 mg/kg/dose QID for 10 days —OR— Vancomycin tapered and pulsed —OR— Vancomycin 10 mg/kg/dose QID for 10 days, and then rifaximin 400 mg TID for 20 days —OR— FMT

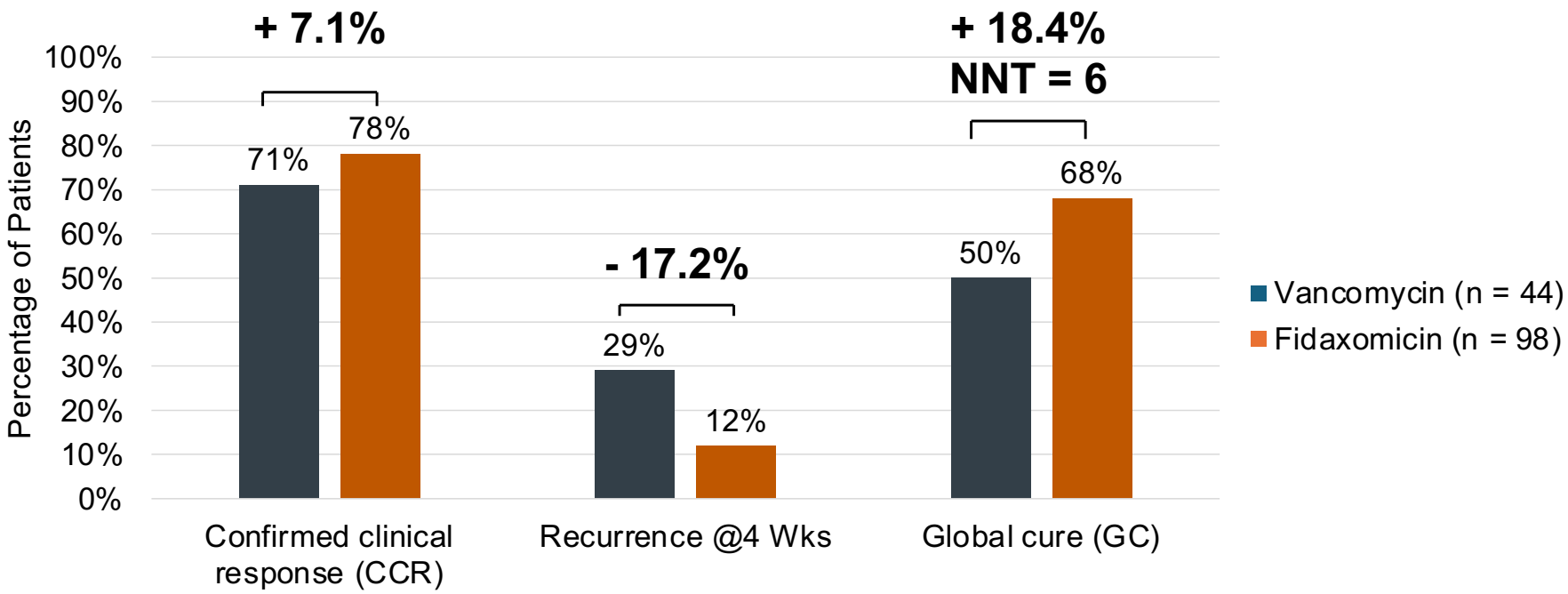
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-48.

Treatment of Nonsevere CDI With Vancomycin or Metronidazole: Propensity Score Weighted Study



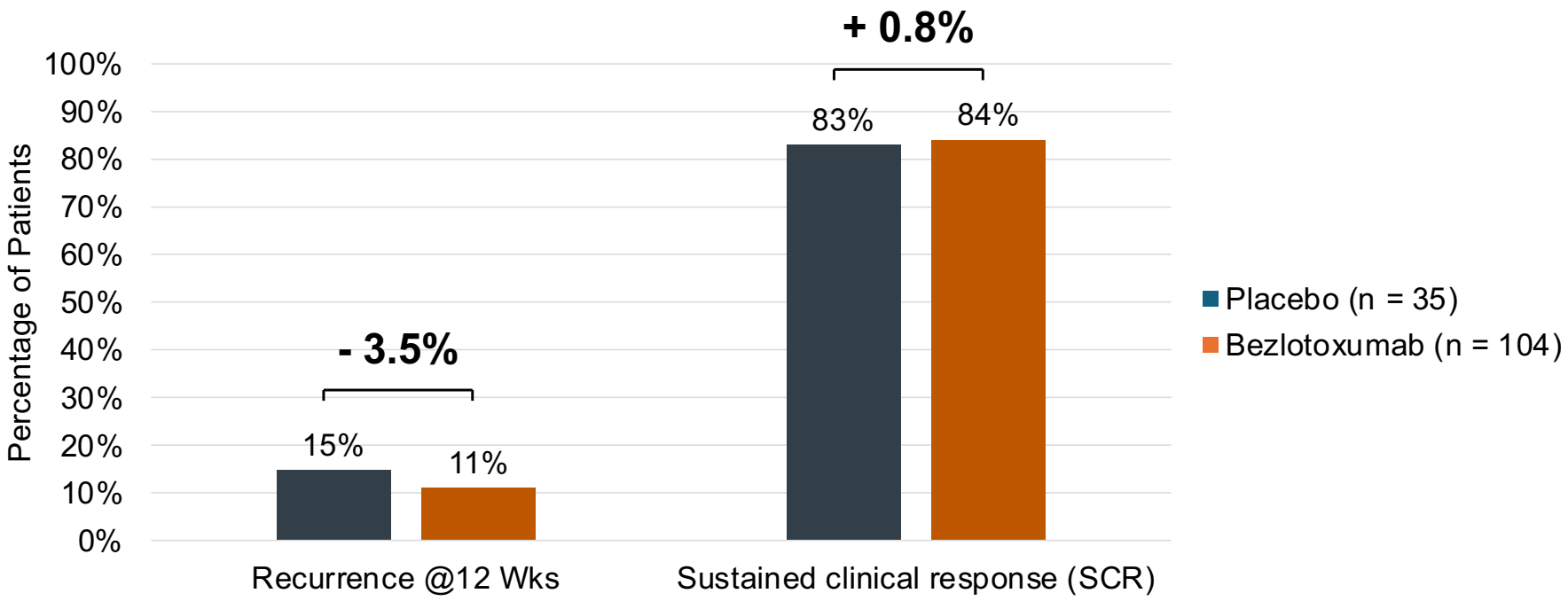
Yin J, et al. *Open Forum Infect Dis*. 2019;6(12):ofz492.

Fidaxomicin vs. Vancomycin: The SUNSHINE Trial



Wolf J, et al. *Clin Infect Dis*. 2020;71(10):2581-2588.

Bezlotoxumab vs. Placebo Following SOC Antibiotics: The MODIFY III Trial



Sferra TJ, et al. *J Pediatr Infect Dis Soc*. 2023;12(6):334-341.

How It's Going…

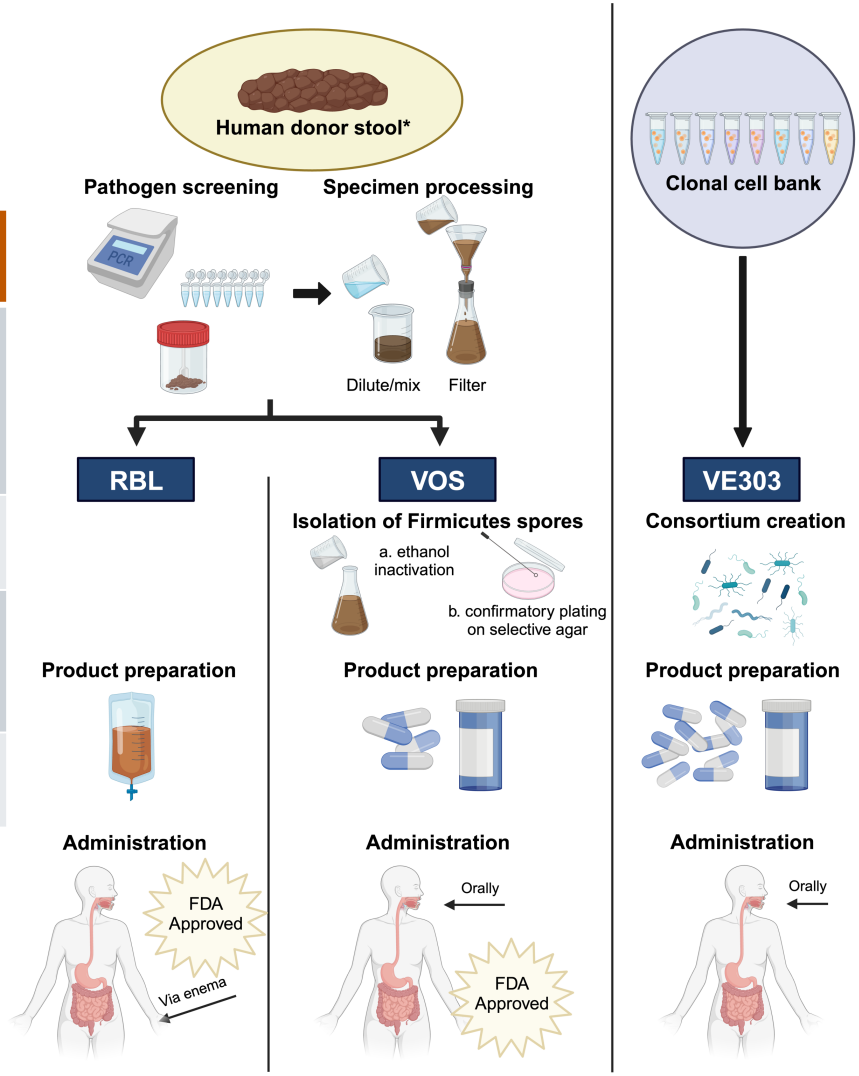
- Keighley 1978 - "~~All [*C. difficile*] strains are sensitive to metronidazole~~, but this agent is unlikely to be of value in PMC because it is rapidly absorbed from the small bowel and fails to reach therapeutic concentrations in the colon."
  - **Update the guideline treatment recommendations - remove metronidazole & add fidaxomicin**
- Teasley 1983 - "… no single test seems to be totally reliable in the diagnosis of *C. difficile* [infection]…"
  - **Distinguishing CDI from colonization using host immune markers (serum G-CSF, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-15, MCP-1, VEGF-A, TNF-α, and anti-toxin A and B IgA/IgG/IgM; stool calprotectin, anti-toxin B IgA/IgG)**
- First CDI antibiotic (fidaxomicin) FDA-approved on the basis of robust RCT data in children
  - **Update the guideline treatment recommendations - remove metronidazole & add fidaxomicin**
- ~~Bezlotoxumab FDA-approved for use in children~~
  - **To be discontinued on January 31, 2025**

Gonzales-Luna AJ, et al. *Open Forum Infect Dis*. 2021;8(8):ofab365.
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-48.
Sandora TJ, et al. *J Pediatr Infect Dis Soc*. 2022;11(10):454-458.
Kelly CP, et al. *Clin Infect Dis*. 2020;70(6):1083-1093.
Wolf J, et al. *Clin Infect Dis*. 2020;71(10):2581-2588.
Drug Shortages. FDA. Updated December 23, 2024. Accessed January 15, 2025. https://dps.fda.gov/drugshortages/discontinuations/bezlotoxumab-injection

FMT & Live Biotherapeutic Products

Product	Studied in Children?	FDA-approved Formulation
Traditional FMT	Yes	OpenBiome voluntarily suspended distribution of their investigational FMT products on September 29, 2024
Fecal microbiota, live-jslm (Rebyota)	No	150 mL retention enema
Fecal microbiota spores, live-brpk (Vowst)	No	4 capsules taken once daily for 3 days
VE-303	Yes (12 and older)	Site-less, decentralized phase 3 RCT enrolling now

OpenBiome Voluntarily Suspends FMT Shipments. OpenBiome. Accessed January 15, 2025. https://openbiome.org/feature/openbiome-voluntarily-suspends-fmt-shipments/
Rebyota. Prescribing information. Rebiotix, Inc.; 2022. Accessed January 15, 2025. https://www.rebyota.com/
Vowst. Prescribing information. Seres Therapeutics, Inc.; 2024. Accessed January 15, 2025. https://www.vowst.com/
VE-303 Study Snapshot. Science37. Accessed January 15, 2025. https://studies.science37.com/s37/inf-dis/



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