SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina

13° CONGRESSO NAZIONALE
PADOVA | 23-24 novembre 2023

Venerdì 24 novembre

Sessione 8 | Il "multifaceted plan" nella terapia e prevenzione delle infezioni

Moderatori: *S. Parisi (Padova), C. Torti (Catanzaro)*

Strategie di prevenzione primaria e secondaria delle infezioni da *Clostridioides difficile*

Alberto Enrico Maraolo, MD MSc FESCMID

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Prima Divisione – Malattie Infettive emergenti e ad alta contagiosità (ex Malattie Infettive ad indirizzo neurologico)

A.O.R.N. dei Colli – P.O. Cotugno, Napoli

DISCLOSURE

Il sottoscritto ALBERTO ENRICO MARAOLO
ai sensi dell'art. 76 comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017

dichiara

per l'evento in oggetto l'esistenza negli ultimi due anni di rapporti di natura finanziaria e/o lavorativa con le seguenti imprese commerciali operanti in ambito sanitario:

- Nessuno

IPC PERSPECTIVE

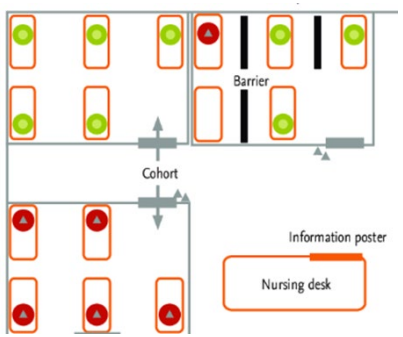
Infection Control & Hospital Epidemiology (2023), **44**, 527–549
doi:10.1017/ice.2023.18

SHEA

SHEA/IDSA/APIC Practice Recommendation

Strategies to prevent *Clostridioides difficile* infections in acute-care hospitals: 2022 Update

3.	Use contact precautions for infected patients, single-patient room preferred. (Quality of evidence: LOW for hand hygiene; MODERATE for gloves; LOW for gowns; LOW for single-patient room)
	a. Perform hand hygiene based on CDC or WHO guidelines before and after entering the room (ie, immediately before donning and after removing personal protective equipment).
	b. Place patients with CDI on contact precautions to help reduce patient-to-patient spread of the organism.
	c. Cohorting of patients with CDI is acceptable when single private rooms are not available.
	d. Ensure that adequate supplies for contact precautions are readily available.
	e. Follow appropriate criteria for discontinuing contact precautions.
4.	Adequately clean and disinfect equipment and the environment of patients with CDI. (Quality of evidence: LOW for equipment; LOW for environment)
	a. *C. difficile* spores contaminate the environment in which patients are housed and the equipment used to care for them.
	b. Contaminated surfaces and equipment are potential reservoirs for transmission of *C. difficile*.
	c. Develop and implement protocols for disinfection of equipment and the environment.
	d. Dedicate noncritical patient care items, such as blood pressure cuffs, stethoscopes, and thermometers, to a single patient with *C. difficile*.



4. Prolong the duration of contact precautions after the patient becomes asymptomatic until hospital discharge. (Quality of evidence: LOW)
   a. For patients with CDI, CDC currently recommends[114] contact precautions for at least 48 hours after diarrhea resolves. However, some hospitals may choose to extend contact precautions for the duration of hospitalization even if symptoms have resolved. This is the recommendation for patients who have diarrhea and are positive by NAAT, irrespective of EIA result (ie, even if patient is *C. difficile* positive but is suspected to be colonized and to have an alternate cause of diarrhea).

Clinical Infectious Diseases
IDSA GUIDELINE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
Clinical Infectious Diseases® 2018;66(7):e1–e48

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)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

XVI. How long should isolation be continued?

Recommendations

1. Continue contact precautions for at least 48 hours after diarrhea has resolved *(weak recommendation, low quality of evidence)*.
2. Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI *(weak recommendation, low quality of evidence)*.

XXIV. Should asymptomatic carriers of *C. difficile* be identified and isolated if positive?

Recommendation

1. There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions *(no recommendation)*.

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®
August 2018 Volume 56 Issue 8 e00782-18
POINT-COUNTERPOINT

Check for updates

Point-Counterpoint: Active Surveillance for Carriers of Toxigenic *Clostridium difficile* Should Be Performed To Guide Prevention Efforts

L. Clifford McDonald,[a] Daniel J. Diekema[b,c]

Screening and isolation of asymptomatic carriers may be a prevention strategy to be considered in addition to currently recommended strategies of antibiotic stewardship, i.e., rapid and accurate diagnosis combined with timely implementation of contact precautions and effective environmental cleaning and disinfection strategies

Existing data **do not support** the **routine use of active surveillance for asymptomatic C. difficile carriage**.
We should instead continue to invest in improved implementation of practices known to reduce risk for all health care associated infections, CDI included.
In particular, we should expand and optimize active antibiotic stewardship in all at-risk populations.

C. DIFFICILE TRANSMISSION

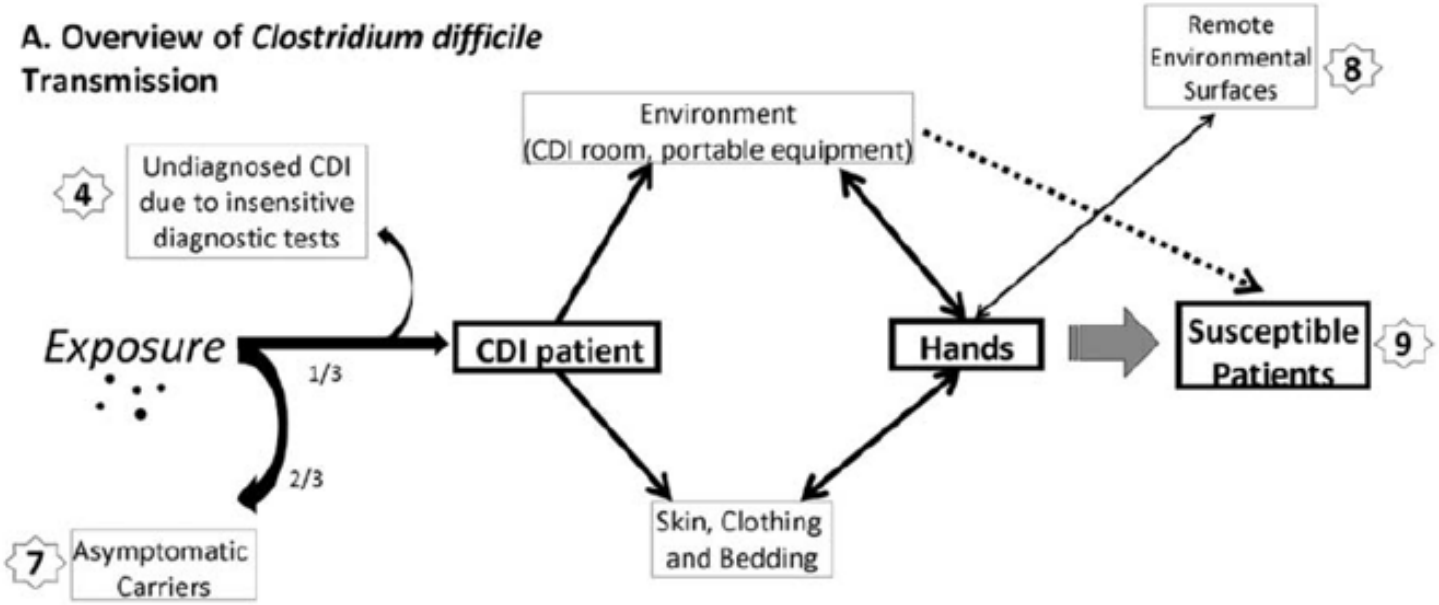
Preventing Transmission of *Clostridium difficile*: Is the Answer Blowing in the Wind?

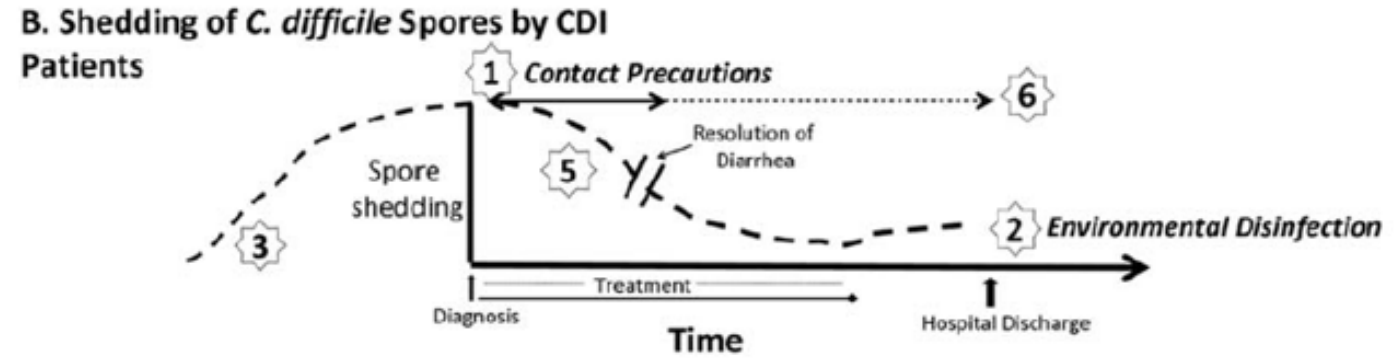
Curtis J. Donskey

Clinical Infectious Diseases 2010;50(11):1458–1461

Approximately one-third of patients who acquire *C. difficile* colonization develop CDI, whereas the remaining two-thirds become asymptomatic carriers. **Patients with CDI shed spores through fecal contamination. Susceptible patients acquire spores from the contaminated hands of health care workers or from contaminated environmental surfaces.** Basic measures to prevent transmission include

(1) contact precautions while diarrhea is present and
(2) environmental disinfection of CDI rooms after discharge of patients. Other potential sources of transmission and potential interventions include the following:
(3) CDI not being diagnosed and patients not being isolated in a timely fashion (intervention: preemptive isolation of patients with suspected CDI);
(4) CDI not being diagnosed because of insensitive testing methods, such as enzyme immunoassay for toxin (intervention: use of testing methods with increased sensitivity);
(5) environmental surfaces in CDI rooms and the skin of patients with CDI (interventions: daily disinfection of surfaces in isolation rooms and daily bathing to reduce the burden of spores on skin);
(6) persistent shedding of spores after resolution of diarrhea (intervention: continuation of contact precautions to time of discharge);
(7) asymptomatic carriers (intervention: improve environmental disinfection in non-CDI rooms);
(8) contaminated surfaces outside patient rooms (intervention: improve environmental disinfection); and
(9) overuse of antibiotics contributing to high numbers of susceptible patients (intervention:antimicrobial stewardship).





EPIDEMIOLOGICAL PERSPECTIVE

nature
International journal of science

Article | Published: 03 January 2018

Dietary trehalose enhances virulence of epidemic *Clostridium difficile*

J. Collins, C. Robinson, H. Danhof, C. W. Knetsch, H. C. van Leeuwen, T. D. Lawley, J. M. Auchtung & R. A. Britton

We propose that the implementation of trehalose as a food additive into the human diet, shortly before the emergence of two epidemic lineages (Ribotypes RT027 and RT078), helped select for their emergence and contributed to hypervirulence.

Medical News & Perspectives

JAMA Published online March 21, 2018

Did a Sugar Called Trehalose Contribute to the *Clostridium difficile* Epidemic?

Jennifer Abbasi

"The impact of food additives on the microbiome is a knowledge gap right now in the field... the ingredients potentially could either exacerbate or promote the onset and progression of disease."

EBioMedicine 43 (2019) 347–355

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

ELSEVIER

EBioMedicine
Published by THE LANCET

Research paper

Clostridium difficile trehalose metabolism variants are common and not associated with adverse patient outcomes when variably present in the same lineage

David W. Eyre [a,b,*], Xavier Didelot [c], Anthony M. Buckley [d], Jane Freeman [d], Ines B. Moura [d], Derrick W. Crook [b,e,f], Tim E.A. Peto [b,e,f], A. Sarah Walker [b,e,f], Mark H. Wilcox [d,1], Kate E. Dingle [b,1]

4. Discussion

Convincing evidence, including molecular experiments using gene deletions and recombinants, demonstrates that trehalose metabolism variants in *C. difficile* confer the ability to metabolise low concentrations of trehalose and that this provides a competitive advantage in growth media and laboratory animals [6]. However, we have shown here that trehalose metabolism variants are widespread in multiple distinct *C. difficile* genotypes causing human infections, representing genetically divergent *C. difficile* clades. The *treR* mutations conferring the L172I and C171S substitutions are ancient and widely conserved within clades 2 and 4 respectively. Similarly, the genetic diversity within the four-gene cluster follows the *C. difficile* population structure. While the importance of trehalose metabolism variants in the success of ribotype-027 and ribotype-078 cannot be discounted, other hypotheses are required to explain why these lineages have been so successful when many other lineages with the same trehalose metabolism variants, many from the same clades, have not been.

ONE HEALTH PERSPECTIVE

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
2021, VOL. 19, NO. 12, 1543–1552
https://doi.org/10.1080/14787210.2021.1967746

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Clostridioides difficile infection: an emerging zoonosis?

Chin-Shiang Tsai[a,b,c], Yuan-Pin Hung[d], Jen-Chieh Lee[c], Ling-Shan Syue[c], Po-Ren Hsueh[e] and Wen-Chien Ko[c,f]

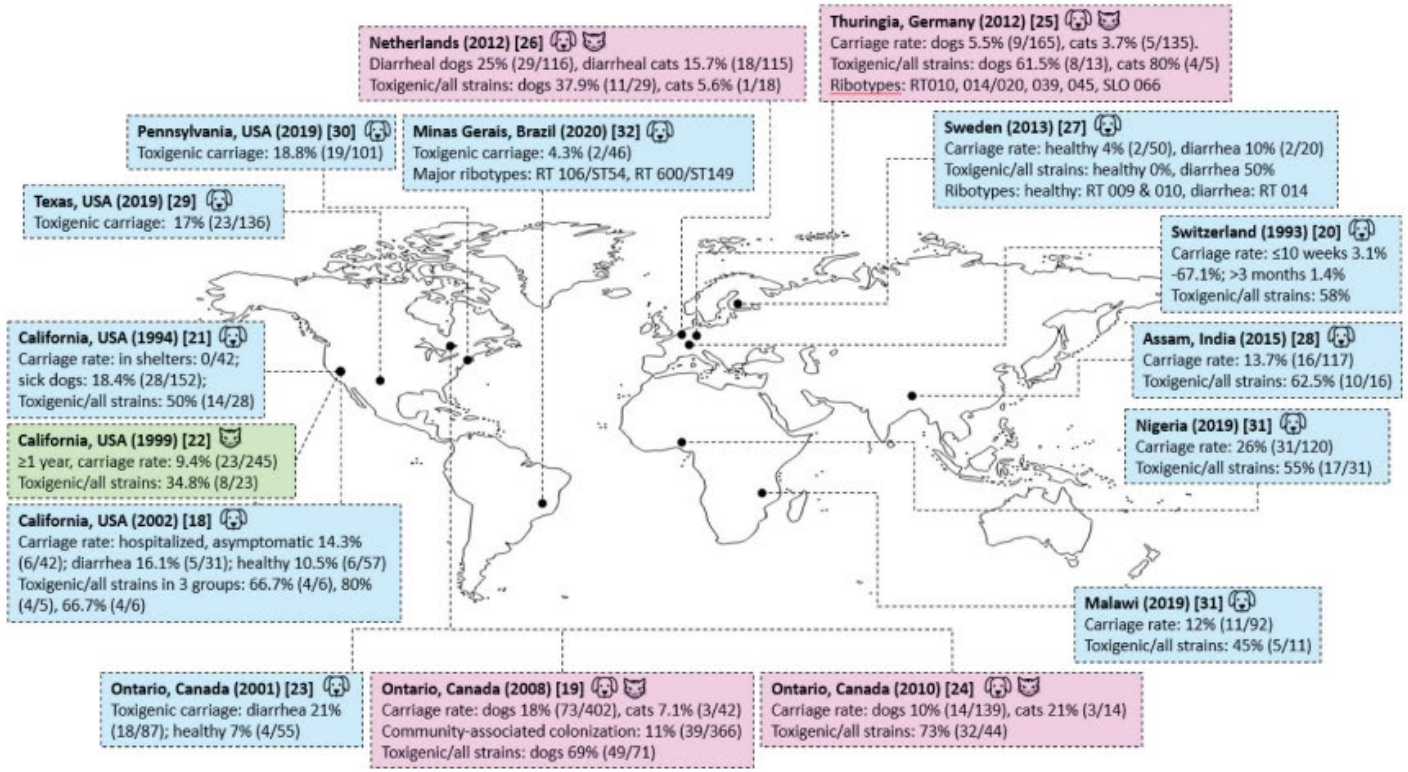


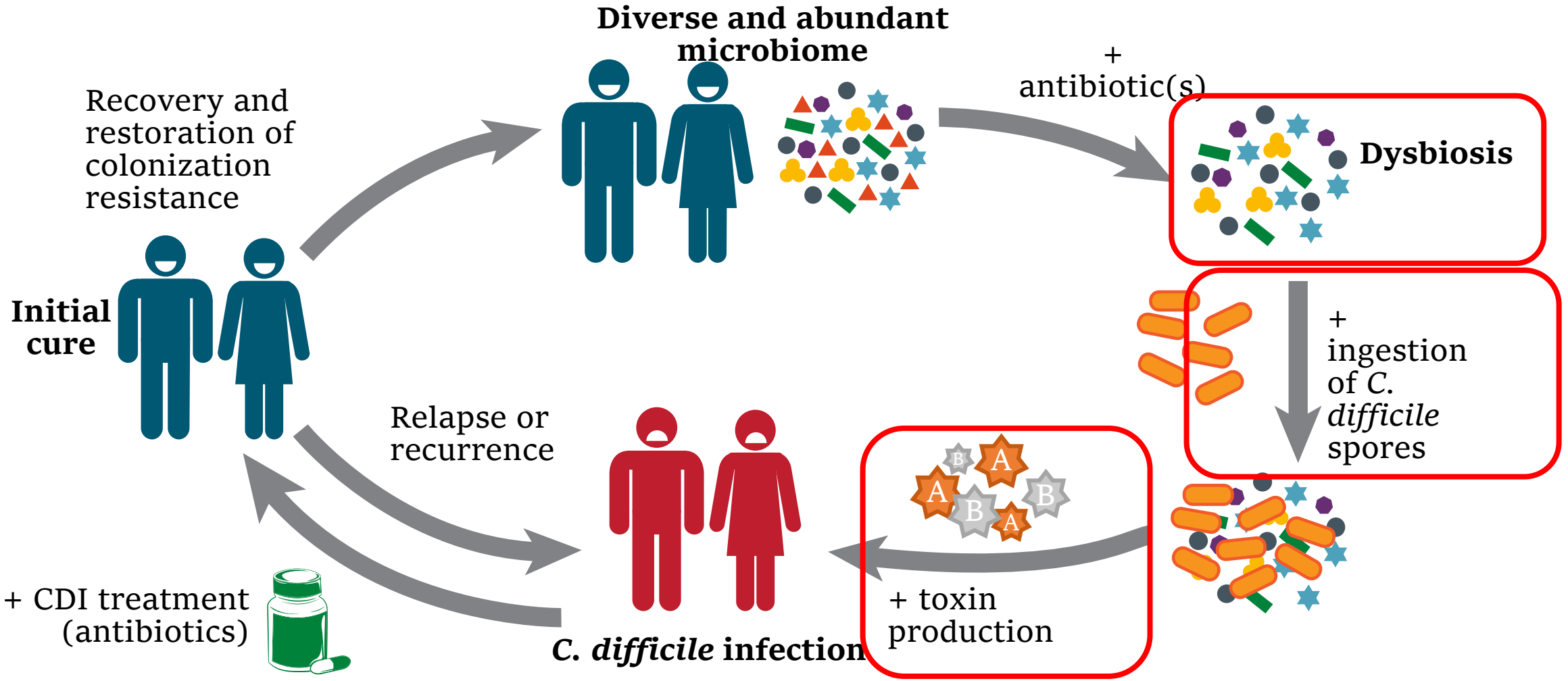
Figure 1. Published studies since 1990s showing *Clostridioides difficile* carriage rates, toxigenic strains, and ribotypes in household pets from different countries.

*In each box, there is a title marked in bold that includes the study province/state and country, publication year, reference number, animal species, followed by C. *difficile* carriage rate, the rate of toxigenic strains, and major ribotypes (if any).

Article highlights

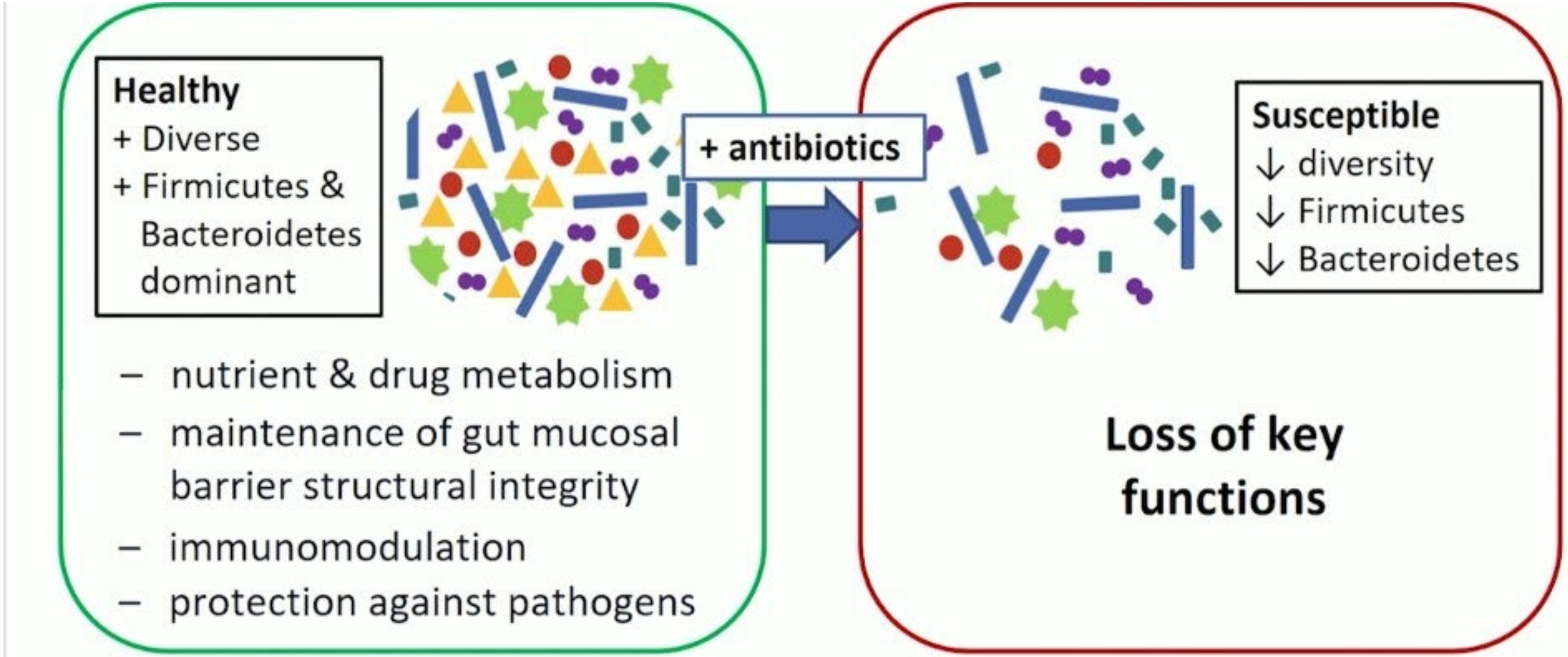
- There is increasing concern for community-associated *Clostridioides difficile* infection (CDI) and a growing number of reports on CDI in animals. The potential for zoonotic transmission cannot be overemphasized.
- Asymptomatic carriage of *C. difficile* toxigenic strains pathogenic to humans was noted in household pets.
- Exposure to pastures, slaughterhouses, or meat processing of livestock have been associated with the risk of *C. difficile* transmission to humans.
- Risk factors for *C. difficile* colonization in livestock include exposure to individuals susceptible to CDI, exposure to environments contaminated with *C. difficile*, dietary changes, and antibiotic abuse.
- Hypervirulent *C. difficile* strains including RT 078, 126, and 127 are found in pig farms. Moreover, there is genetic relatedness between RT 078 isolates from patients and pigs, indicative of zoonotic transfer to human.
- Seafood could be contaminated by *C. difficile*, but the transmission from seafood to humans is not well confirmed.
- Whole genome sequencing proves objective evidence suggestive of mutual spread of RT 078, 014, and 046 between animals and humans.

CDI PATHOGENESIS



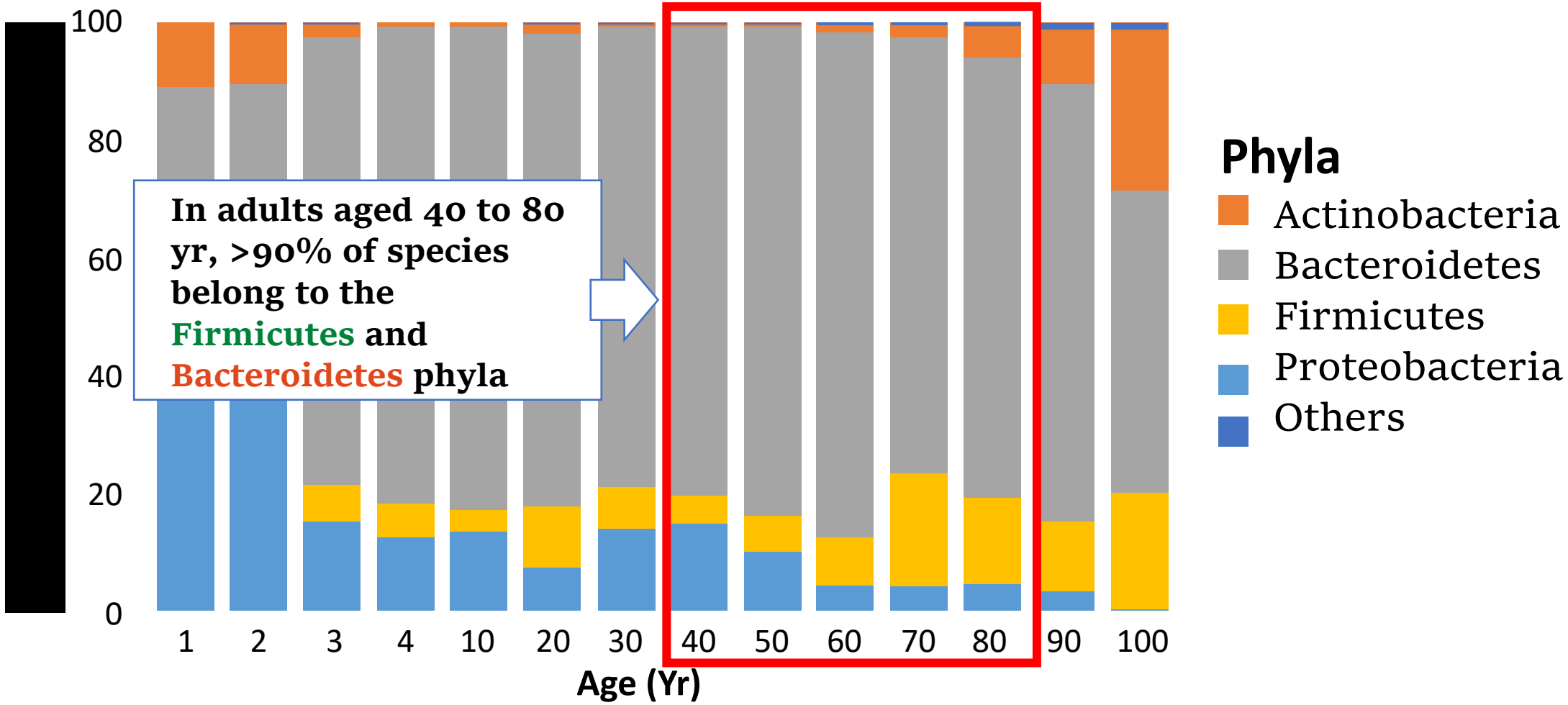
Britton. Gastroenterology. 2014;146:1547.

A MICROBIOTA-MEDIATED DISEASE



Shreiner AB et al. *Curr Opin Gastroenterol*. 2015; 31(1):69-75.

DEFINING A "HEALTHY" MICROBIOME



Odamaki. BMC Microbiology. 2016;16:90. Qin. Nature. 2010;464:59.

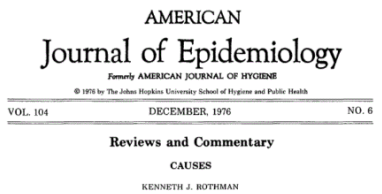
CAUSAL FRAMEWORK FOR C. DIFF.

The sufficient-component cause model	Necessary	Sufficient
Antibiotic exposure	✗	✗
C. difficile acquisition	✓	?

"You can suffer C. difficile infection without exposure to antibiotics, but you can't suffer C. difficile infection without exposure to C. difficile..."

Courtesy of Jon Otter, 2018, www.jonotter.net

The sufficient cause framework conceptualizes **causation as a collection of different sufficient conditions or causes for the occurrence of an outcome (effect). Each sufficient condition or cause is usually conceived of as consisting of various (necessary) component causes, with the property that if all components are present the sufficient cause is complete and the outcome occurs**. Best known among epidemiologists is Rothman's sufficient-component cause (SCC) model. Rothman conceived of each sufficient cause as representing a mechanism that produces the outcome, such that if all components were present then a mechanistic sequence would be set in motion that would inevitably produce the outcome.


AMERICAN
Journal of Epidemiology
Formerly AMERICAN JOURNAL OF HYGIENE
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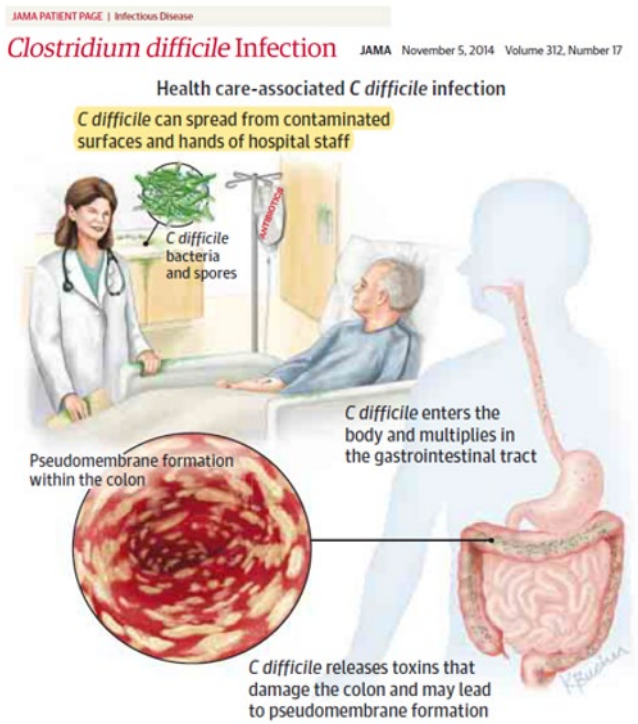
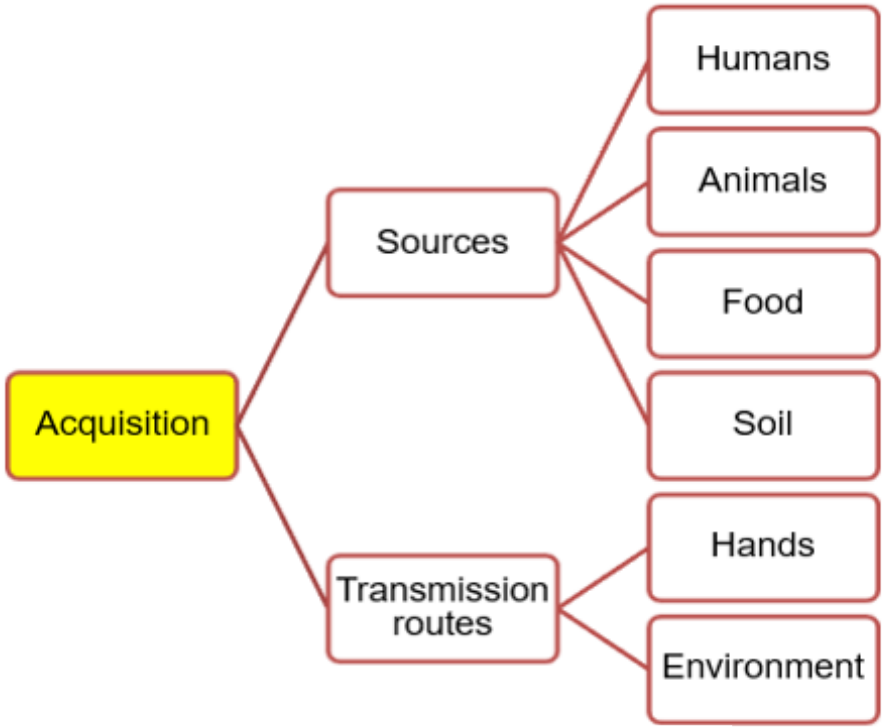
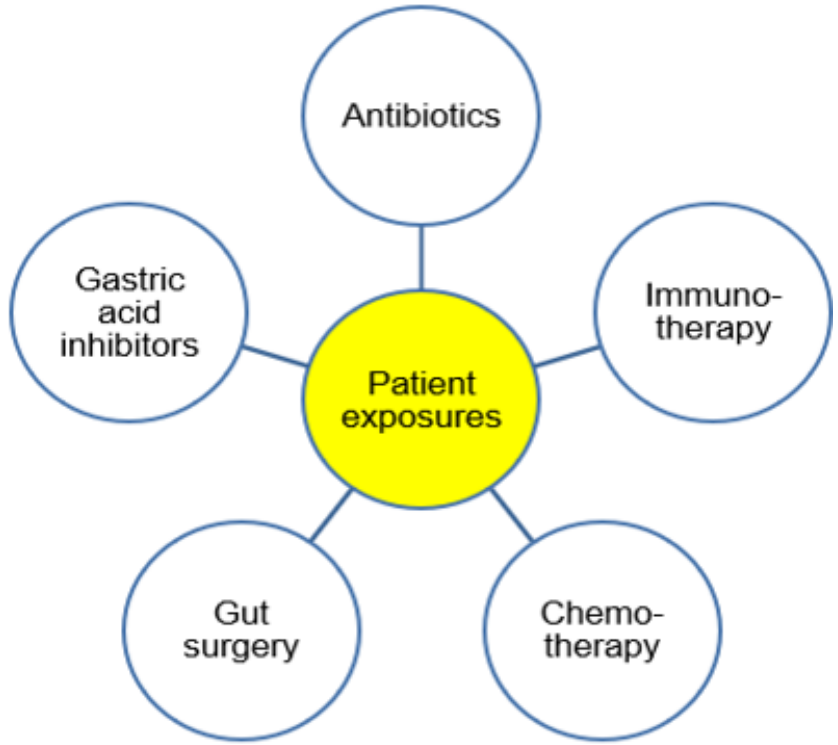
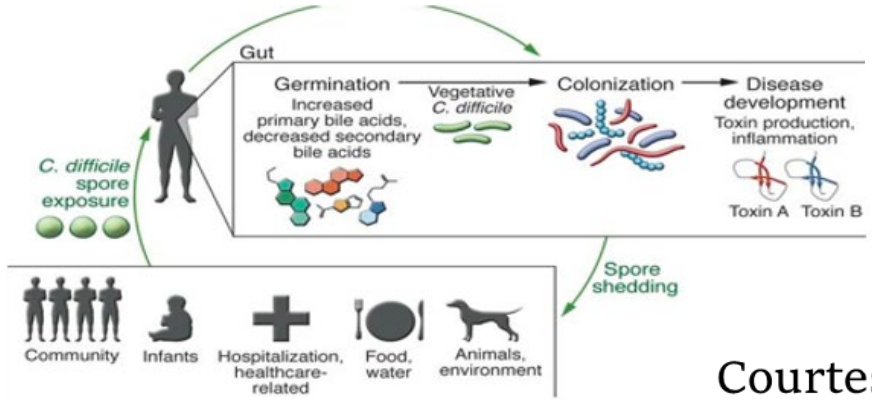
VOL. 104 DECEMBER, 1976 NO. 6
Reviews and Commentary
CAUSES
KENNETH J. ROTHMAN

C. DIFFICILE INFECTION: DRIVERS









Courtesy of Jon Otter, 2018, www.jonotter.net

GUT-MICROBIOME-BRAIN AXIS

A Supplement to

Gastroenterology & Endoscopy News | IDSE Infectious Disease Special Edition | Pharmacy Practice News

Special REPORT

Kerry LaPlante, PharmD, FCCP, FIDSA, FIDP

Robert Orenstein, DO

Glenn Tillotson, PharmD, FIDSA, FCCP

Restoring the Full Diversity of the Gut Microbiome:

Can It Break the Cycle of Recurrent *C. Difficile* Infection?

Perturbation of the gut microbiome may lead to loss of diversity or function, a condition sometimes referred to as dysbiosis.[1,6] A persistent reduction in microbial diversity may lead to adverse consequences for the host, including overgrowth of undesirable organisms or pathogens.[1,4] Although most often associated with consumption of antimicrobials, diet, chemotherapy, pathogenic microorganisms and genetics also may adversely impact the microbiome (Figure 1).[1,14-16]

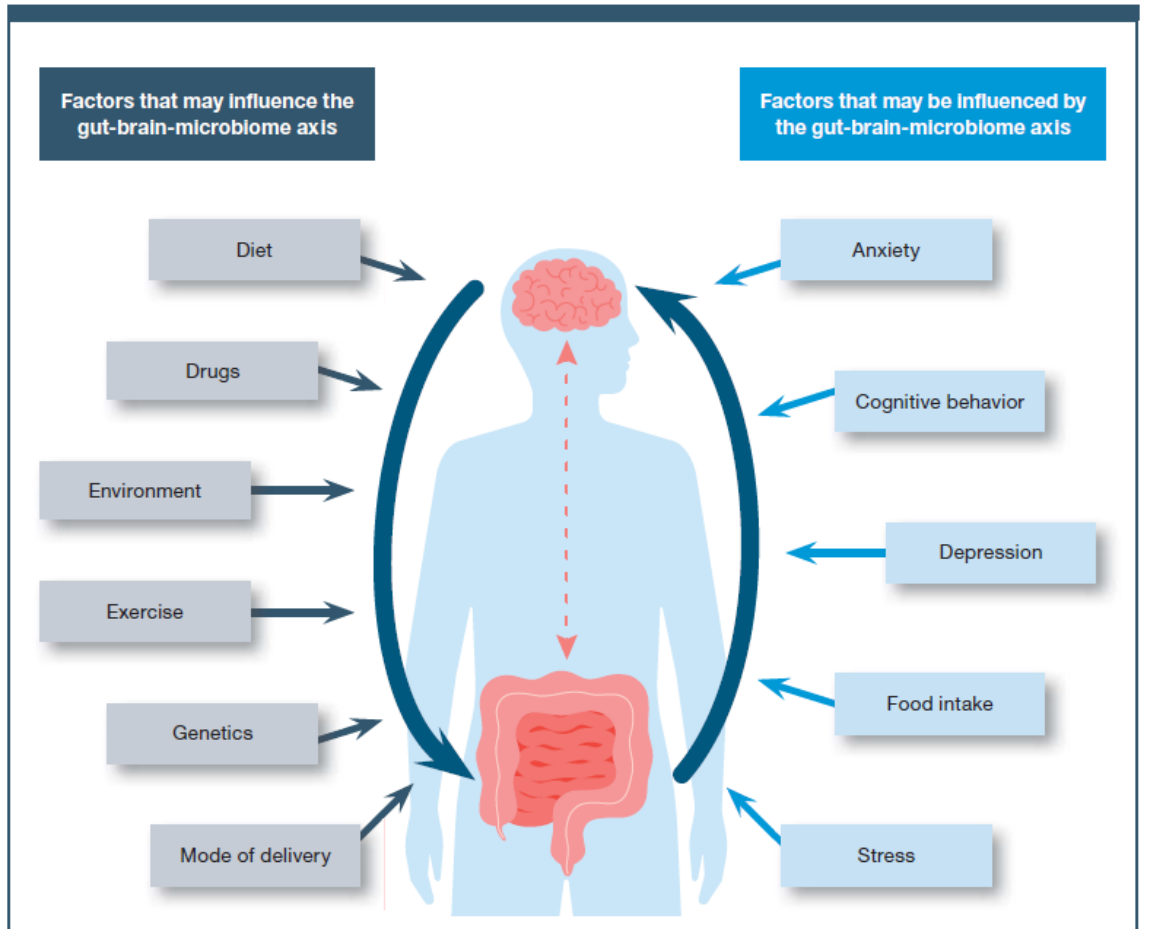
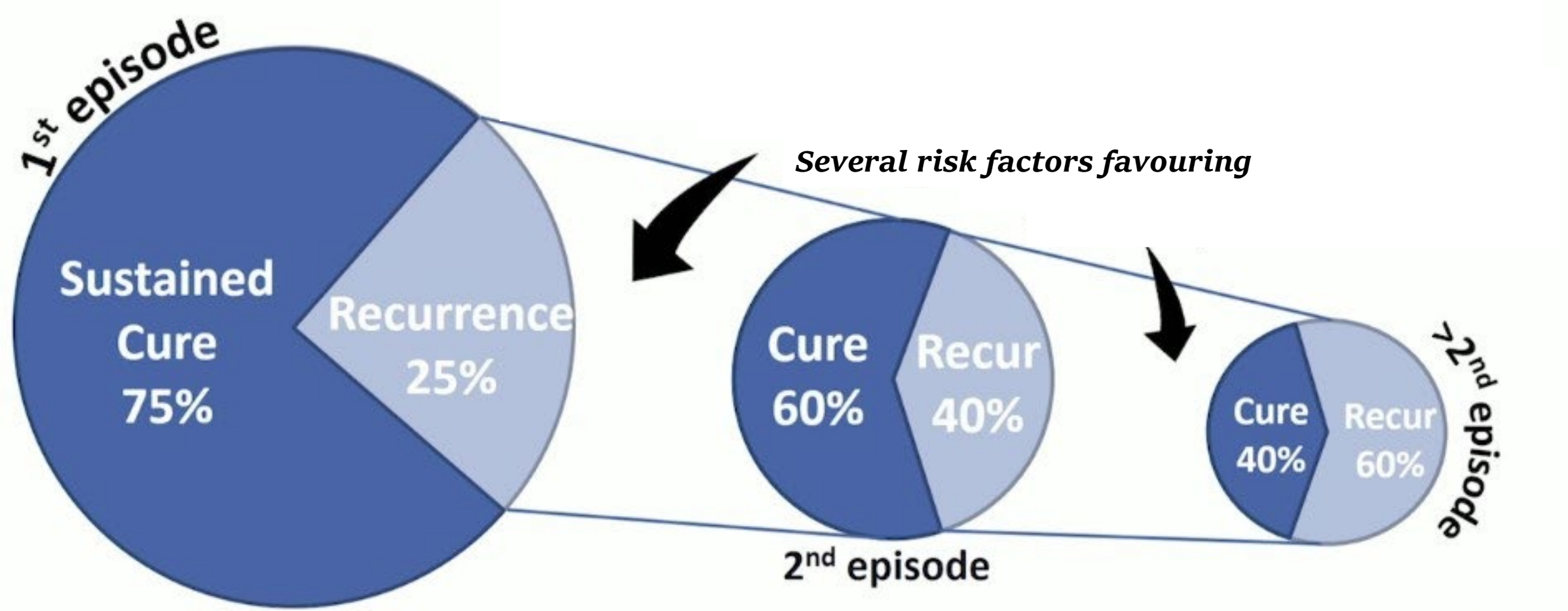


Figure 1. Factors that may affect the gut-microbiome-brain axis.

Several factors affect the network of interactions between the brain and the gut microbiota that can alter signaling mechanisms and affect different systems, including the immune system.

Based on references 14 and 16.

THE CYCLE OF RECURRENCE



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.

MECHANISMS OF RECURRENCE

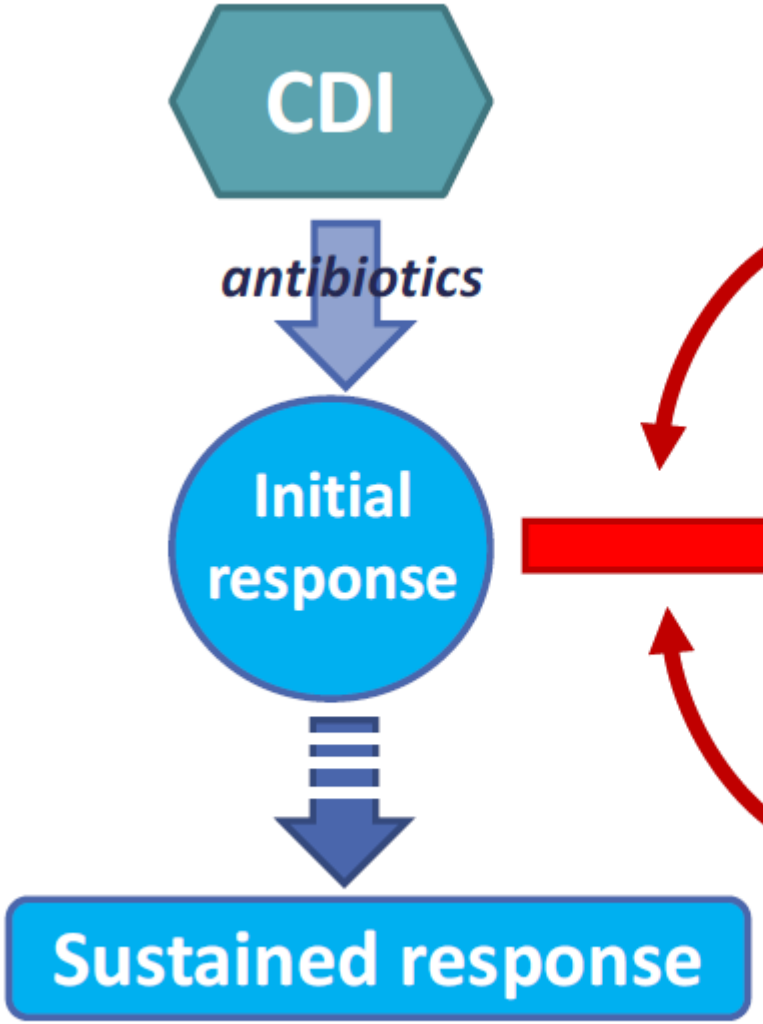
- The primary risk factor for CDI is exposure to broad-spectrum antibiotics
  - Firmicutes essential for host defense and colonization resistance
    - Primary bile acids versus secondary bile acids
  - Microbiota resilience is critical for a durable clinical response
    - Recovery of beneficial resident bacteria after discontinuation of antimicrobial use

Theriot CM et al. *mSphere.* 2016; 1(1):e00045-15.
Sorg JA et al. *J Bacteriol.* 2009; 191:1115-7.

- "Window of vulnerability"
  - Most recurrences occur within days to weeks after completion of antibiotic therapy
    - Continued disruption of the microbiota facilitating *C. difficile* spore germination

Abujamel T et al. *PLoS One.* 2013; 8(10):e76269.
Louie TJ et al. *Clin Infect Dis.* 2012; 55(Suppl 2):S132–42.

CDI OUTCOMES AND DETERMINANTS

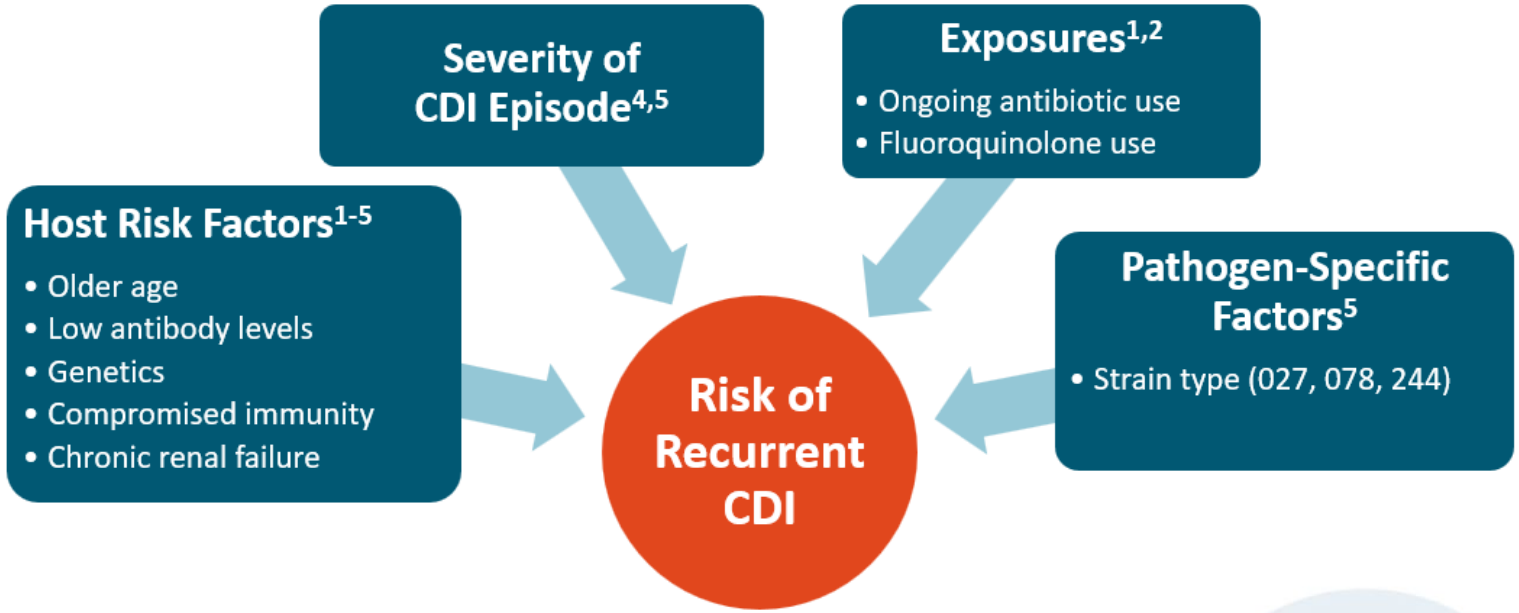


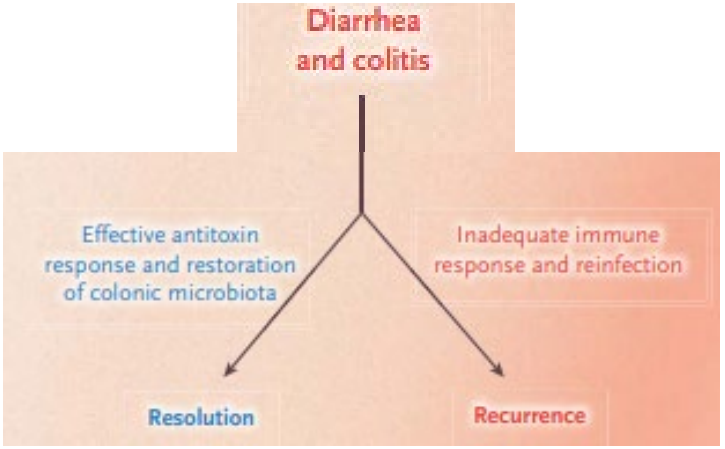
Reason #1: Failure to defend against infecting bacteria during window of vulnerability

Recurrence

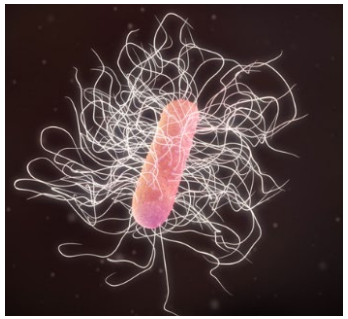
Reason #2: Failure to restore healthy microbiota & colonization resistance

RISK FACTORS FOR RECURRENCE





1. Deshpande. Infect Control Hosp Epidemiol. 2015;36:452. 2. Abou Chakra. PLoS One. 2014;9:e98400. 3. Garey. J Hosp Infect. 2008;70:298. 4. D'Agostino. Clin Infect Dis. 2014;58:1386. 5. Gerding. Clin Infect Dis. 2018;67:649.



Recurrent CDI risk factors based on the ESCMID 2021 guidelines

- Older age (> 65 y)
- Prior CDI episode(s)
- Episode of HA-CDI and hospitalization in the past 3 mo
- Concomitant non-CDI antibiotic use after the diagnosis of CDI
- Use of PPIs started during/after CDI diagnosis

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; PPI, proton pump inhibitor.
van Prehn J, et al. Clin Microbiol Infect. 2021;27(suppl 2):S1-S21.

RECURRENCE: DEFINITION

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION

Stockholm, April 2017

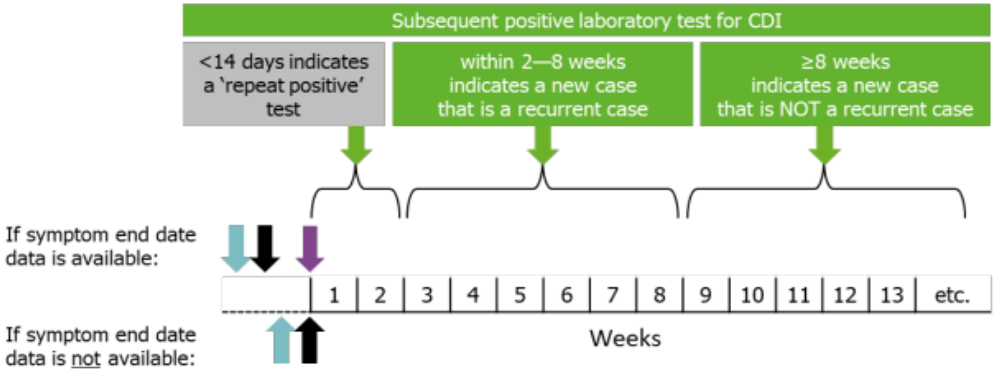
Repeat positives

CDI cases with a positive *C. difficile* stool specimen less than 14 days since the last positive specimen are considered duplicate episodes, and are not reported as separate cases (Figure 1).

Figure 1. Designation of new CDI episodes as a recurrent case and/or a new case, based the date of positive laboratory tests for CDI

Key:

- CDI symptom onset date
- First positive laboratory test for CDI
- Symptom end date
- Subsequent positive laboratory test for CDI



Recurrent CDI cases

In clinical practice, it is not possible to differentiate between a relapse involving the same strain and re-infection with a different strain. The term 'recurrence' is used as a designation for both.

Recurrent CDI cases are patients meeting the CDI case definition with an episode of CDI (return of diarrhoeal stools with a positive laboratory test after the end of treatment) more than two weeks and less than eight weeks following the onset of a previous episode (no matter where that previous episode occurred).

CDI cases with symptom onset more than eight weeks after the onset of a previous episode are included as new CDI cases. When evaluating the time window, the date of the return of the CDI symptoms should be considered. Only consider the date of sampling if the date of onset of symptoms is unknown.

TIMING ISSUES

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Oral Vancomycin as Secondary Prophylaxis for Prevention of Recurrent *Clostridioides difficile* Infection

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023

CASE VIGNETTE

A Woman with a UTI and a History of *Clostridioides difficile* Infection

Leslie L. Chang, M.D.

A 72-year-old woman with a history of spinal cord injury and resultant quadriplegia from a motor vehicle accident many years earlier presents to the emergency department with fevers, abdominal pain, and increased urinary frequency. She has a neurogenic bladder for which intermittent straight catheterization is performed at home. Over the past 2 years, she has been admitted to the hospital several times for recurrent urinary tract infections (UTIs), for which she has received intravenous antibiotic therapy. Her most recent admission, 3 months ago, was complicated by a diagnosis of nonsevere *Clostridioides difficile* infection, which was treated with fidaxomicin.

In the emergency department, she is febrile (temperature, 38.4°C) and her condition is hemodynamically stable. Examination reveals a tired-appearing woman with suprapubic tenderness and dry mucous membranes. She reports no diarrhea, nausea, or vomiting. Laboratory studies show a neutrophilic-predominant leukocytosis and mildly elevated creatinine level, and a straight-catheter urinalysis is consistent with infection. Urine culture is pending. As the admitting general medicine provider, you review her previous microbial data and note that cultures have never grown a multidrug-resistant organism. You decide to initiate intravenous ceftriaxone for treatment of her UTI, but you must also consider whether oral vancomycin should be administered prophylactically to reduce her risk of recurrent *C. difficile* infection.

OPTION 1

Recommend Prophylactic Oral Vancomycin

Jessica Allegretti, M.D., M.P.H.

Option 1

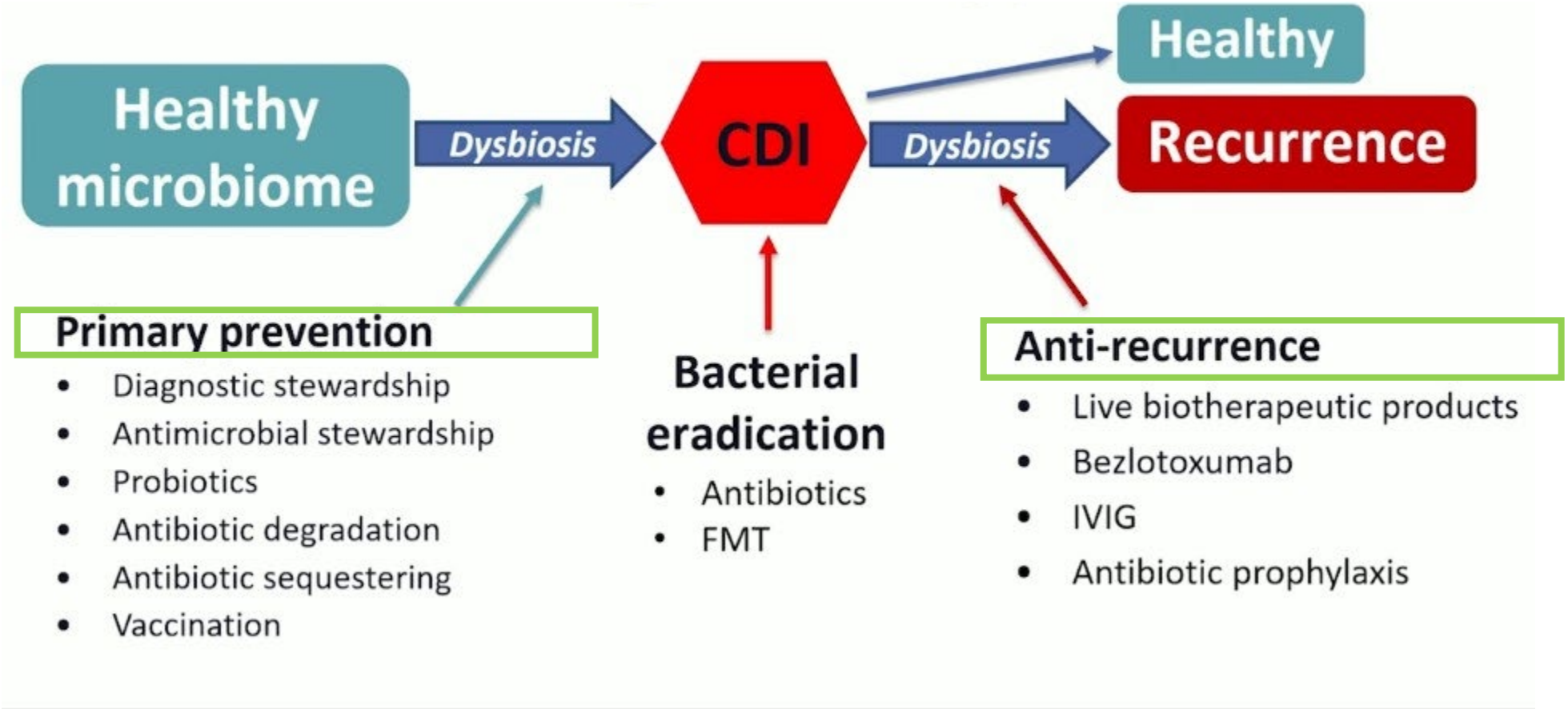
Option 2

OPTION 2

Do Not Recommend Prophylactic Oral Vancomycin

Andrew M. Skinner, M.D., and
Erik R. Dubberke, M.D., M.S.P.H.

THE MOMENTS FOR PREVENTION



HOW TO PREVENT CDI

Clinical Microbiology and Infection

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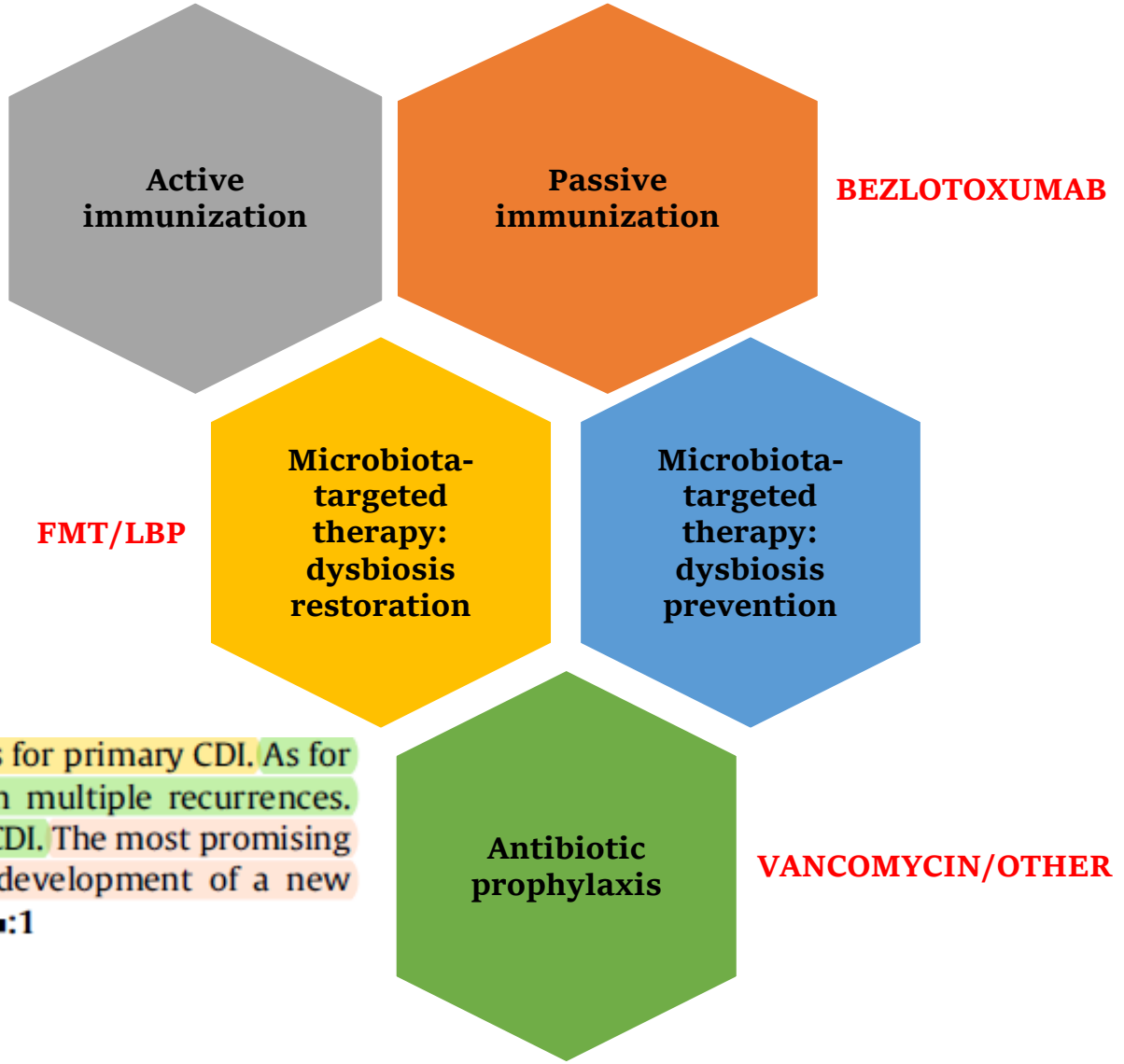
How to: prophylactic interventions for prevention of *Clostridioides difficile* infection

Elena Reigadas [1,2,*], Joffrey van Prehn [3], Marco Falcone [4], Fidelma Fitzpatrick [5,6], Maria J.G.T. Vehreschild [7], Ed J. Kuijper [3,8], Emilio Bouza [1,2], on behalf of the European Society of Clinical Microbiology and Infectious Diseases Study Group on *Clostridioides difficile* (ESGCD) and Study Group for Host and Microbiota interaction (ESGHAMI)

Implications: There are no proven effective, evidenced-based prophylaxis options for primary CDI. As for secondary prevention, FMT is considered the option of choice in patients with multiple recurrences. Bezlotoxumab can be added to standard treatment for patients at high risk for R-CDI. The most promising strategies are those aimed at reducing changes in intestinal microbiota and development of a new effective non-toxin-based vaccine. **Elena Reigadas, Clin Microbiol Infect 2021;▪:1**



CDI PREVENTION: WHAT LGs SAY

microorganisms

MDPI

Review

Controversies in the Prevention and Treatment of *Clostridioides difficile* Infection in Adults: A Narrative Review

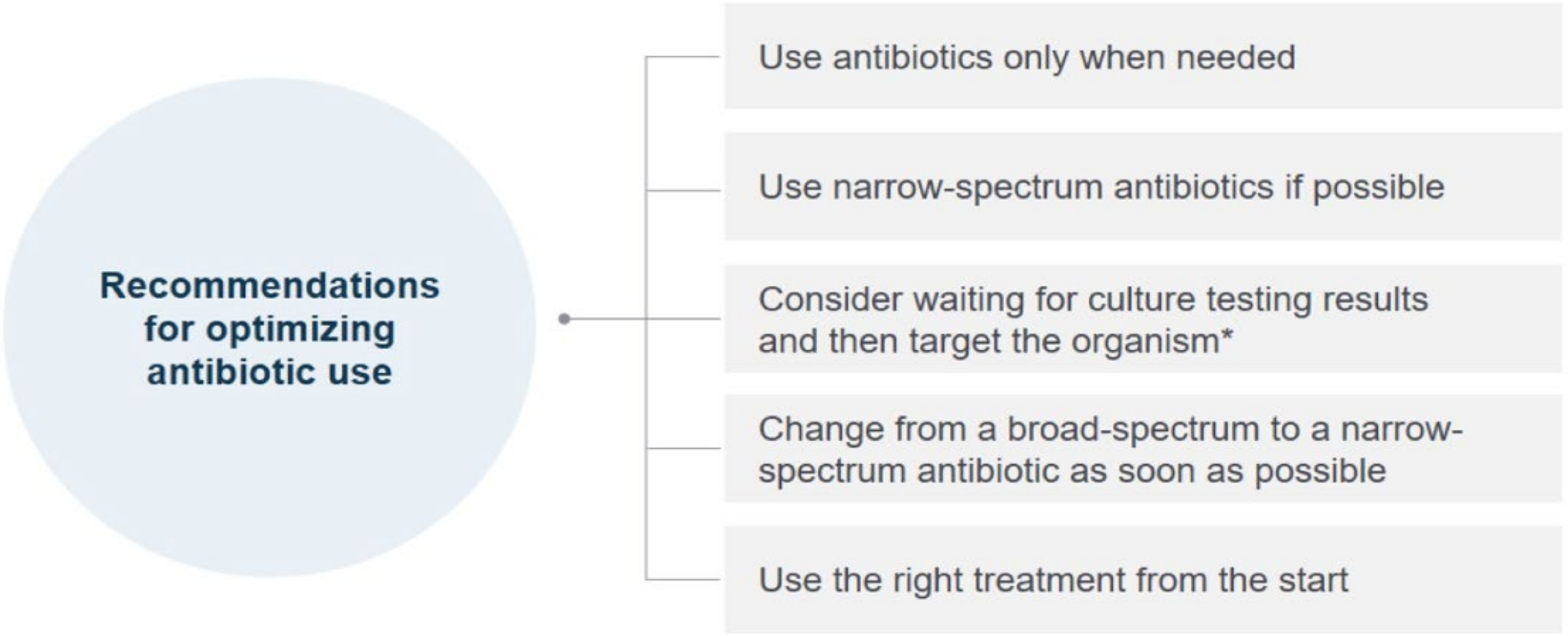
Taryn B. Bainum [1], Kelly R. Reveles [2,3], Ronald G. Hall II [1], Kelli Cornell [1] and Carlos A. Alvarez [1,4,*]

Microorganisms **2023**, *11*, 387. https://doi.org/10.3390/microorganisms11020387

Table 2. Preventative Strategies in CDI.

	IDSA / SHEA	ACG	ESCMID	Current Review
Primary Prophylaxis to Prevent an Initial CDI Episode				
Probiotics for primary prevention	Insufficient evidence	Recommends against	Not routinely recommended	Optimal role to be defined in populations with >5% risk of CDI
Antimicrobial prophylaxis	Not specifically addressed	Not specifically addressed	Not routinely recommended	To be considered in patients with sufficiently high baseline risk
PPI Discontinuation	Insufficient evidence to recommend discontinuation as a prevention measure	Recommends against discontinuation if an appropriate indication exists	Use should be reviewed	Ensure PPIs have a valid indication Used cautiously in high-risk patients
Strategies to Prevent Recurrent CDI episodes				
Antimicrobial prophylaxis	Insufficient evidence to recommend suppressive or prophylactic agents	Suppressive vancomycin may be used in patients who cannot undergo or fail FMT and require frequent antibiotics; vancomycin prophylaxis may be considered during antibiotic use in patients with CDI history who are at high risk of recurrence	Prophylactic therapy may be warranted in select patients with multiple recurrences	Considered on a case-by-case basis
FMT	≥2 recurrences	≥2 recurrences	≥2 recurrences	Current recommendation is ≥2 recurrences. Role in primary CDI is of future interest
Bezlotoxumab	Recurrent infection in the last 6 months	Considered in patients at high risk for recurrence	First and subsequent recurrences	Main advantage is that it can be administered during antibiotic therapy. Its comparative effectiveness to FMT is unknown

FOR STARTERS: WISE ANTIBIOTIC USE



*Only if the patient does not have a documented infection and lacks signs of sepsis, and if deemed appropriate by the treating clinician.

Tsigrelis. Cleve Clin J Med. 2020; 87: 347-359.

ANTIBIOTICS: THE RISK DIFFERS

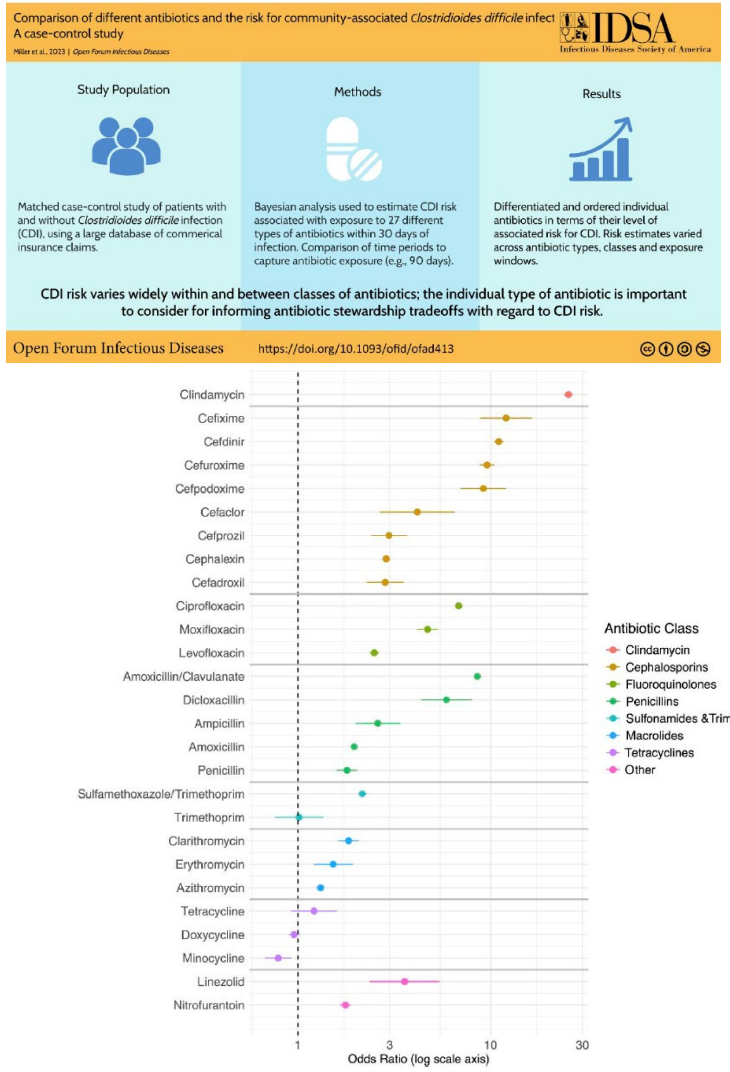


Figure 1. Visual comparison of effect estimates across antibiotic types, grouped by antibiotic class. Point estimates are depicted by the circle and 95% credible intervals t the line segments. Exact values can be found in Table 2.

Antibiotic Selection Risk

KY Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Individual antibiotic or antibiotic class CDI risk vary across multiple studies and are generally summarized below.[3-7]

Low Risk	Moderate Risk	High Risk
Tetracyclines (e.g. doxycycline) Nitrofurantoin Aminoglycosides (e.g. tobramycin) Vancomycin	Trimethoprim-Sulfamethoxazole Penicillins 1st generation cephalosporins (e.g. cefazolin) Macrolides (e.g. azithromycin)	2nd generation cephalosporins (e.g. cefuroxime) 3rd generation cephalosporins (e.g. ceftriaxone) 4th generation cephalosporins (e.g. cefepime) Carbapenems Clindamycin Aztreonam Fluoroquinolones
	(Odds Ratio 0-2)	**(Odds Ratio 5-15)**

Antibiotic Length of Therapy Risk

Longer lengths of antibiotic therapy cause more damage to the GI flora. One study found that compared to patients who got <4 days of antibiotic therapy, *C. difficile* risk was 3 times higher in patients who received 8-18 days of antibiotics. Using the shortest effective length of therapy helps minimize *C. difficile* risk.[8]

Key Takeaway: When multiple antibiotic options are available, the risk of *C. difficile* infection can be minimized by selecting the lowest risk antibiotic for the shortest recommended duration.

3. Brown KA, Langford B, Schwartz KL, Diong C, Garber G, Daneman N. Antibiotic Prescribing Choices and Their Comparative C. Difficile Infection Risks: A Longitudinal Case-Cohort Study. Clin Infect Dis. 2021;72(5):836-44.
4. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013;68(9):1951-1961. doi:10.1093/jac/dkt129
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6. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(4):881-891. doi:10.1093/jac/dkt477
7. Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016;48(1):1-10. doi:10.1016/j.ijantimicag.2016.03.008
8. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. Clin Infect Dis. 2011;53(1):42-48. doi:10.1093/cid/cir301

PROBIOTICS: TOO MANY, MUCH MESS

CURRENT MEDICAL RESEARCH AND OPINION
2023, VOL. 39, NO. 6, 889–891
https://doi.org/10.1080/03007995.2023.2205333
Article ST-0067.R1/2205333

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COMMENTARY

Probiotics for primary prevention of *Clostridioides difficile* infection: revisiting the evidence

Jesse Fajnzylber[a*], Will Patterson[a*] and Abhishek Deshpande[a,b,c]

Table 1. Probiotic administration recommendation and strength by medical society.

Society	Recommendation	Strength
AGA	"In adults and children on antibiotic treatment, we suggest the use of *S boulardii*; or the 2-strain combination of *L acidophilus* CL1285 and *L casei* LBC80R; or the 3-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, and *Bifidobacterium bifidum*; or the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *Streptococcus salivarius* subsp *thermophilus* over no or other probiotics for prevention of *C difficile* infection"[7].	Conditional recommendation, low quality of evidence
ACG	"We recommend against probiotics for the prevention of CDI in patients being treated with antibiotics (primary prevention)"[8].	Conditional recommendation, moderate quality of evidence
IDSA	"There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials"[9].	No recommendation
ECCMID	"Routine administration of probiotics to prevent CDI when on antibiotic treatment is not recommended"[10].	Strong recommendation, low quality of evidence

Conclusions

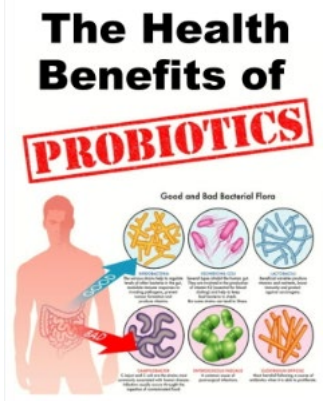
Current meta-analyses suggest that prophylactic probiotics are effective in reducing the risk of CDI. However, issues with meta-analytic study design such as trial weighting, unresolved subgroup effects, low power, and heterogeneity of probiotic microorganisms threaten the validity of these findings. All the professional societies agree that there is a need for more high-quality and adequately powered RCTs to definitively conclude the efficacy of prophylactic probiotics.

Open

Why Do ACG and AGA Guidelines Differ for the Use of Probiotics and the Prevention of CDI?

Lynne V. McFarland, PhD[1], Ravina Kullar, PharmD[2], Stuart Johnson, MD[3], Jason C. Sniffen, DO[4], Kristin Woolard, APRN[4] and Ellie J.C. Goldstein, MD[5]

Am J Gastroenterol 2022;117:501. https://doi.org/10.14309/ajg.0000000000001567



Response to McFarland et al.

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

Am J Gastroenterol 2022;117:501–502. https://doi.org/10.14309/ajg.0000000000001638

We appreciate the communication from McFarland et al. (1) (and note their disclosure that all serve on the Scientific Advisory Board for Bio-K+ International) but stand by our recommendations against probiotic treatment for the prevention of either primary or secondary *Clostridioides difficile* infections (CDI) and the unbiased

date analysis of the best available data, which underlies the same. For example, PLACIDE, the highest quality randomized controlled trial (RCT) thus far of probiotics for primary prevention of CDI, enrolled 2,800 high-risk elderly hospitalized patients receiving antibiotics and found no difference (2). If still underpowered at 2,800 patients, what is the number needed to treat to prevent 1 case of CDI? Practically speaking, the marginal benefit, if any, of routine probiotic use for primary prevention is low

ANTIBIOTIC PROPHYLAXIS: 'PREVANCTION'

antibiotics *Antibiotics* 2022, *11*, 183. https://doi.org/10.3390/antibiotics11020183 MDPI

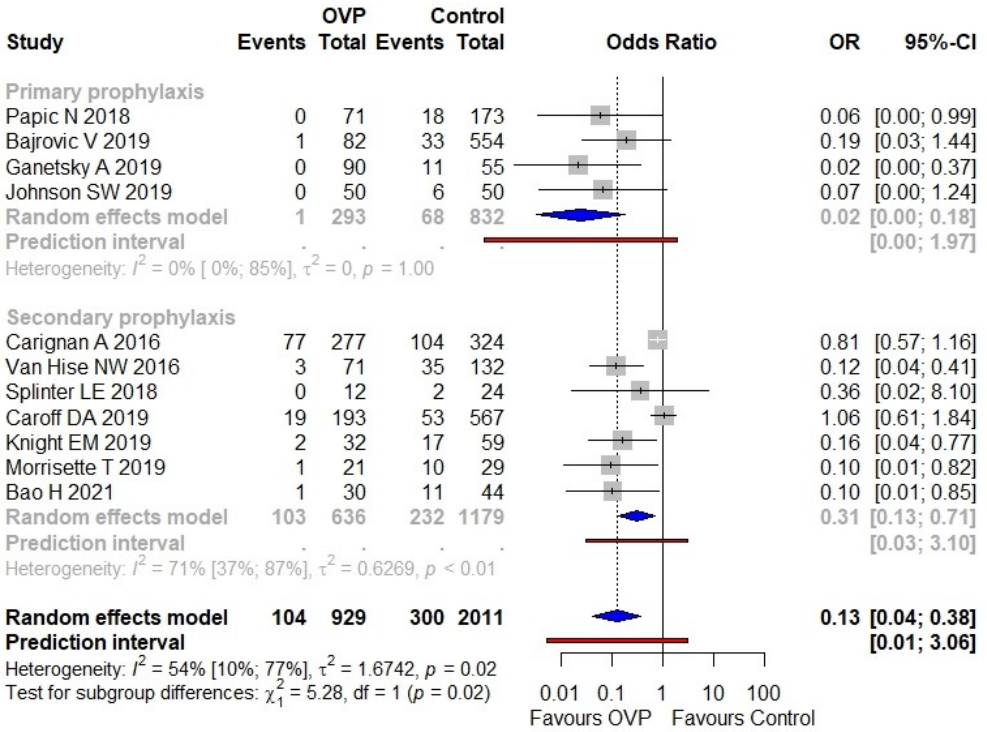
Systematic Review

Oral Vancomycin Prophylaxis for Primary and Secondary Prevention of *Clostridioides difficile* Infection in Patients Treated with Systemic Antibiotic Therapy: A Systematic Review, Meta-Analysis and Trial Sequential Analysis

Alberto Enrico Maraolo [1,*], Maria Mazzitelli [2,3], Emanuela Zappulo [4], Riccardo Scotto [4], Guido Granata [5], Roberto Andini [6,7], Emanuele Durante-Mangoni [6,7], Nicola Petrosillo [8] and Ivan Gentile [4]

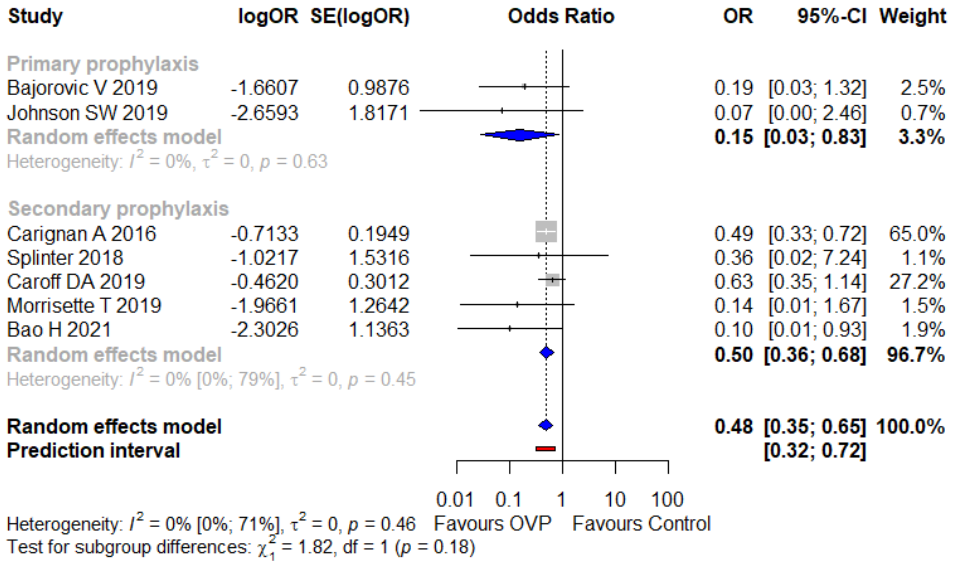
5. Conclusions

OVP represents a promising preventive weapon for both primary and recurrent CDI, and authoritative guidelines have already endorsed it, although cautiously in the light of the low-quality underlying evidence. Many lingering questions remain about its exact schedule (dose and duration) as well as the ideal patient profile benefitting the most from this approach. Pending further data, a prudent strategy would be represented by the use of OVP at a low dose (125 mg once or twice daily) in very selected subjects, namely the ones undergoing SAT with high-risk antibiotics and having relevant likelihood to develop CDI according to available prediction models. Well-conducted RCTs will shed some light on the aspects still in search of an answer regarding this preventive strategy.



Pooling raw data

Pooling adjusted ES



VANCOMYCIN FOR PREVENTION

antibiotics *Antibiotics* 2022, *11*, 183. https://doi.org/10.3390/antibiotics11020183 MDPI

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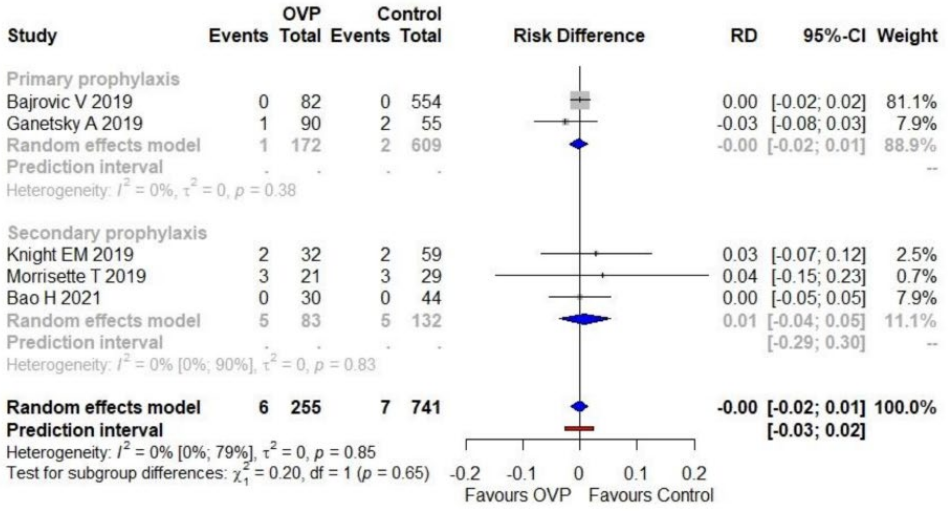


Figure 5. Meta-analysis regarding the risk difference between OVP group and comparators as the secondary outcome (VRE infections). Abbreviations: CDI, *Clostridioides difficile* infection; OVP, oral vancomycin prophylaxis; RD, risk difference; VRE, vancomycin-resistant *Enterococci*; 95%-CI, confidence intervals at 95%. Vertical line indicates the 'no difference' point between the two options. Squares represent adjusted odds ratios. Diamonds represent pooled risk difference for all studies. Horizontal lines represent 95% CI.

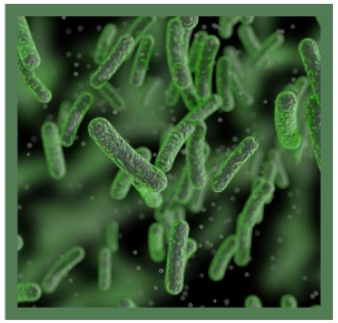
Table 2. Subgroup analysis of CDI occurrence under OVP versus no intervention in the overall population.

Variable	Included Studies, *n*	Sample Size, *n*	OR (95% CI)	I^2	Test for Subgroup Difference, *p* Value
Study place					
US	9	2095	0.15 (0.06–0.36)	59%	0.51
Not US	2	845	0.31 (0.04–2.26)	0%	
Study design					
Retrospective	10	2840	0.19 (0.09–0.44)	59.4%	0.99
Prospective	1	100	0.07 (0.00–1.24)	-	
Study population					
Adult hospitalized	6	1999	0.27 (0.10–0.78)	64.1%	0.30
SOT	2	672	0.16 (0.02–1.21)	0%	
Hematological	2	195	0.03 (0.00–0.23)	0%	
Pediatric	1	74	0.10 (0.01–0.85)	-	
OVP dose *					
125 mg od	2	344	0.06 (0.01–0.48)	0%	0.11
125 bid	5	951	0.11 (0.04–0.32)	0%	
Other (variable/mixed dosages)	4	1645	0.43 (0.15–1.23)	78.5%	
Timing of follow-up					
28/30-day	2	239	0.12 (0.03–0.39)	0%	<0.01
90-day	3	1461	0.82 (0.61–1.11)	0%	
In-hospital	3	1025	0.03 (0.00–0.22)	0%	
Other	3	207	0.12 (0.04–0.36)	0%	
Mean duration of OVP (Compared with SAT)					0.01
Longer	7	1244	0.08 (0.03–0.18)	0%	
Shorter	4	1696	0.44 (0.16–1.23)	40%	

VRE RISK

AR-ISS: sorveglianza nazionale dell'Antibiotico-Resistenza

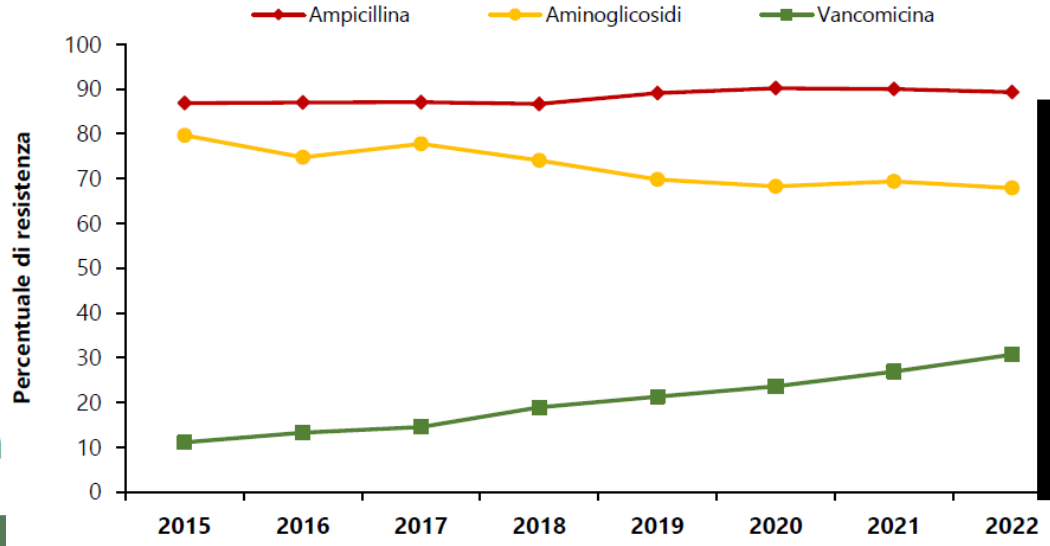
Dati 2022



Istituto Superiore di Sanità

Roma, novembre 2023

Simone Iacchini*, Stefano Boros*, Patrizio Pezzotti*, Alessandra Carami Giulia Errico*, Maria Del Grosso*, Romina Camilli*, Maria Giufrè*, Annalisa Pantosti§, Francesco Maraglino^, Anna Teresa Palamara*, Fortunato "Paolo" D'Ancona*, Monica Monaco*
e il gruppo di lavoro AR-ISS

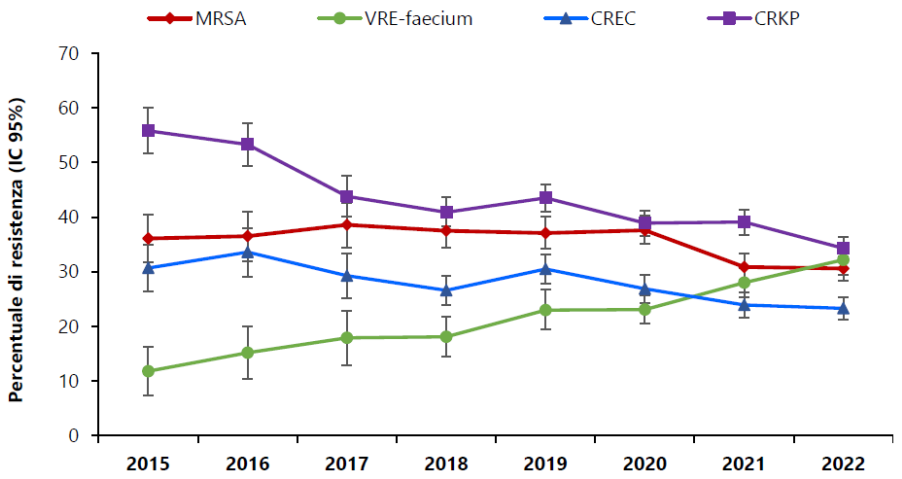


Enterococcus faecium

Per *E. faecium* la percentuale di resistenza agli aminoglicosidi ad alto dosaggio (gentamicina, streptomicina) è diminuita negli ultimi anni (da 79,7% nel 2015 a 67,9% nel 2022) e si mantiene stabile negli ultimi tre anni ad un valore medio di circa 68%, mentre la resistenza all'ampicillina nel 2022 si mantiene alta, pari all'89,3% (Figura 9).

Si continua ad osservare un progressivo e preoccupante incremento nella percentuale di resistenza alla vancomicina, che è passata dall'11,1% del 2015 al 30,7% nel 2022. È evidente la necessità di ulteriori approfondimenti per comprendere meglio l'epidemiologia, la diversità dei ceppi e i fattori di rischio associati all'infezione.

Figura 9. *E. faecium*: resistenza ad ampicillina, aminoglicosidi e vancomicina. Italia 2015-2022



MRSA *S. aureus* resistente alla meticillina;
VRE-*faecium* *E. faecium* resistente alla vancomicina
CREC *E. coli* resistente alle cefalosporine di terza generazione
CRKP *K. pneumoniae* resistente ai carbapenemi

Figura 4. Percentuale di resistenza delle principali combinazioni patogeno/antibiotico nei reparti di Terapia Intensiva. Italia 2015-2022

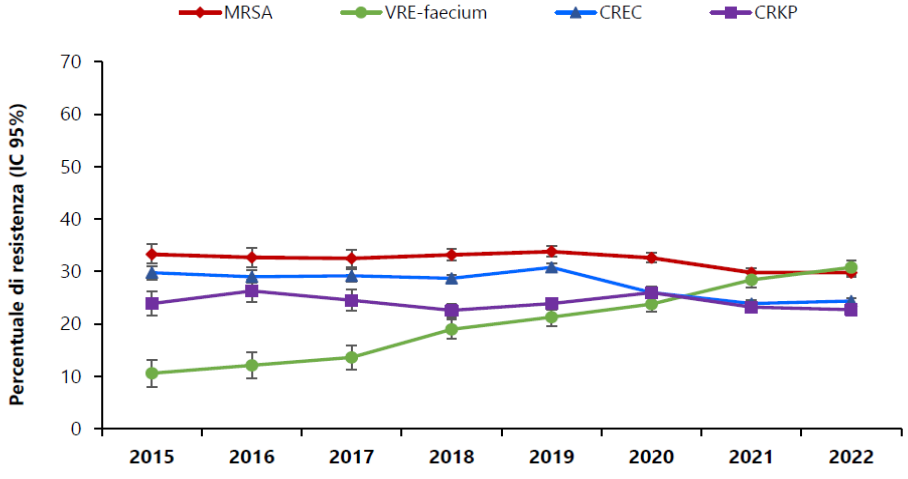


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Figura 5. Percentuale di resistenza delle principali combinazioni patogeno/antibiotico in altri reparti. Italia 2015-2022

PRIMARY PROPHYLAXIS: FIDAXOMICIN

Clinical Infectious Diseases

MAJOR ARTICLE

196 • CID 2019:68 (15 January) • Mullane et al

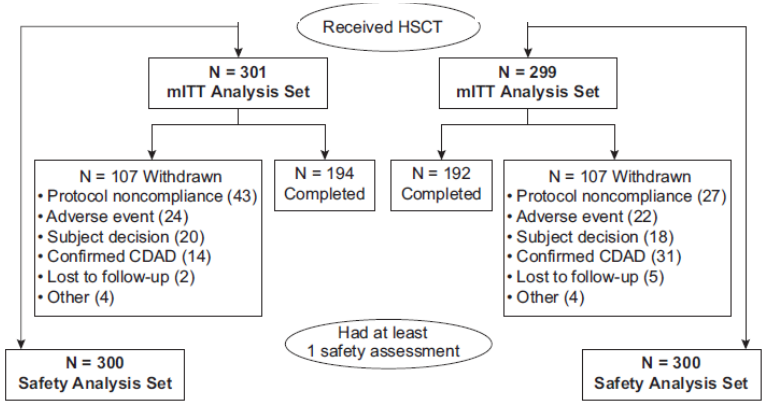
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of *Clostridium difficile*–associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation

Kathleen M. Mullane,[1] Drew J. Winston,[2] Ajay Nooka,[3] Michele I. Morris,[4] Patrick Stiff,[5] Michael J. Dugan,[6] Henry Holland,[7] Kevin Gregg,[8] Javier A. Adachi,[9] Steven A. Pergam,[10] Barbara D. Alexander,[11] Erik R. Dubberke,[12] Natalya Broyde,[13] Sherwood L. Gorbach,[14] and Pamela S. Sears[13]

Table 2. Efficacy Analyses (Modified Intent-to-treat Population)

	Fidaxomicin (N = 301)	Placebo (N = 299)	Placebo – FDX (95% CI)[a]	*P*-value[b]
Primary analysis: prophylaxis failure (composite endpoint), n (%)				
Primary time point				
30 days after end of treatment	86 (28.6)	92 (30.8)	2.2 (-5.1, 9.5)	.2778
Confirmed CDAD	13 (4.3)	32 (10.7)	6.4 (2.2, 10.6)	.0014
CDAD-effective medication[c]	12 (4.0)	11 (3.7)	-0.3 (-3.4, 2.8)	.4222
Missing data (death or AE)	19 (6.3)	16 (5.4)	-1.0 (-4.7, 2.8)	.3077
Missing data (other reason[d])	42 (14.0)	33 (11.0)	-3.0 (-8.2, 2.4)	.1397
Secondary time points				
60 days after end of treatment	106 (35.2)	107 (35.8)	0.6 (-7.1, 8.2)	.4420
70 days after start of treatment	88 (29.2)	93 (31.1)	1.9 (-5.5, 9.2)	.3091
Sensitivity analysis: confirmed CDAD only, n (%)				
Primary time point				
30 days after end of treatment	13 (4.3)	32 (10.7)	6.4 (2.2, 10.6)	.0014
Autologous transplant	5/176 (2.8)	14/176 (8.0)	5.1 (0.4, 9.8)	.0163
Allogeneic transplant	8/125 (6.4)	18/123 (14.6)	8.2 (0.7, 15.8)	.0166
Secondary time points				
60 days after end of treatment	17 (5.6)	32 (10.7)	5.1 (0.7, 9.4)	.0117
Autologous transplant	6/176 (3.4)	14/176 (8.0)	4.5 (-0.3, 9.4)	.0321
Allogeneic transplant	11/125 (8.8)	18/123 (14.6)	5.8 (-2.1, 13.8)	.0759
70 days after start of treatment	14 (4.7)	32 (10.7)	6.1 (1.8, 10.3)	.0026



Methods. In this double-blind study, subjects undergoing HSCT with fluoroquinolone prophylaxis stratified by transplant type (autologous/allogeneic) were randomized to once-daily oral fidaxomicin (200 mg) or a matching placebo. Dosing began within 2 days of starting conditioning or fluoroquinolone prophylaxis and continued until 7 days after neutrophil engraftment or completion of fluoroquinolone prophylaxis/clinically-indicated antimicrobials for up to 40 days. The primary endpoint was CDAD incidence through 30 days after study medication. The primary endpoint analysis counted confirmed CDAD, receipt of CDAD-effective medications (for any indication), and missing CDAD assessment (for any reason, including death) as failures; this composite analysis is referred to as "prophylaxis failure" to distinguish from the pre-specified sensitivity analysis, which counted only confirmed CDAD (by toxin immunoassay or nucleic acid amplification test) as failure.

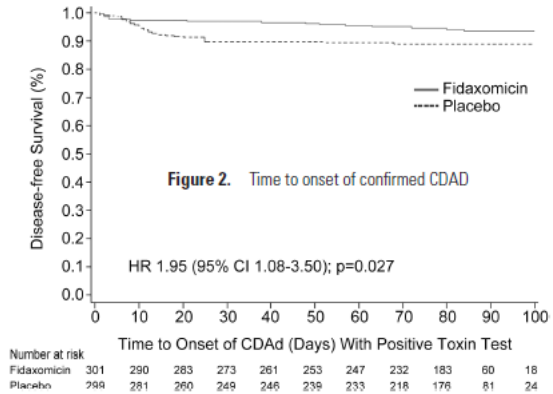


Figure 2. Time to onset of confirmed CDAD

The mean (±SD) duration of treatment was 22.0 (±8.61) days in the fidaxomicin group and 22.7 (±8.99) days in the placebo group

PRIMARY PROPHYLAXIS: METRONIDAZOLE

ORIGINAL ARTICLE Gastroenterol Hepatol. 2018;41(6):362–368

Metronidazole in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* infection in high-risk hospitalised patients☆

Marco Tobar-Marcillo[a,*], Maria Guerrero-Duran[a], Ariana Avecillas-Segovia[a], Lillana Pacchiano-Aleman[a], Roberto Basante-Díaz[a], Hiram Vela-Vizcaino[a], Eduardo Espinosa-Aznar[a], Pedro Castorena García[a], Ricardo Santiago-Ramírez[a], Ixel Rivas-Bucio[b]

Methods: A prospective randomised, open-label study was conducted in a tertiary hospital in Mexico City, selecting patients at high risk of acquiring in-hospital diarrhoea and assigning them to a group taking metronidazole 500mg orally every eight hours for seven days or an observation group. The primary endpoint was the presence of antibiotic-associated diarrhoea and Clostridium difficile (C. difficile) infection during the seven days of evaluation. The study was approved by the institutional ethics committee. Registration number (11.2017) of 14 March 2017.

Materials and methods

Study design and participants

A randomised, open-label clinical trial approved by the institutional ethics committee with registration number 11.2017 on 14 March 2017 was conducted. The trial enrolled patients hospitalised in the Internal Medicine department of Hospital Regional Licenciado Adolfo López Mateos in Mexico City from 1 May to 30 September 2017 who met the following inclusion criteria: age between 55 and 75 years (patients over 75 years of age were excluded due to a risk of enhancing possible adverse effects related to the use of other medicines)[19,20]; use of a proton pump inhibitor; use of broad-spectrum antibiotics, including one of the following: third-generation cephalosporins, levofloxacin and/or clindamycin (as these are those that are most often used at the institution); and a hospital stay less than 72 h before the intervention. Patients were excluded if they had diarrhoea on admission, documented *C. difficile* infection in the past 6 months, altered mental state, use of metronidazole to treat a concomitant disease during hospitalisation, use of medicines with major interactions with metronidazole,[21] pregnancy or alcohol consumption at least 48 h before the intervention.[22] All patients selected were invited to participate through an informed consent form. Patients who did not agree to take part, presented oral intolerance during the intervention, declined to continue taking the medicine or died due to causes unrelated to the onset of diarrhoea were eliminated.

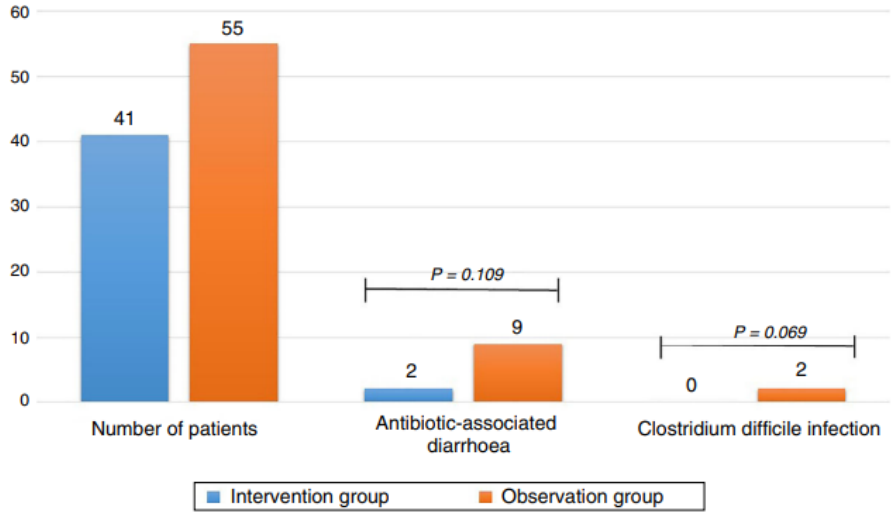
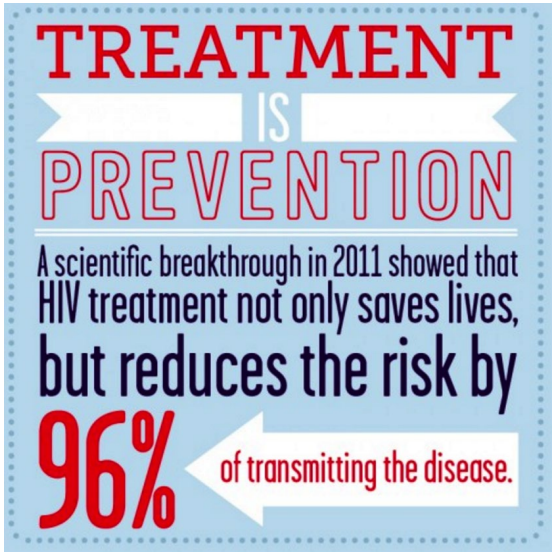
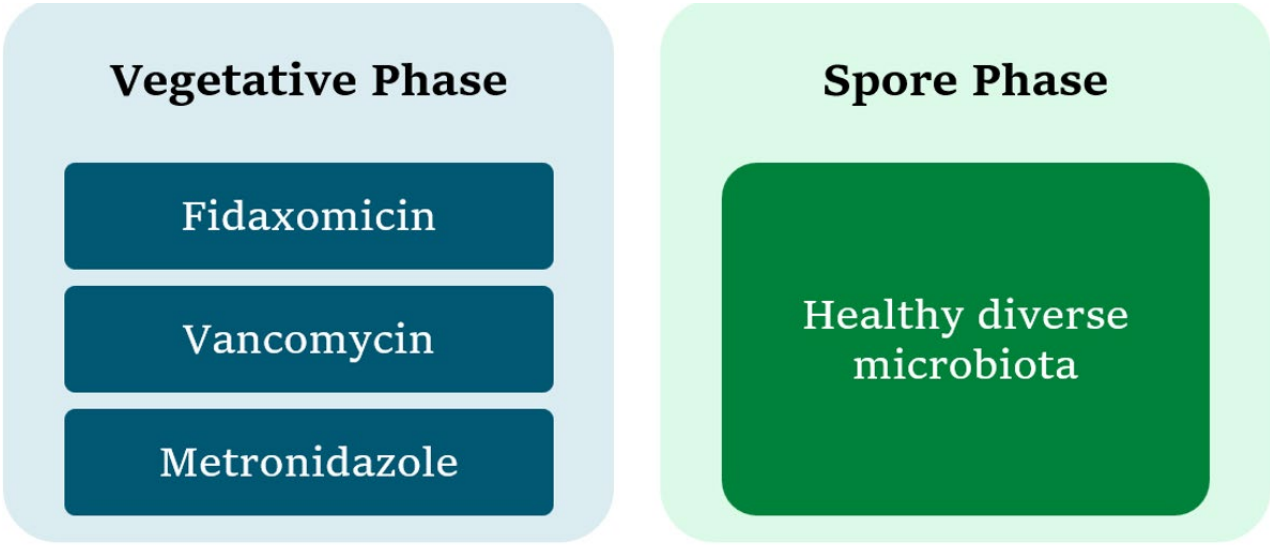


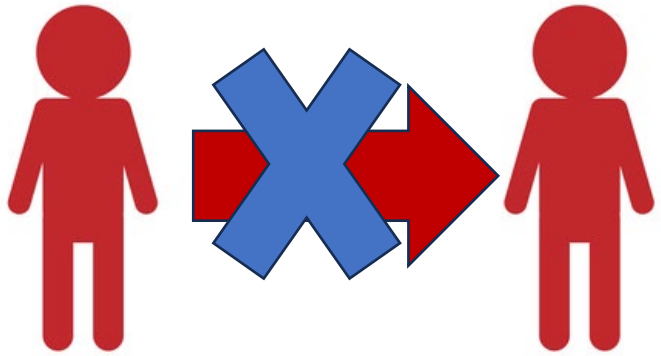
Figure 2 Antibiotic-associated diarrhoea and *Clostridium difficile* infection.

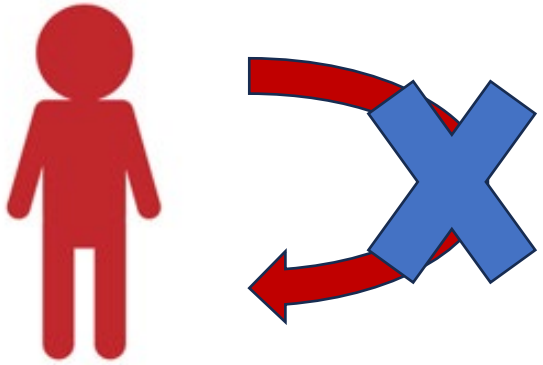
TaSP: NOT ONLY FOR HIV





Chaar. Therap Adv Gastroenterol. 2021;14:17562848211011953.





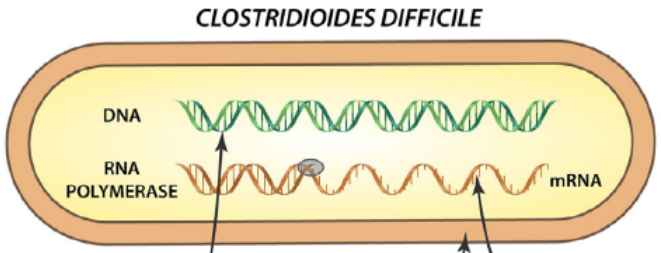
THERAPY: DIFFERENCES ACROSS DRUGS

Review

International Journal of Infectious Diseases 124 (2022) 118–123

Clostridioides difficile infection: are the three currently used antibiotic treatment options equal from pharmacological and microbiological points of view?

Marcela Krutova[1,2,*], Mark Wilcox[2,3], Ed Kuijper[2,4,5]



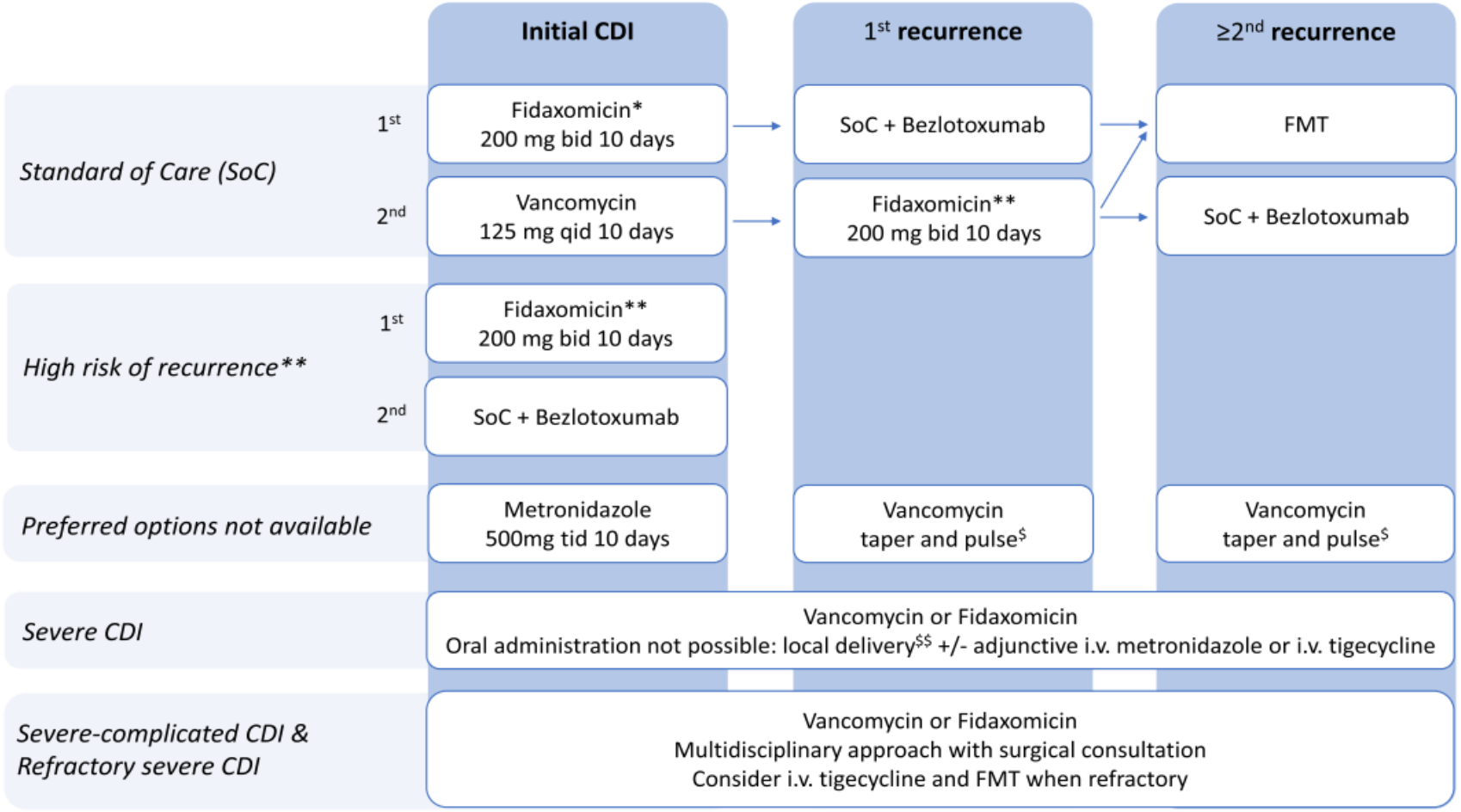
	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST	LOWER	LOWER (STEEPER)
SPOROCIDAL EFFECT	—	NO	YES
INHIBITION OF SPORULATION	NO	NO	YES

SUPPORTIVE · LESS-SUPPORTIVE · NON-SUPPORTIVE · — NO DATA

Overview of pharmacodynamic, pharmacokinetic and microbiological properties for oral administration of metronidazole, vancomycin and fidaxomicin.

- Metronidazole is a nitroimidazole that inhibits DNA synthesis.
- Vancomycin is a glycopeptide antimicrobial with bacteriostatic activity that inhibits peptidoglycan biosynthesis.
- Fidaxomicin is a narrow-spectrum macrocyclic antibiotic that targets bacterial RNA polymerase.

THERAPY: ESCMID ALGORITHM



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.

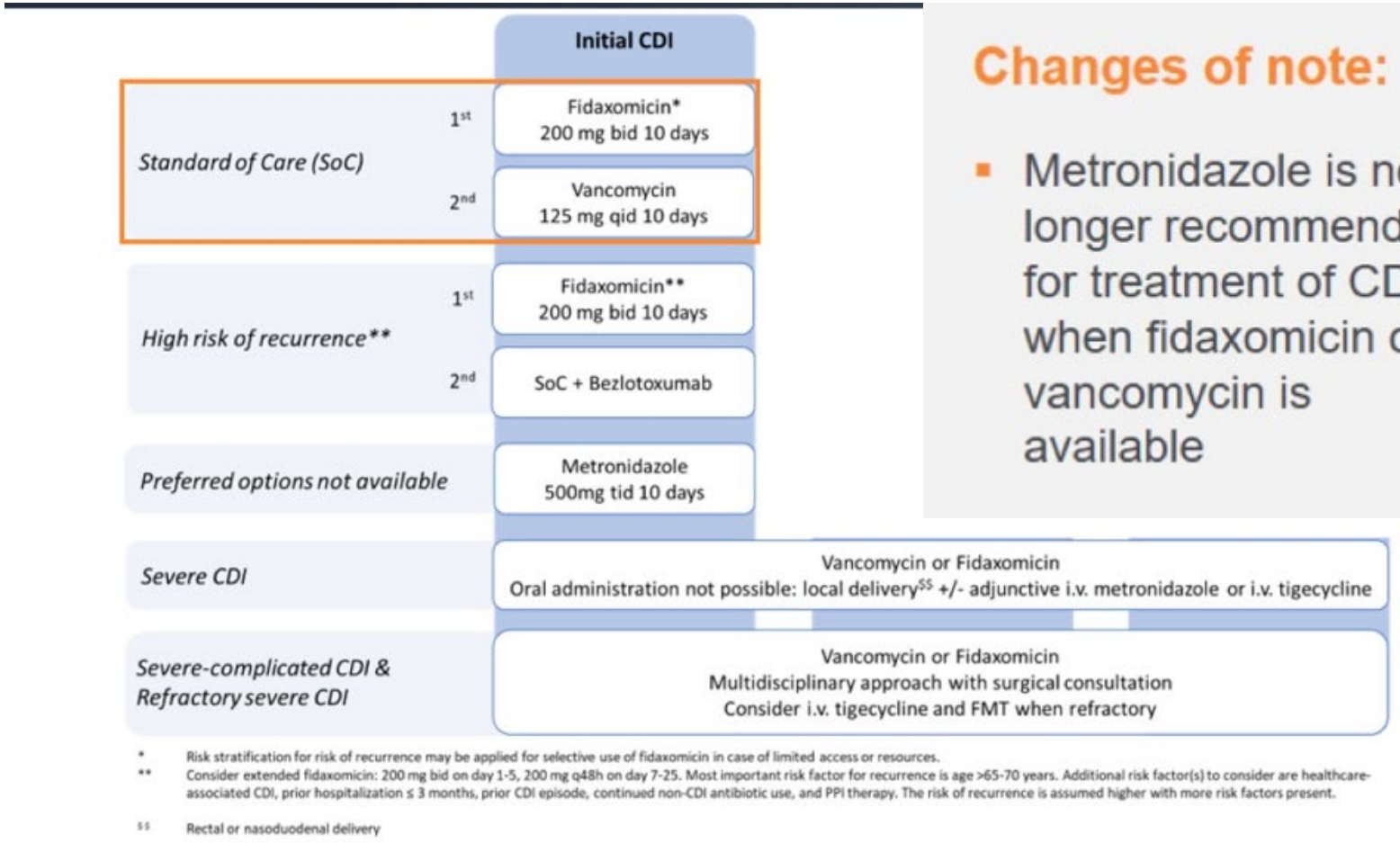
** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use, and PPI therapy started during/after CDI diagnosis. The risk of recurrence is assumed higher with more risk factors present.

$ Vancomycin taper and pulse: 2 weeks 125 mg qid, followed by 1 week 125 mg bid, then 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h for 1 week.

$$ Rectal or nasoduodenal delivery

Van Prehn. Clin Microb Infect. 2021; 27: S1-S27.

THERAPY: INITIAL CDI - ESCMID



bid, twice daily; FMT, fecal microbiotal transplant; i.v., intravenous; q48h, every 48 h; q72h, every 72 h; qd, once daily; qid, 4 times daily; tid, 3 times daily.

Changes of note:

- Metronidazole is no longer recommended for treatment of CDI when fidaxomicin or vancomycin is available
- Fidaxomicin is the preferred agent for treatment of initial CDI when available and feasible

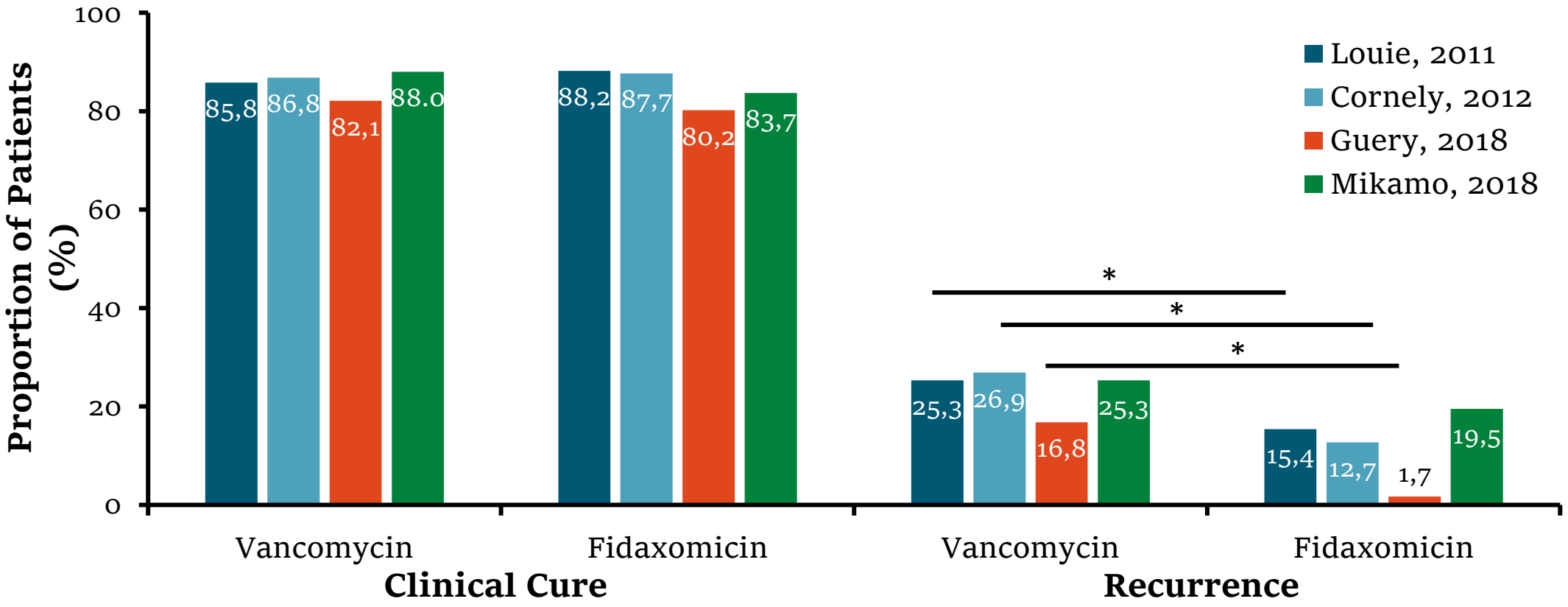
Van Prehn. Clin Microb Infect. 2021; 27: S1-S27.

GOODBYE METRONIDAZOLE

- A large meta-analysis involving 5361 patients and 13 different treatments for CDI revealed that metronidazole is inferior to vancomycin and fidaxomicin
  - Odds ratio of sustained clinical response (metronidazole versus vancomycin): 0.73 (95% CI: 0.56 – 0.95)
  - Odds ratio of sustained clinical response (metronidazole versus fidaxomicin): 0.49 (95% CI: 0.35 – 0.68)

Beinortas T et al. *Lancet Infect Dis*. 2022; 18(9):1035-44.

CDI ANTIBIOTIC-ASSOCIATED RECURRENCE

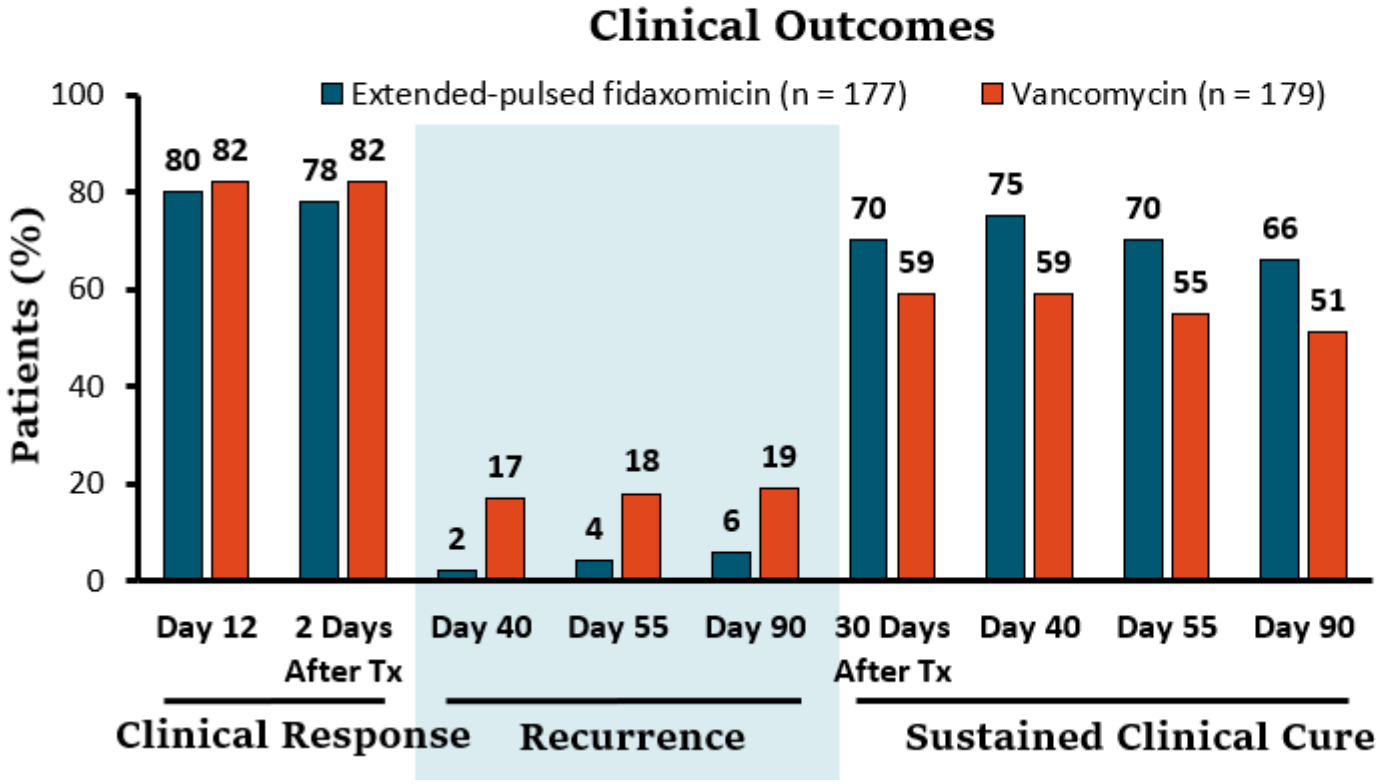


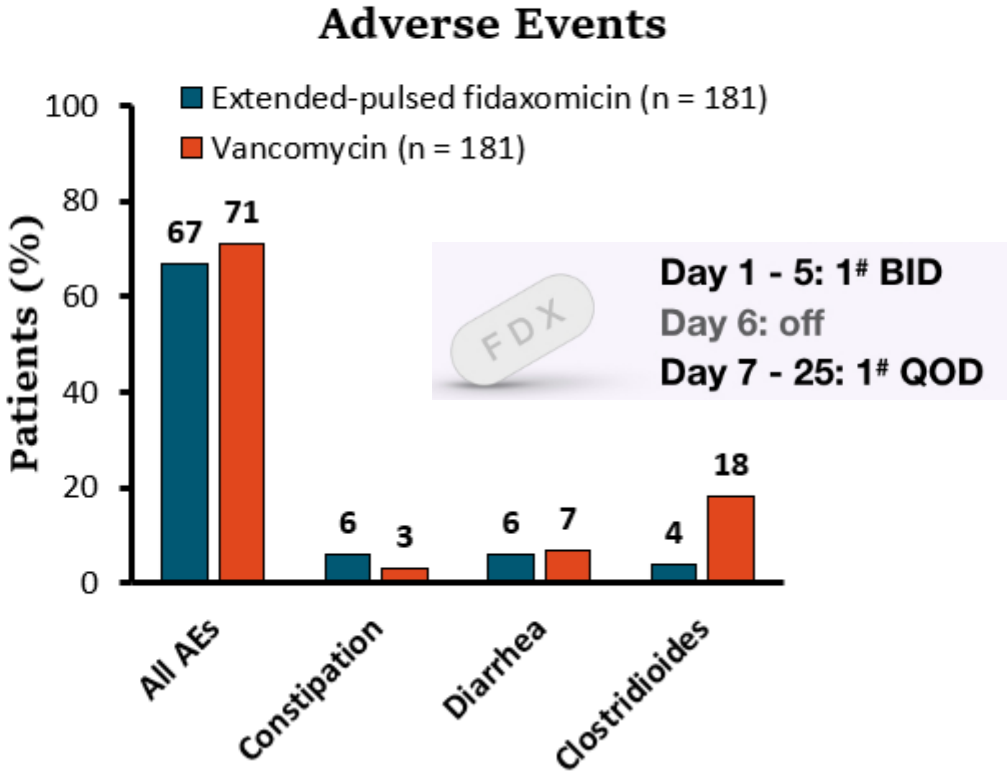
*Difference was statistically significant

1. Louie. NEJM. 2011;364:422. 2. Cornely. Lancet Infect Dis. 2012;12:281.
3. Guery. Lancet Infect Dis. 2018;18:296. 4. Mikamo. J Infect Chemother. 2018;24:744.

EXTENDED-PULSED FIDAXOMICIN

- Randomized, controlled, open-label phase IIIb/IV trial in patients ≥60 yr of age with initial or recurrent CDI confirmed by presence of toxins A or B in stool sample





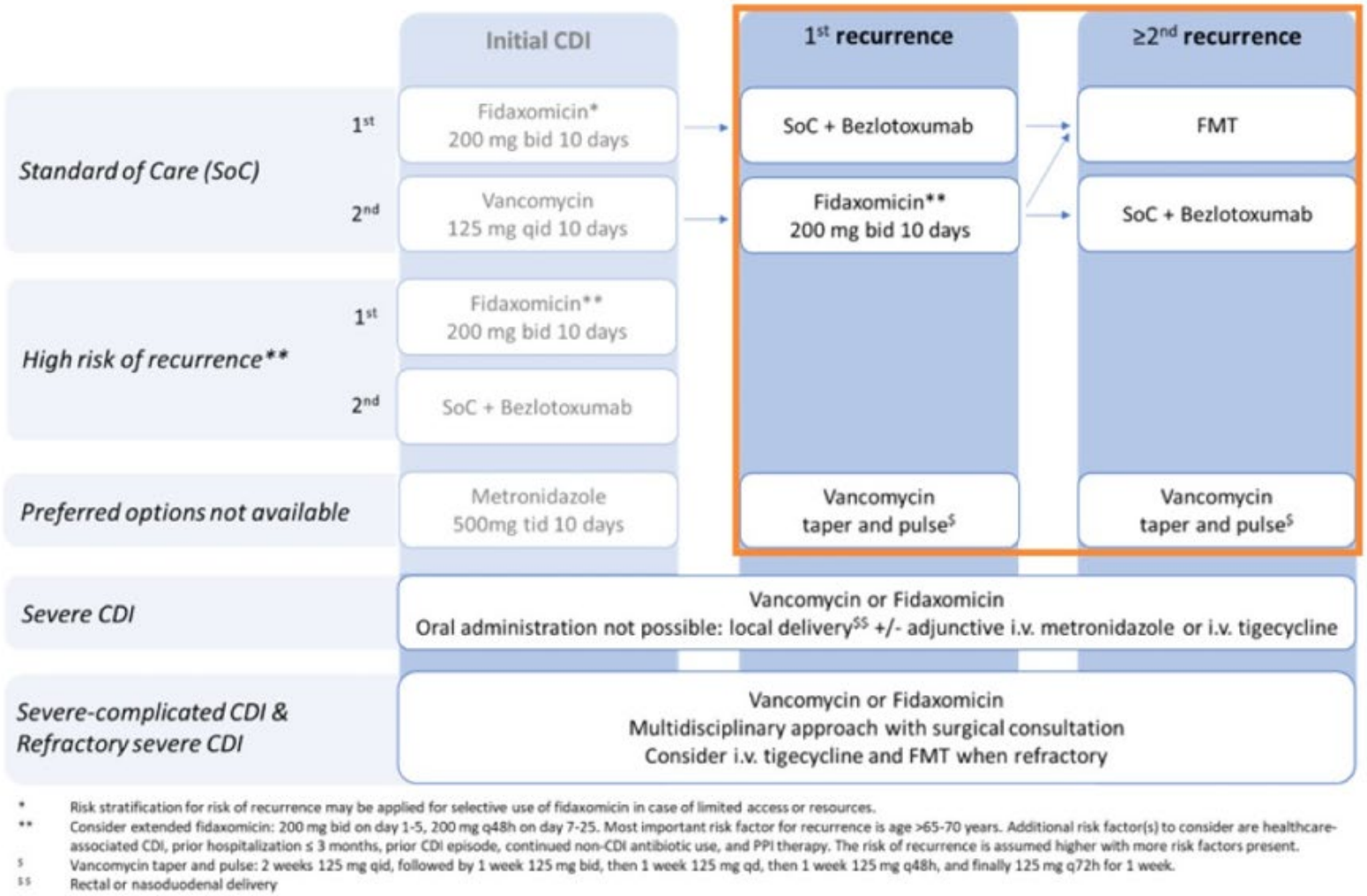
Guery. Lancet Infect Dis. 2018; 18: 296.

EXTENDED-PULSED FIDAXOMICIN: SUMMARY

- Regimen
  - Day 1 to 5: fidaxomicin 200 mg twice daily
  - Day 6 to 26: fidaxomicin 200 mg once every other day
- Sustained Clinical Cure at 30 days
  - Extended Fidaxomicin Course: 70% (124/177)
  - 10-day Vancomycin Course: 59% (106/179)
  - OR: 1.62 (95% CI, 1.04 – 2.54)
- **Has only been compared with standard vancomycin dosing**

Guery. Lancet Infect Dis. 2018; 18: 296.

THERAPY: RECURRENT CDI - ESCMID



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.

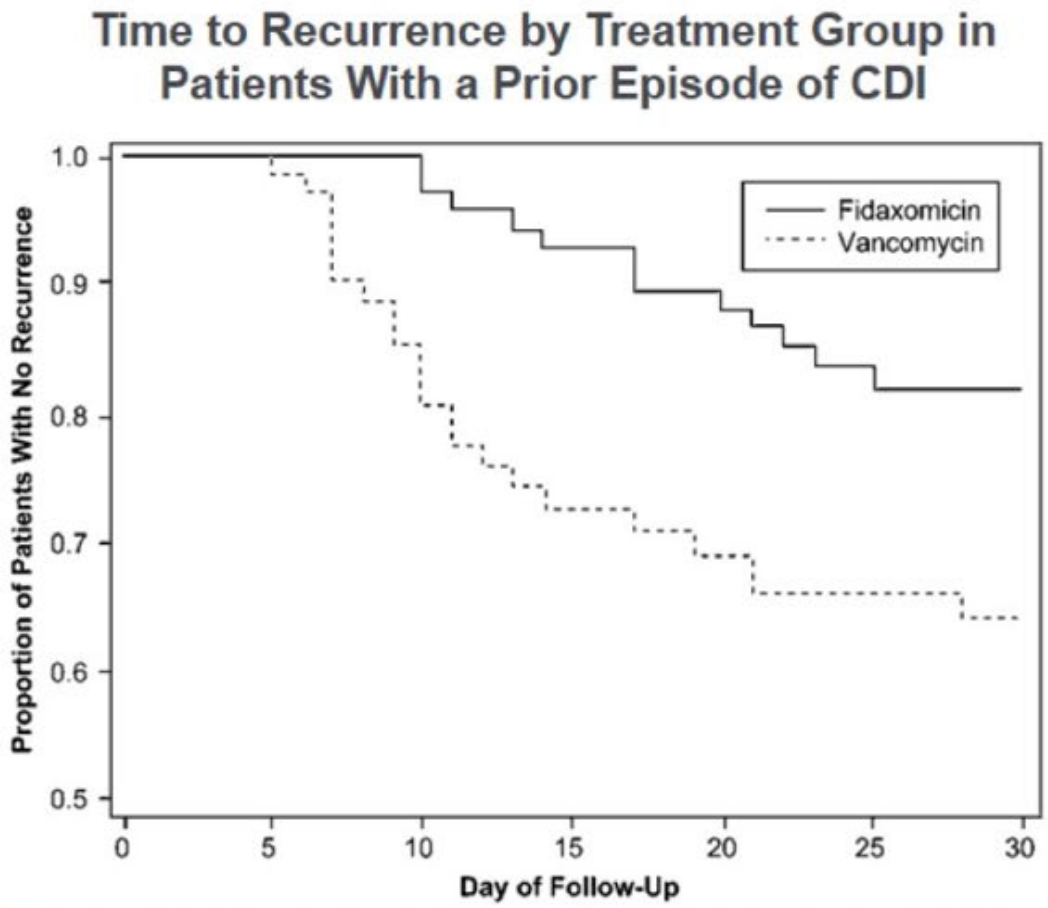
** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use, and PPI therapy. The risk of recurrence is assumed higher with more risk factors present.

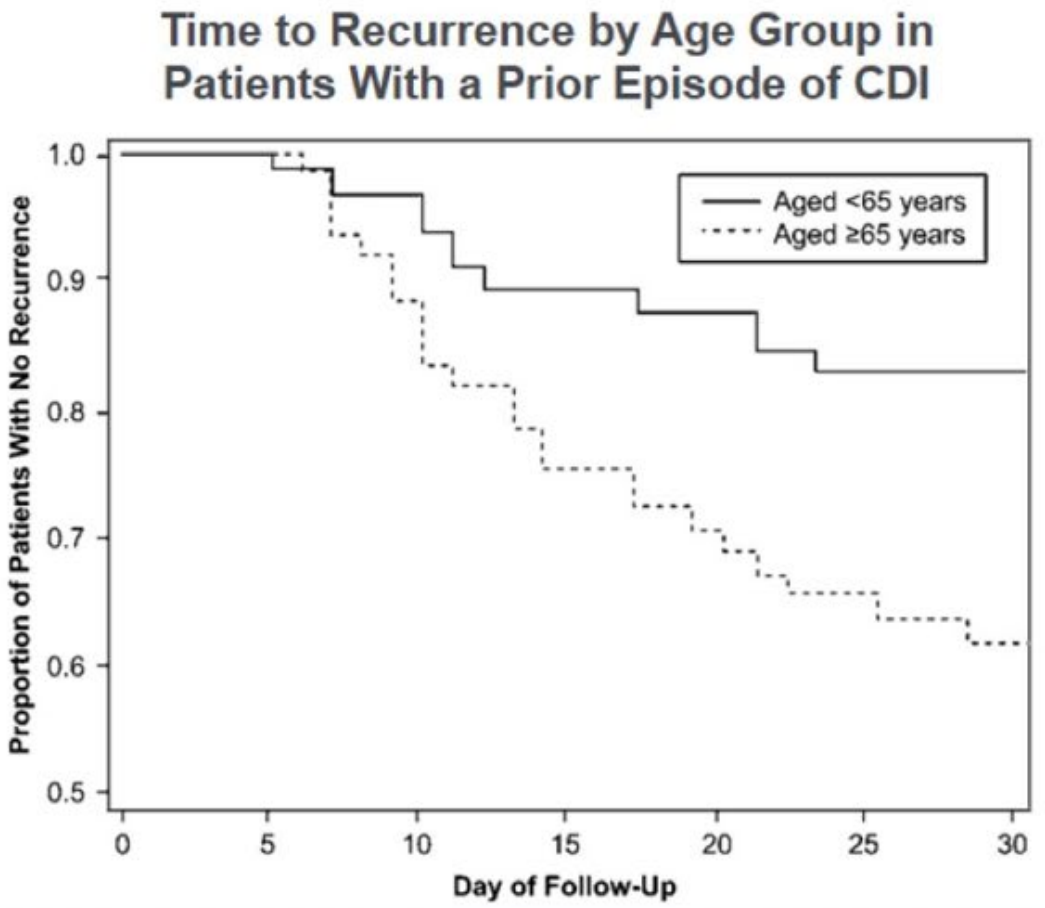
$ Vancomycin taper and pulse: 2 weeks 125 mg qid, followed by 1 week 125 mg bid, then 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h for 1 week.

$$ Rectal or nasoduodenal delivery

Van Prehn. Clin Microb Infect. 2021; 27: S1-S27.

THERAPY: FIRST RECURRENCE (FDX VS VAN)





FDX was associated with a lower risk of and longer time to recurrence than with VAN; age was associated with risk of recurrence

Cornely OA, et al. Clin Infect Dis. 2012;55(suppl 2):S154-S161.

THERAPY: FIRST RECURRENCE

In 2 phase 3 RCTs conducted in US, Canada, and Europe, patients with CDI received FDX 200 mg twice daily or VAN 125 mg 4 times daily for 10 d

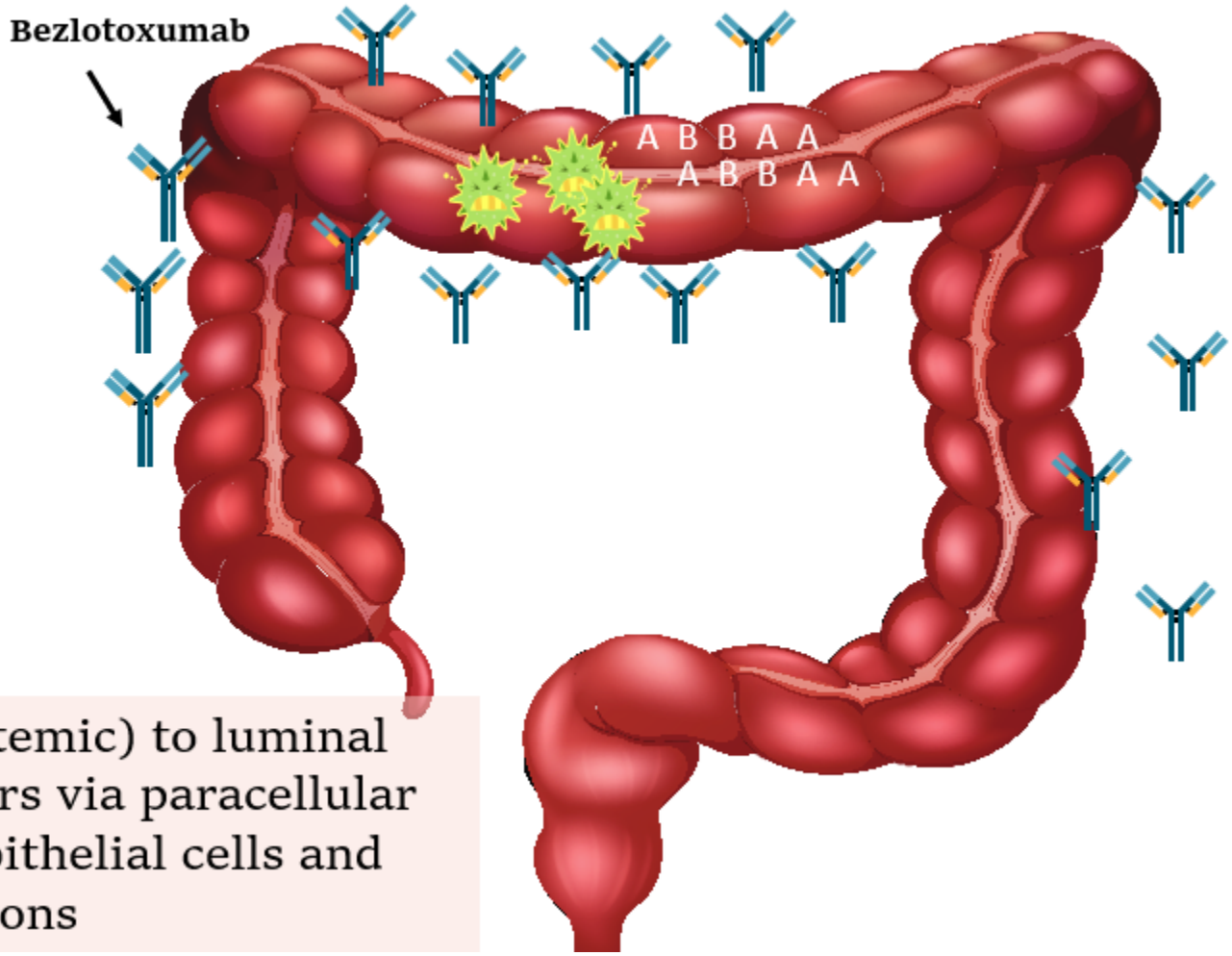
***Clostridium difficile* Infection Recurrence Following Successful Fidaxomicin or Vancomycin Treatment**

Population Subgroup	Proportion of Patients (n/N)		*P* Value
	FDX	VAN	
Per protocol			
No prior episode, n = 666	11.7% (38/325)	22.6% (77/341)	<.001
1 prior episode, n = 128	19.7% (13/66)	35.5% (22/62)	.045
mITT			
No prior episode, n = 803	12.9% (51/395)	24.8% (101/408)	<.001
1 prior episode, n = 159	20.3% (16/79)	32.3% (26/80)	.08

Cornely OA, et al. Clin Infect Dis. 2012;55(suppl 2):S154-S161.

ABOUT BEZLOTOXUMAB

- Fully human IgG1 monoclonal antibody against *C. difficile* toxin B
- Single infusion (10 mg/kg) over
  60 min while receiving standard of care antibiotics
- $T_{1/2}$ = 19 days

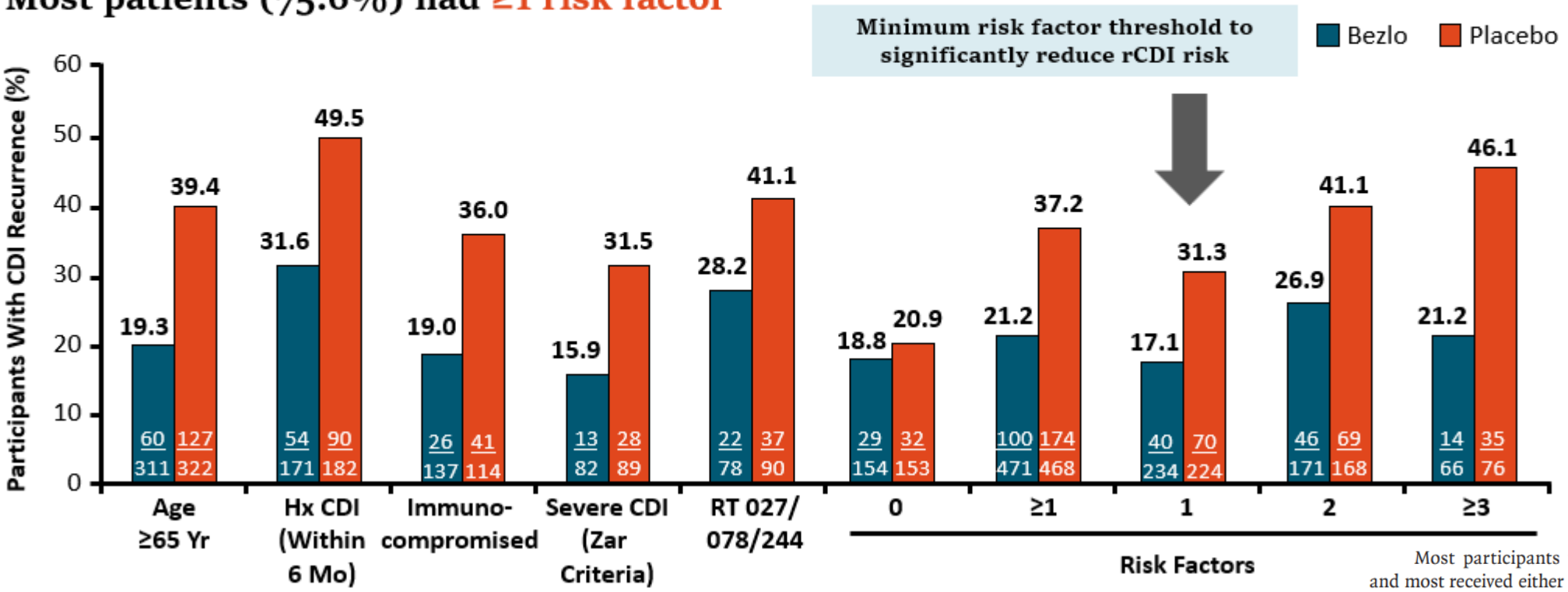


Transport from basolateral (systemic) to luminal compartment of colonocytes occurs via paracellular path after toxin disruption of epithelial cells and intercellular junctions

Giacobbe. Infect Dis Ther. 2020; 9: 481.

GOING FOR BEZLOTOXUMAB

- Analysis using 2 double-blind, randomized, placebo-controlled phase III trials (N = 1554) and prespecified rCDI risk factors (age ≥65 yr, history of CDI in past 6 mo, compromised immunity, severe CDI [Zar score ≥2 points], and ribotypes 027/078/244)
- **Most patients (75.6%) had ≥1 risk factor**



Most participants were inpatients (68%), and most received either metronidazole (47%) or vancomycin (48%) as the oral standard-of-care antibiotic; only 4% received fidaxomicin. In 94% of the participants, the study agent was infused within 6 days after initiation of standard-of-care antibiotic treatment (median, 3 days in all groups)

Gerding. Clin Infect Dis. 2018; 67: 649

REAL WORLD EVIDENCE BEZLOTOXUMAB

International Journal of Infectious Diseases 131 (2023) 147–154

Efficacy of bezlotoxumab in preventing the recurrence of *Clostridioides difficile* infection: an Italian multicenter cohort study

Marianna Meschiari[1,*], Alessandro Cozzi-Lepri[2], Adriana Cervo[1], Guido Granata[3], Carlotta Rogati[1], Erica Franceschini[1], Stefania Casolari[4], Paola Tatarelli[4], Daniele Roberto Giacobbe[5,6], Matteo Bassetti[5,6], Simone Mornese Pinna[7], Francesco Giuseppe De Rosa[7], Francesco Barchiesi[8], Benedetta Canovari[9], Carolina Lorusso[10], Giuseppe Russo[10], Giovanni Cenderello[11], Antonio Cascio[12], Nicola Petrosillo[13], Cristina Mussini[1]

Results

Overall, 442 participants with CDI were included in this analysis: 135 (31%) were treated with BEZ in combination with SoC therapy, and 307 (69%) were treated with SoC alone.

Regarding CDI therapy, vancomycin was the most frequently used drug, adopted in fixed dose (65%), in tapered regimen (4%), and in association with metronidazole (9%). As expected, the tapered regimen was mostly used in participants treated with BEZ + SoC (11% vs 1%, P >0.001). Fidaxomicin was used mostly in participants of the BEZ + SoC group than in those treated with SoC alone (25% vs 5%, P <0.001).

Table 4
Effectiveness of BEZ associated with SoC versus SoC alone by primary (recurrence of CDI) and secondary (rCDI or death) end point at 30 days of follow-up.

	Unweighted and weighted marginal relative risk			
	Unweighted RR (95% CI)	*P*-value	Weighted RR (95% CI)[a]	*P*-value
	All patients			
Primary end point (rCDI at day 30)				
SoC	1.00		1.00	
SoC+BEZ	0.58 (0.31, 1.09)	0.092	0.40 (0.18, 0.88)	0.023
Secondary end point (rCDI or death at day 30)				
SoC	1.00		1.00	
SoC+BEZ	0.47 (0.26, 0.85)	0.012	0.35 (0.17, 0.73)	0.005

[a] Adjusted for age, Zar score, immunosuppression, CDI episodes within 8 weeks using inverse probability weightingAbbreviations: BEZ, bezlotoxumab; CDI, *Clostridioides difficile* infection; CI, confidence interval; rCDI, CDI recurrence; RR, relative risk; SoC, standard of care.

Our study design is that of a multicenter cohort, enrolling participants from 18 Italian hospitals, including academic or tertiary referral hospitals (see full detailed list in Supplementary Table S1). All adult participants (aged >18 years) admitted to these participating sites over the period January 2018 to January 2022 had at least an episode of CDI and (i) ≥1 risk factor for rCDI, (ii) at least ≥30 days of documented follow-up after the end of antimicrobial treatment for CDI episode in question (baseline), and (iii) were treated with either BEZ + SoC or only SoC.

The SoC cohort was an historical comparator group of participants included in the ReCloDi (Recurrence of CDI) study group cohort, over the period from January 2018 to March 2020 [8]. The BEZ cohort was a newly recruited group from a subset of the sites participating in ReCloDi and three others sites over the more contemporary period of September 2018 to January 2022.

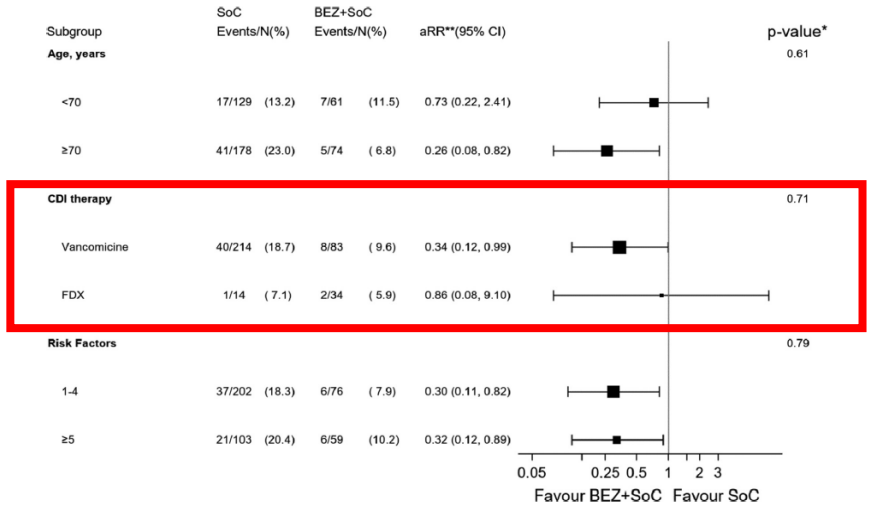


Figure 1. Forest plot of subsets analysis by secondary end point (CDI recurrence or death at day 30).

BEZLOTOXUMAB: GUIDELINES COMPARISON

Primary CDI Episode

Recommendation	IDSA/SHEA[1,2]	ESCMID[3]	ACG[4]
Preferred	**Fidaxomicin** 200 mg PO BID x 10 days	**Fidaxomicin** 200 mg PO BID x 10 days	**Fidaxomicin** 200 mg PO BID x 10 days **Vancomycin** 125 mg PO 4x/day x 10 days
Alternative	**Vancomycin** 125 mg PO 4x/day x 10 days If no other available agents (nonsevere): Metronidazole 500 mg PO 3x/day x 10-14 days	**Vancomycin** 125 mg PO 4x/day x 10 days If no other available agents: Metronidazole 500 mg PO 3x/day x 10 days	If no other available agents (nonsevere): Metronidazole 500 mg PO 3x/day x 10 days
Comments	In settings where logistics are not an issue, consider **addition of bezlotoxumab** in high risk of recurrence	Risk stratify for recurrence with selective use of **fidaxomicin** in limited access/resources Consider **addition of bezlotoxumab** in high risk of recurrence	Consider **addition of bezlotoxumab** in high risk of recurrence Consider **FMT** on case-by-case basis in severe CDI unresponsive to standard therapy

1. McDonald. Clin Infect Dis. 2018;66:e1. 2. Johnson. Clin Infect Dis. 2021;73:e1029.
3. van Prehn. Clin Microbiol Infect. 2021;27:S1. 4. Kelly. Am J Gastroenterol. 2021;116:1124.

BEZLOTOXUMAB: AIFA REGULATIONS

ALLEGATO

Agenzia Italiana del Farmaco
AIFA

Scheda cartacea per la prescrizione della specialità medicinale BEZLOTOXUMAB

Indicazioni terapeutiche: indicato per la prevenzione della recidiva dell'infezione da *Clostridium difficile* (CDI) negli adulti ad alto rischio di recidiva di CDI.

Azienda Sanitaria:_____

Unità Operativa Richiedente: _____ Data: ____/___/____

Paziente (nome, cognome): _____

Data di nascita: _____/_____/_____ Sesso: M ☐ F ☐

Codice Fiscale o Tessera Sanitaria dell'Assistito: _____

ASL di Residenza: _____ Provincia: _____ Regione: _____

La rimborsabilità è limitata ai pazienti con diagnosi microbiologica di recidiva, definita come un periodo di benessere a distanza di almeno 8 settimane tra i singoli episodi, di CDI/CDAD (NAAT o GDH positivo e tossina A/B positiva) già in trattamento con terapia antibiotica, in presenza di almeno 1 tra le seguenti condizioni:

- ☐ soggetti di età >65 anni
- ☐ forma severa di CDI (Zar-score ≥2)
- ☐ soggetti immunocompromessi

PROGRAMMA TERAPEUTICO

	Farmaco	Specialità	Dosaggio
BEZLOTOXUMAB		25 mg/mL concentrato per soluzione per infusione	10 mg/kg

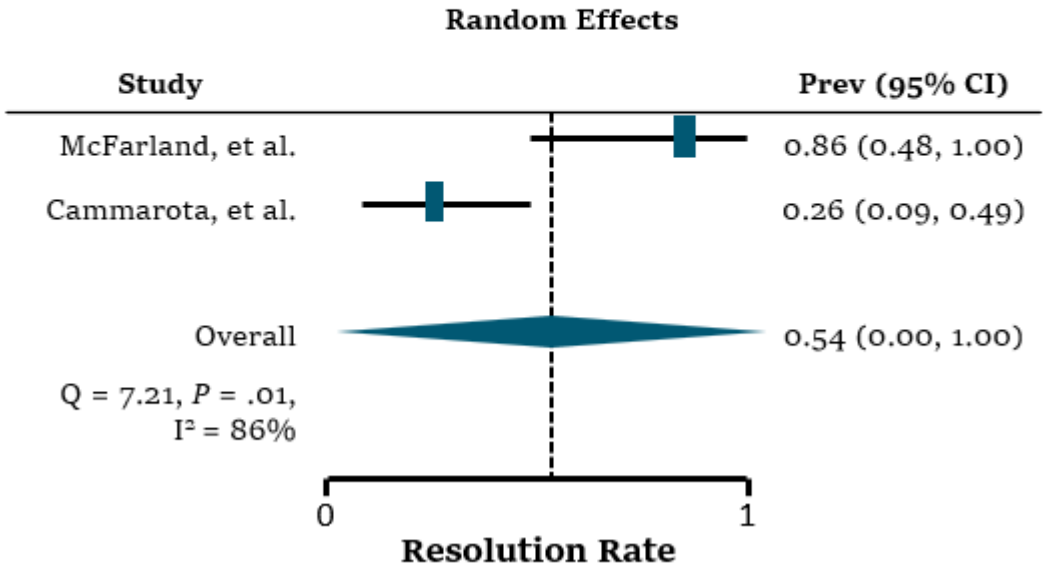
BEZLOTOXUMAB *deve essere somministrato durante il ciclo di terapia antibatterica per CDI, in una singola infusione endovenosa nell'arco di 60 minuti.*

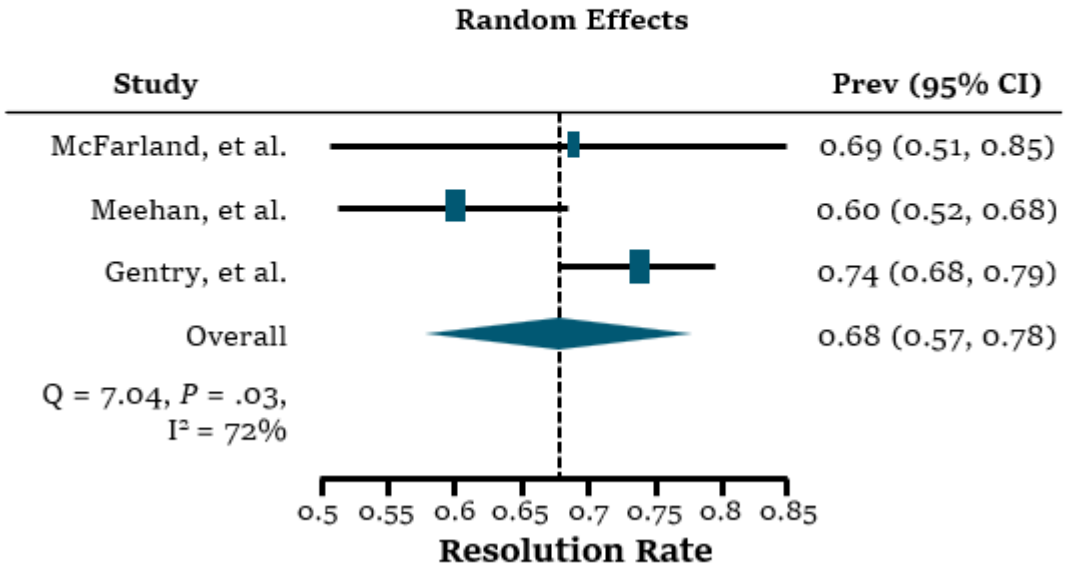
L'esperienza sulla somministrazione di ZINPLAVA nei pazienti è limitata ad un singolo episodio da CDI e ad una singola somministrazione.

VANCOMYCIN PULSE VS TAPER REGIMENS

Pulse: 54% cure with significant heterogeneity (I^2 = 86%)

Taper: 68% cure (range 60%-74%) and heterogeneity (I^2 = 72%)



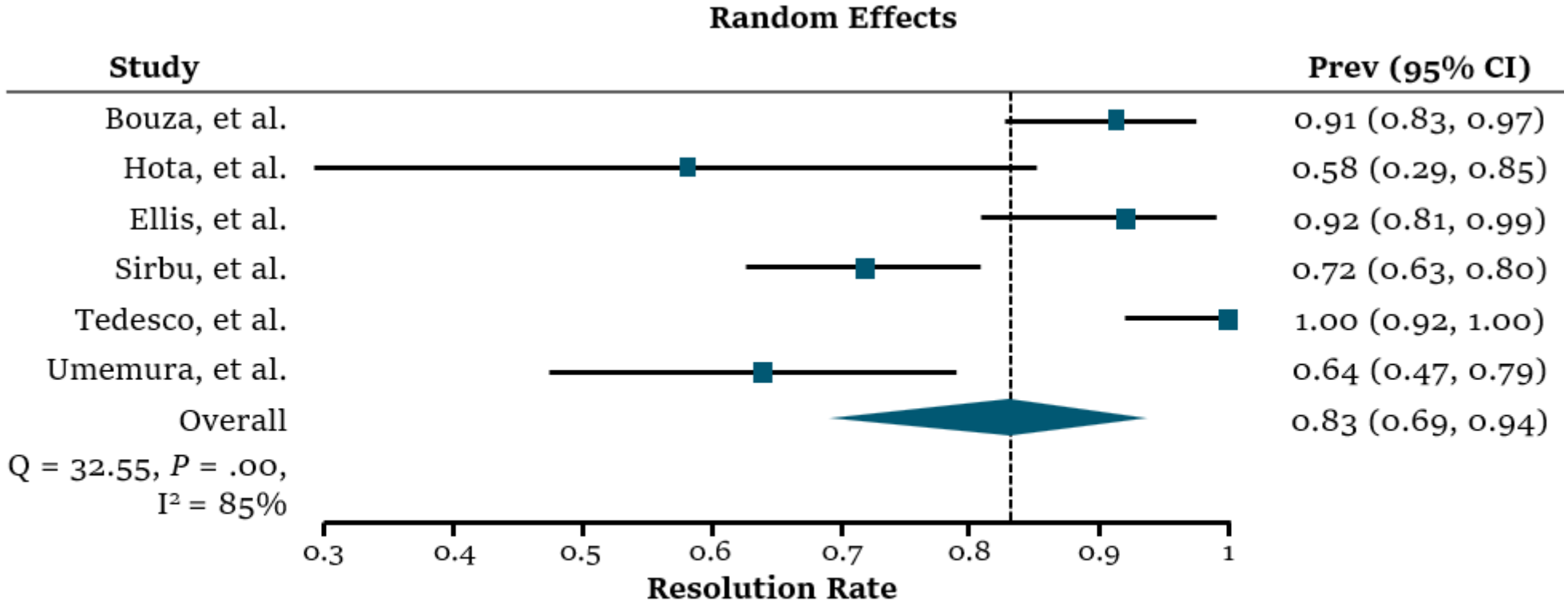


Similar Cure Rates

Taper regimen was defined as dose reduction over time; pulse was a regimen less frequent than daily. Studies assessing CDI resolution rates were included. Meta-analyses for resolution rates were performed using weighted proportion ratios (WPR).

Sehgal. Expert Rev Anti Infect Ther. 2022;20:577.

PULSE PLUS TAPER VS PLUS OR TAPER



- **Taper-and-pulse regimens superior** to taper alone (83% vs 68%, *P* <.0001) and pulse alone (83% vs 54%, *P* <.0004)

Sehgal. Expert Rev Anti Infect Ther. 2022;20:577.

Vancomycin tapered/pulsed example regimen: 125 mg 4x/day x 10-14 days, 2x/day x 7 days, 1x/day x 7 days, then every 2-3 days x 2-8 wk

FMT: GUIDELINES COMPARISON

	IDSA/SHEA[1,2]	ESCMID[3]	ACG[4]
Recommendation	**FMT** may be used for patients experiencing a **2nd or subsequent CDI recurrence**	**FMT** after SOC antibiotics is an option for a **2nd or further CDI recurrence**	Recommend **FMT** for patients experiencing a **2nd or further CDI recurrence**
Comments	Appropriate antibiotic treatment for **at least 2 recurrences (3rd episode)** should be tried prior to offering FMT	An adequate multidisciplinary risk assessment and surgical consult is mandatory and FMT products should be available with standardized preparation and screening	Recommend delivery of FMT by colonoscopy or capsules, or enema if other methods are unavailable Suggest repeating FMT if patient experiences a recurrence within 8 wk of initial FMT

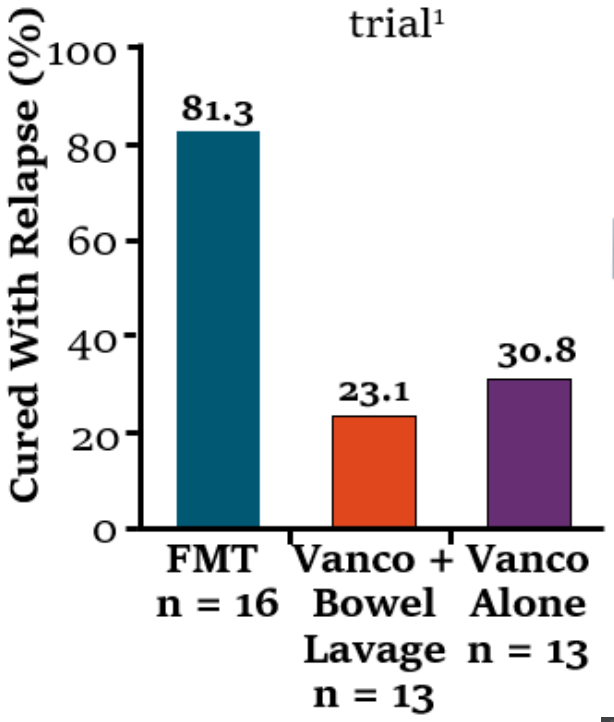
1. McDonald. Clin Infect Dis. 2018;66:e1. 2. Johnson. Clin Infect Dis. 2021;73:e1029.
3. van Prehn. Clin Microbiol Infect. 2021;27:S1. 4. Kelly. Am J Gastroenterol. 2021;116:1124.

FMT: EVOLUTION OVER TIME

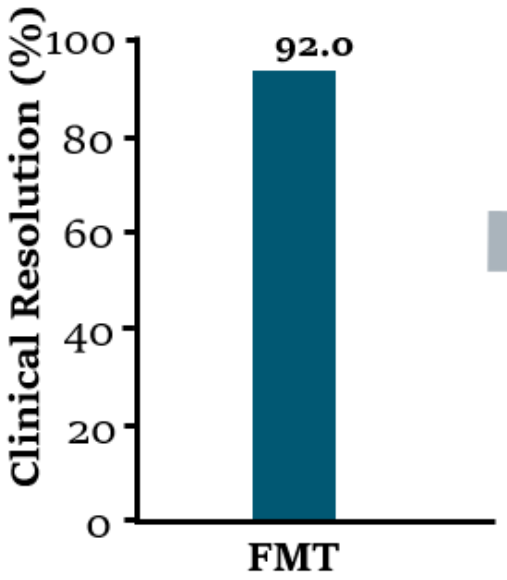
WPR, weighted pooled rate

Subgroups	WPR, % (95% CI)
Delivery modality	
Colonoscopy	87.4 (79.7–95.2)
Enema	66.3 (52.7–79.9)
Oral	81.5 (64.5–98.5)

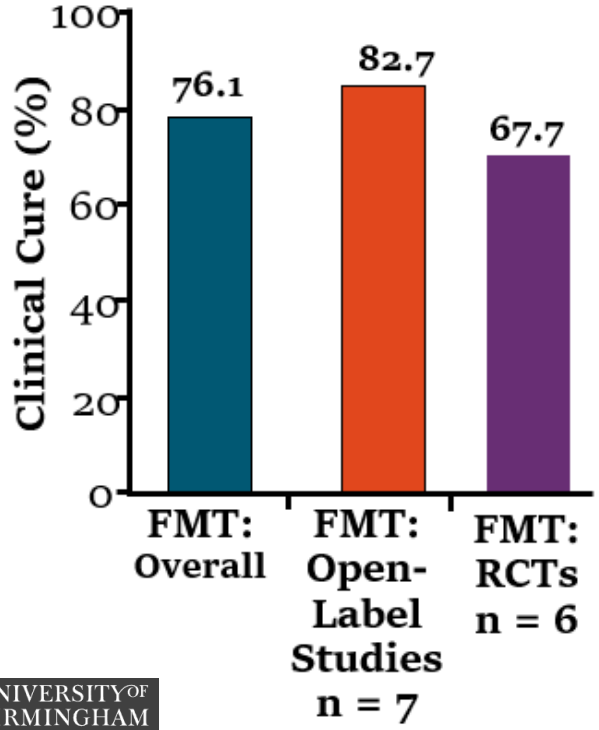
2013: Open-label, randomized, controlled trial[1]



2017: Meta-analysis of 37 studies[2]



2019: Meta-analysis of 13 studies[3]



Meta-analysis

- Examined impact of trial design on clinical outcomes
- Wide variances in reported efficacy rates
- Found that FMT was associated with significantly lower cure rates in RCTs (67.7%) than open-label studies (82.7%) ($P < .001$)

Microbiome Treatment Centre

UNIVERSITY OF BIRMINGHAM

As of 1 December 2022 the cost of each 50ml aliquot of FMT is £1300 (VAT exempt) chargeable to the requesting to the site.

1. van Nood. NEJM. 2013;368:407. 2. Quraishi. Alim Pharm Ther. 2017;46:479. 3. Tariq. Clin Infect Dis. 2019;68:1351.

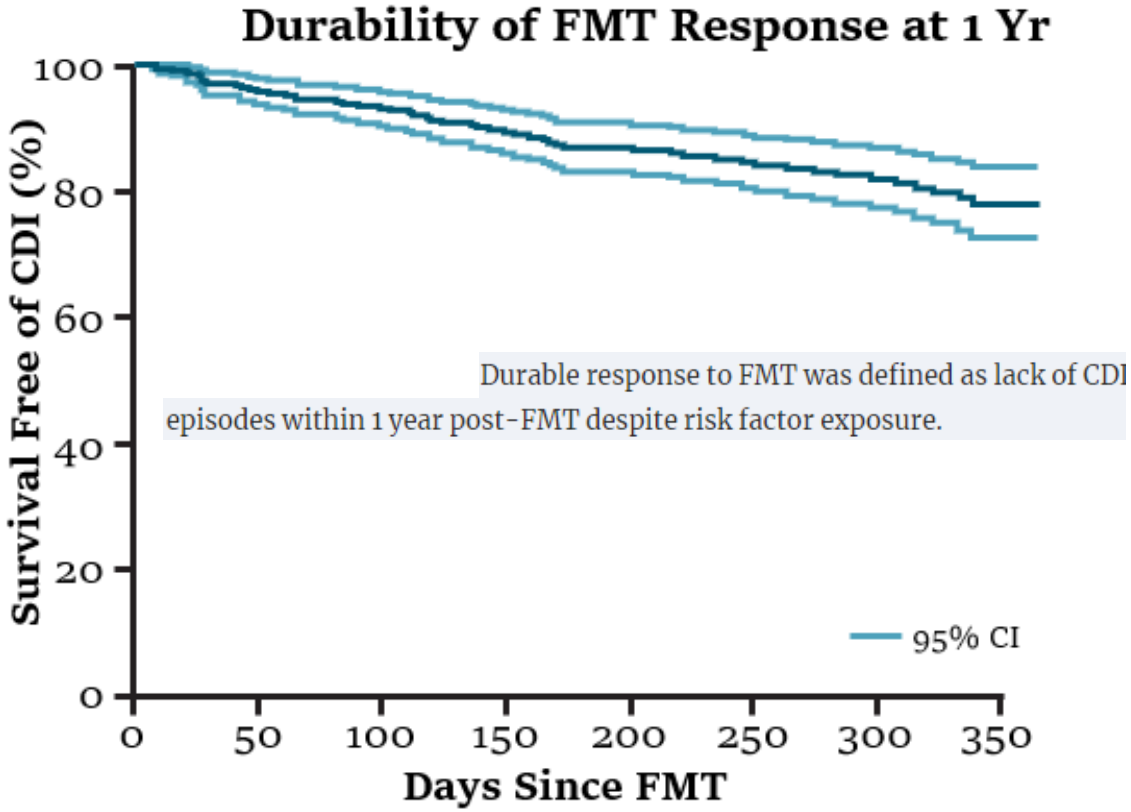
FMT DURABILITY

Study design: retrospective analysis of N = 460 adults who received FMT for rCDI

Interaction of Antibiotic and Healthcare Exposure on FMT Durability at 1 Yr

Cohort	Hazard Ratio (95% CI)	*P* value
No Antibiotic No Healthcare*	Reference	---
No Antibiotic Healthcare*	0.70 (0.28, 1.79)	.46
Antibiotic No Healthcare*	**0.08 (0.02, 0.27)**	**<.001**
Antibiotic Health Care*	**0.23 (0.09, 0.63)**	**.004**

*Healthcare exposure was defined as any outpatient visit, emergency room visit, or hospital admission.

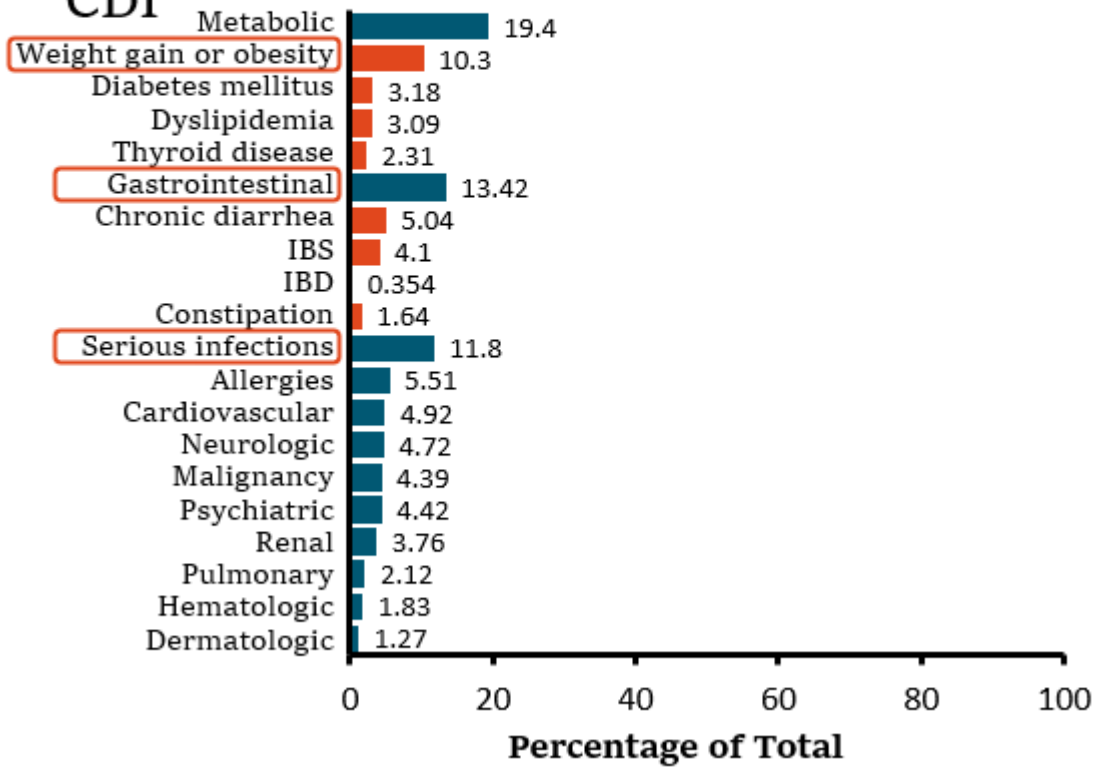


- Durability (lack of CDI episode within 1 yr post-FMT) with risk factor exposure at 1 yr: 78.1% (95% CI: 72.7%-84.0%)

Saha. Clin Infect Dis. 2021;73:e1706.

FMT SAFETY

Study design: prospective survey-based study (September 2012-June 2018) in N = 609 patients undergoing FMT for recurrent CDI



- Median weight gained: 30 lb (range, 10-70 lb)
  - 11 people (23%) had preexisting obesity
- Median time to serious infections: 29 mo (range, 0-73 mo)
  - 5.7% CDI
  - 4.5% pneumonia
  - 1.8% UTI
  - 1.2% sepsis

Saha. Gastroenterology. 2021;160:1961.e3.

FMT CHALLENGES

Manufacturing

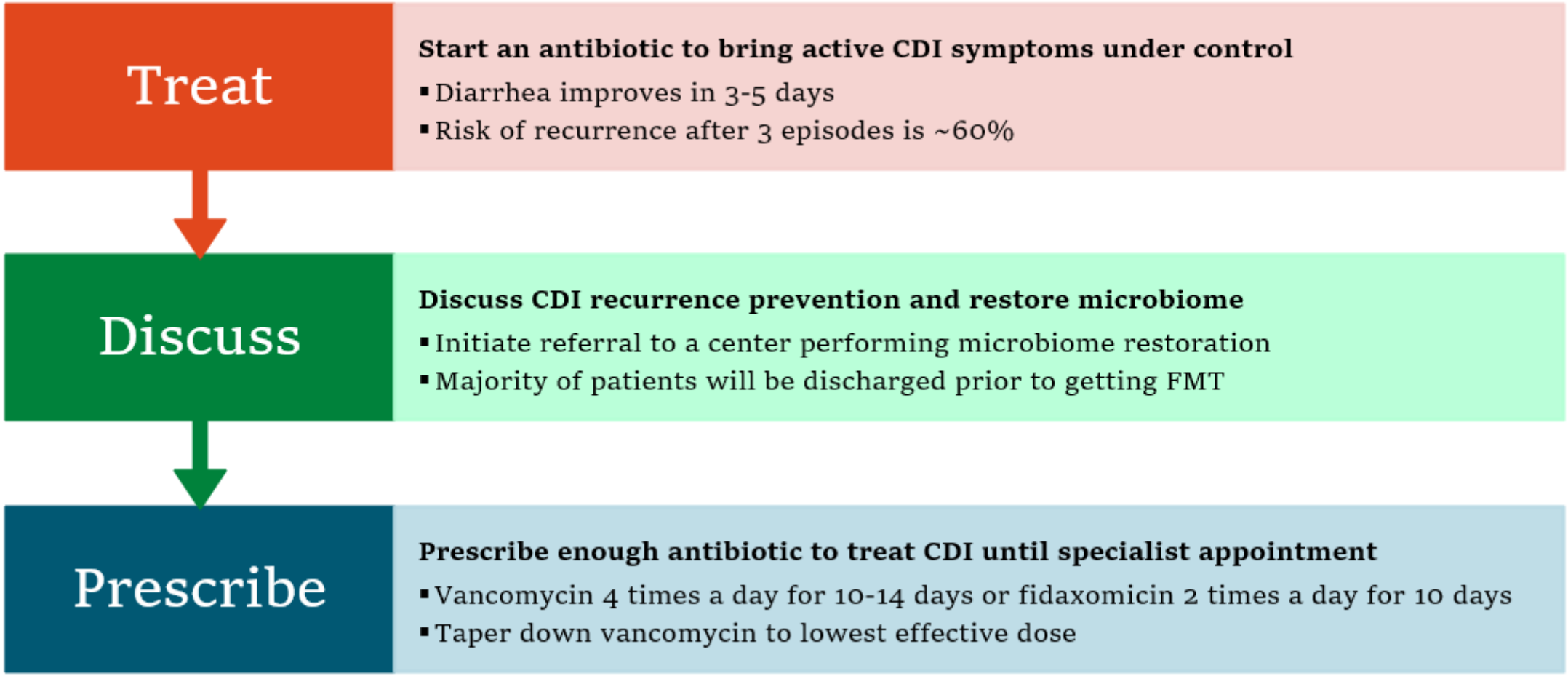
- Donor screening, recruitment, preparation, retention
- Stool testing
- Stool handling (anaerobic needs), diluent, mixing, filtration and storage
- Catalog inventory
- Trace recipient to donor

Administration

- Patient preparation
  - Antibiotics
  - Washout period
  - Bowel preparation
- Dose
- Route of administration

Hocking. Aliment Pharmacol Ther. 2023;57:549.

PREPARING THE PATIENT BEFORE FMT



Voth. Expert Rev Anti Infect Ther. 2020;18:669.

FMT ISSUES

Unapproved FMT Comes with Safety Concerns Due to COVID-19 Lack of Standardization and Regulation

Vaccines and Related Biological Products Advisory Committee September 22, 2022 Meeting Presentation- Sponsor

Consistent Screening Needed

Health and infection screening

Stool tests for donors
- Enteric pathogens, viruses, parasites
- Multi-drug resistant organisms

Blood tests for transmissible infections
- HIV, viral Hepatitis, syphilis, others

Emerging pathogens
- SARS-CoV-2

FDA Alerts

Multidrug resistant organism transmission
- ESBL-producing *E. coli*

SAEs due to transmission of infectious agents from asymptomatic donors
- *EPEC and STEC*

COVID-19

Monkeypox

FMT remains a heterogeneous practice

Donor screening
Stool processing
Administration
Follow-up

1. Khanna, 2021; 2. Khanna et al., 2020; 3. Khanna and Kraft, 2021
EPEC = enteropathogenic *Escherichia coli*; STEC = Shiga toxin-producing *E. coli*; ESBL = extended-spectrum beta-lactamase

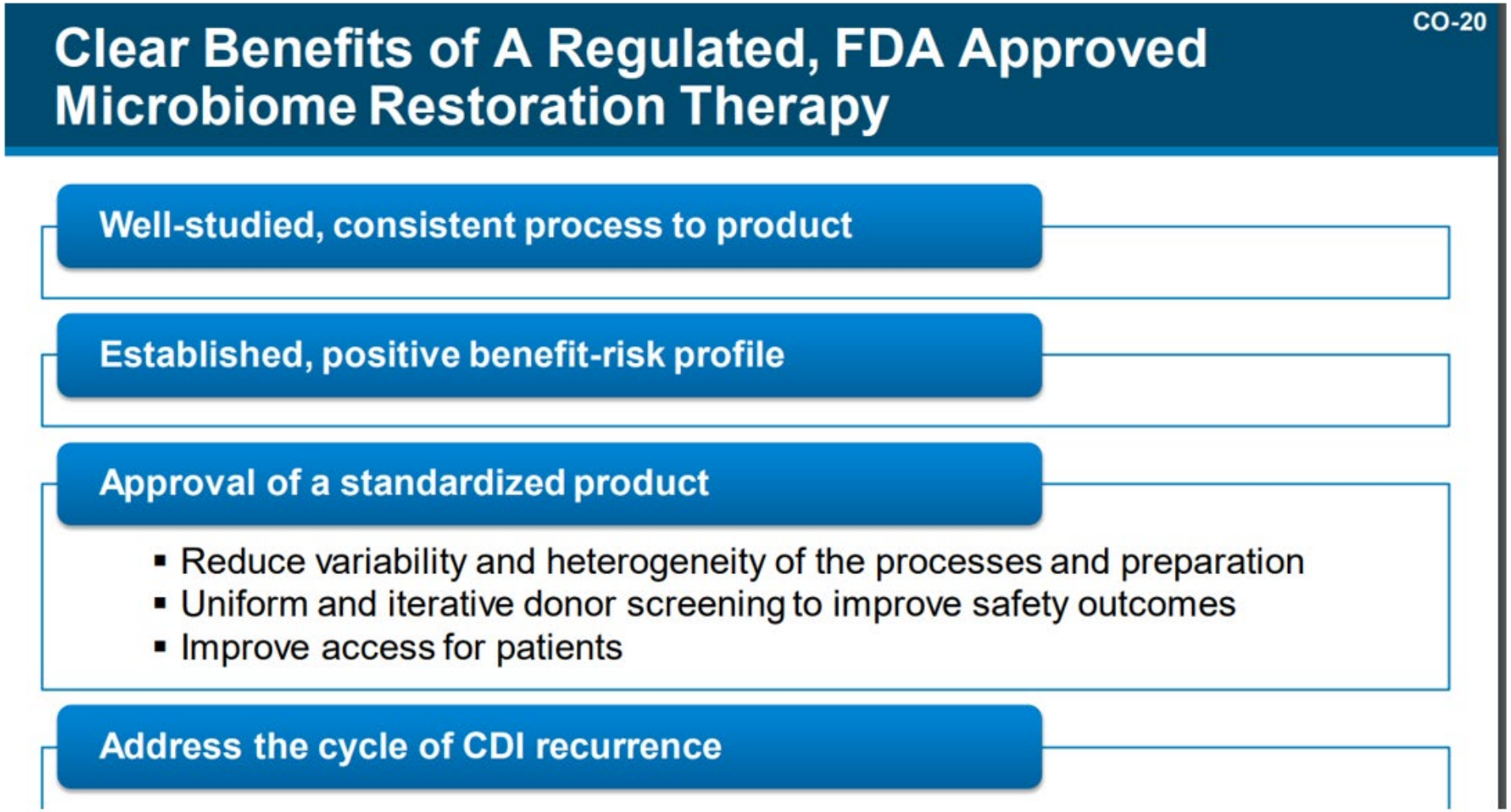
FMT VS LBP

- **FMT**: transfer of stool from a healthy donor into the gastrointestinal tract of a patient
- **LBP**: nonvaccine, biologic products that contain live organisms and are applicable to the prevention, treatment, or cure of a disease or condition

	Fecal Microbiota Transplant	Live Biotherapeutic Product
Donor screening	++	+++
Sample screening	?	+++
Good Manufacturing Practices	?	+++
Clinical trial data	+	+++
Safety data	+/-	+++
Accessibility	?	+

Nagarakanti. Infect Drug Resist. 2023;16:3137.

THE ADVANTAGE OF STANDARDIZATION

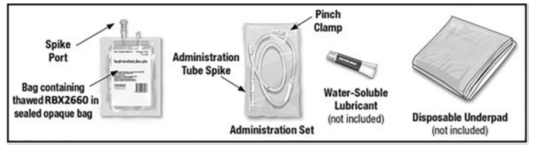


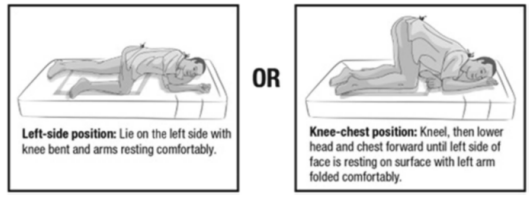
Vaccines and Related Biological Products Advisory Committee September 22, 2022 Meeting Presentation- Sponsor

RECENTLY APPROVED LBPs

Proprietary manufacturing process preserves broad consortium of diverse spore-forming and non–spore-forming bacteria, including **Bacteroidetes** and **Firmicutes**

Between $1x10^8$ and $5x10^{10}$ CFU of fecal microbes per 150 mL treatment.





around $9,487 for a supply of 150 milliliters

	RYA	VST
Administration	One-time dose rectally by a trained medical professional	4 orally administered capsules for 3 consecutive days
Timing of administration	24-72 hours post antibiotic completion	2-4 days post antibiotic completion
Storage requirements	Ultracold (-60C to -90C) freezer; thaw 24 hours prior to administration	Can be stored in the refrigerator but it is not required
Clinical trial leading to FDA approval	PUNCH CD3	ECOSPOR III
Clinical Notes	Patients should refrain from antibiotic use for 8 weeks after administration	Bowel evacuation required prior to first dose

Table 1. Brief comparison of RYA and VST, the newly FDA approved fecal microbiota products

A proprietary manufacturing process removes most fungi, parasites, viruses and non–spore-forming bacteria resulting in predominantly **Firmicutes spores**

3×10^7 CFU per full treatment

Narrow consortium

list price at $17,500 (WAC)

New Fecal Microbiota Options for Prevention of Recurrent Clostridioides difficile

November 9, 2023
Cheryl Wood, PharmD

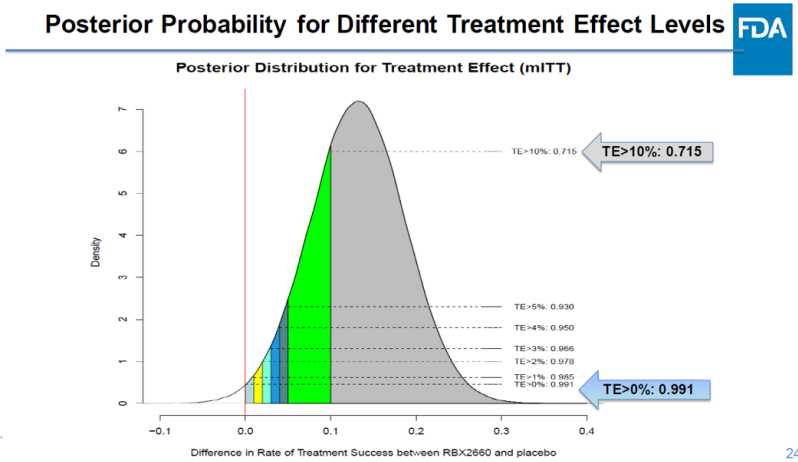
ContagionLive Infectious Diseases Today

ANTIMICROBIAL WASHOUT PRIOR TO LBP

- Time from completion of standard of care antimicrobial to administration of LBP
  - Optimal timing unclear
- **Rationale**: minimize the effects of the standard of care antimicrobial on the administered LBP
- **Goal**: clear as much of the standard of care antimicrobial from the patient's body without providing *C. difficile* the opportunity to regerminate and recur

Feuerstadt. Dig Dis Sci. 2022;67:2763.

RYA (RBX6220) EFFICACY



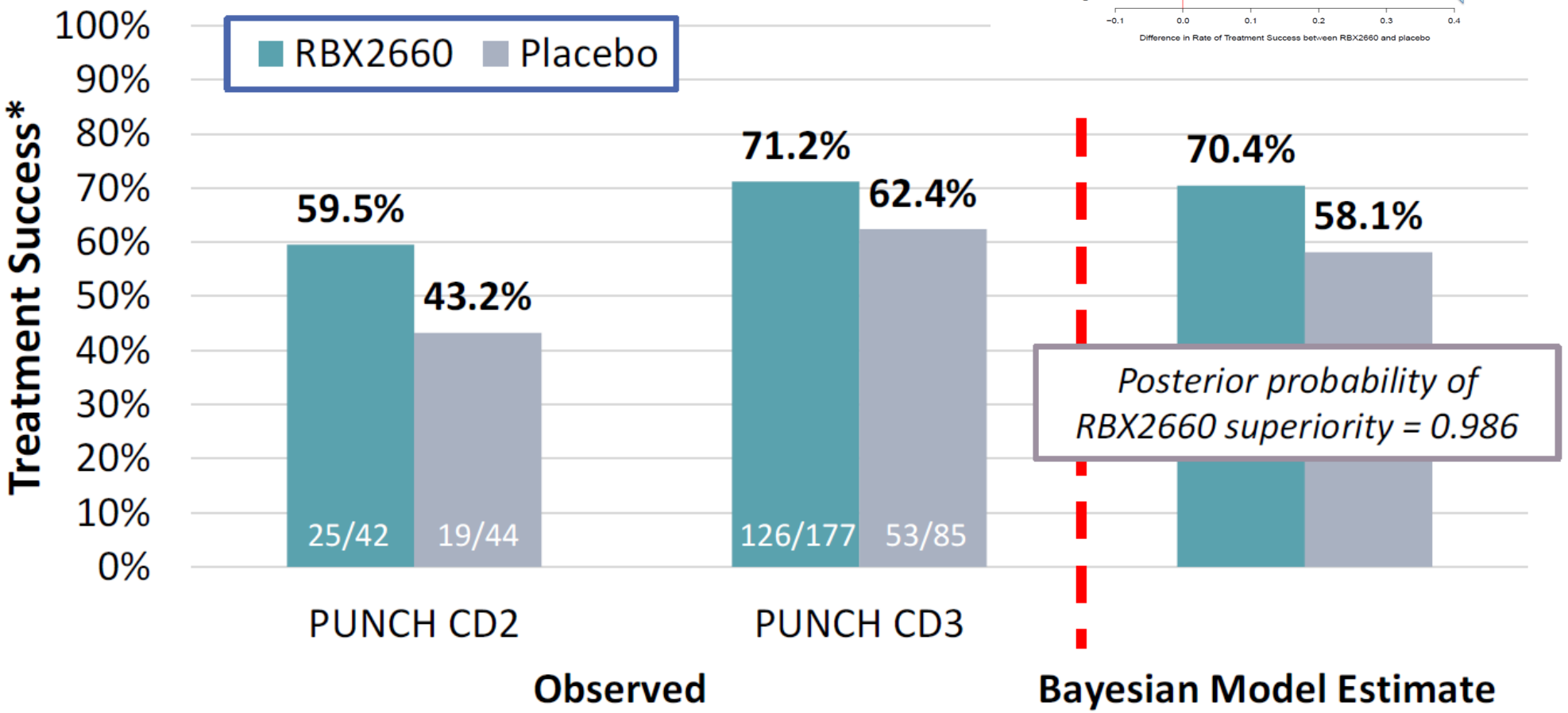
Inclusion

Age ≥18 years with:

- ≥1 rCDI episode (i.e., ≥2 CDI episodes in 8 weeks)

or

- ≥2 episodes of severe CDI resulting in hospitalization in past 12 months



*Defined as the absence of CDI diarrhea within 8 weeks after study treatment
Results from intent-to-treat (ITT) (PUNCH CD2) and modified-ITT (PUNCH CD3) populations

Khanna S et al. *Drugs*. 2022; 82:1527-38.

RYA (RBX6220): MICROBIOTA RESTORATION

Figure 3 Bacteroidia and Clostridia have the highest engraftment percentages in RYA treated participants [73]

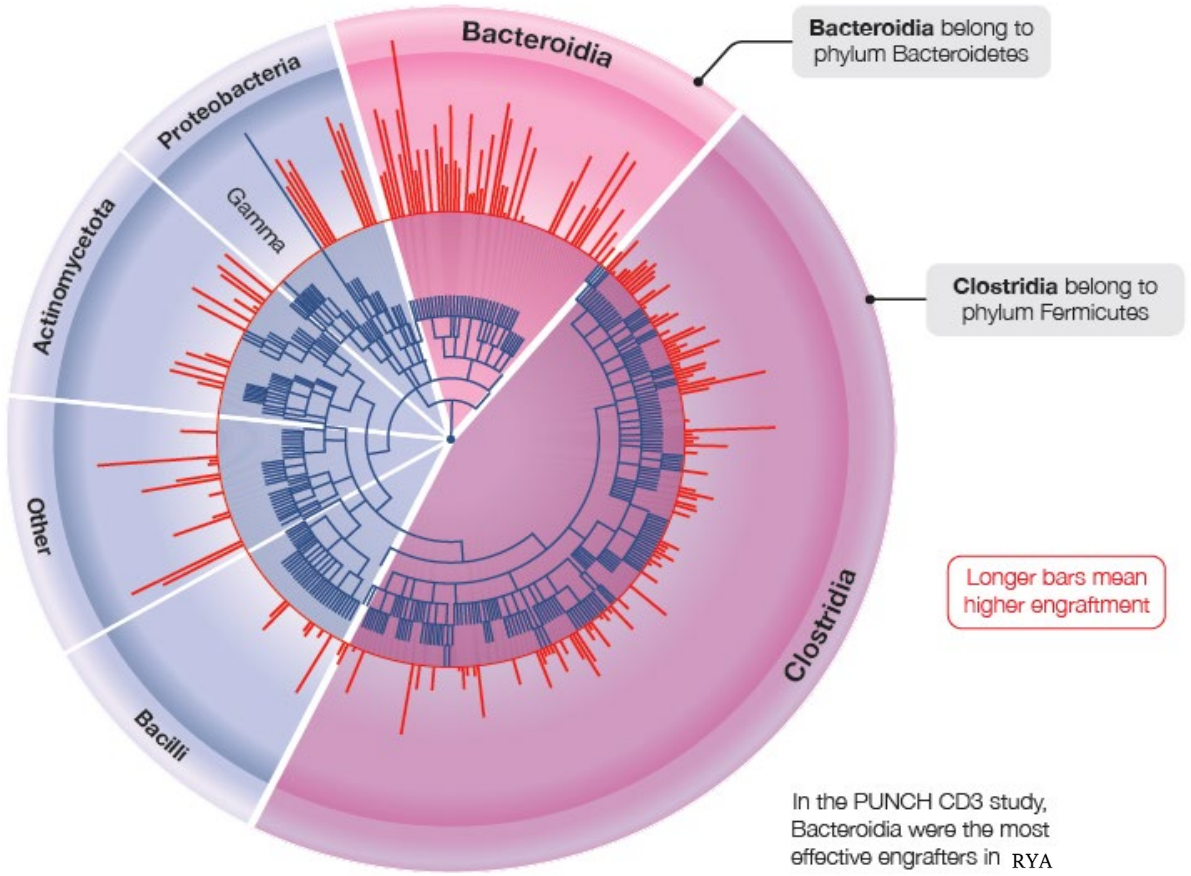
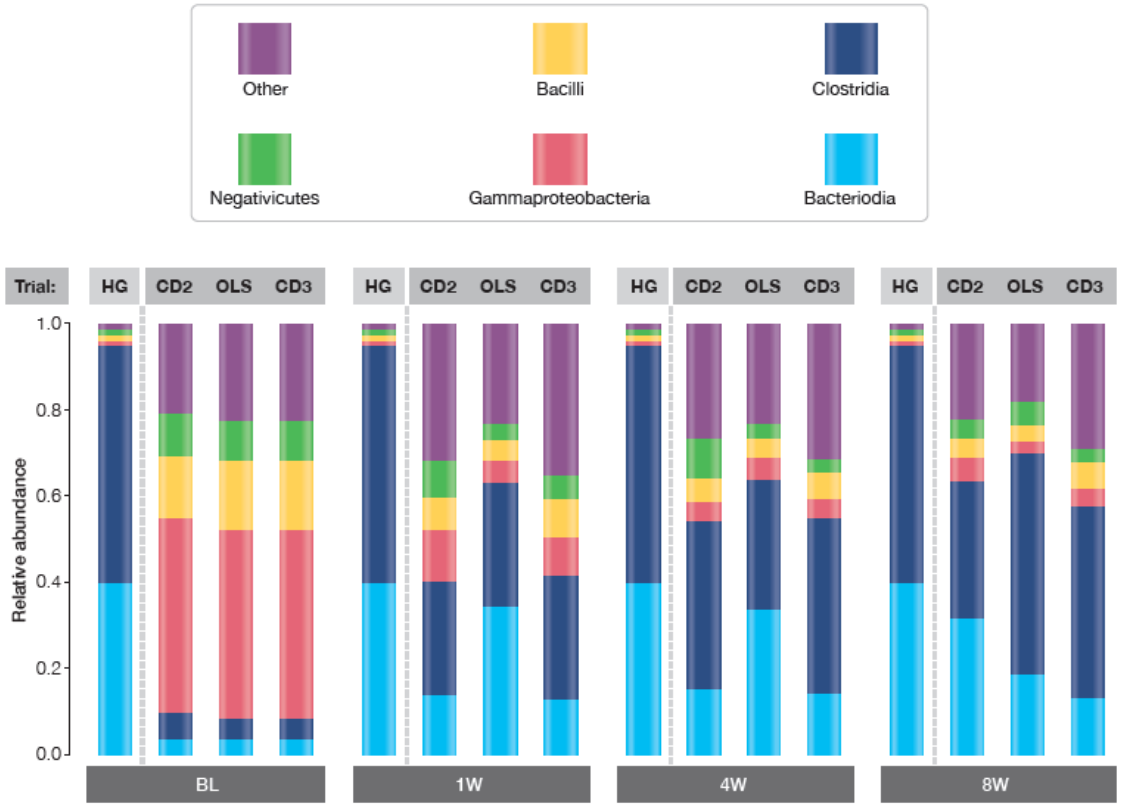


Figure 2 Clinical response to RYA is associated with a microbiota shift reminiscent of a healthy gut consortium [73]



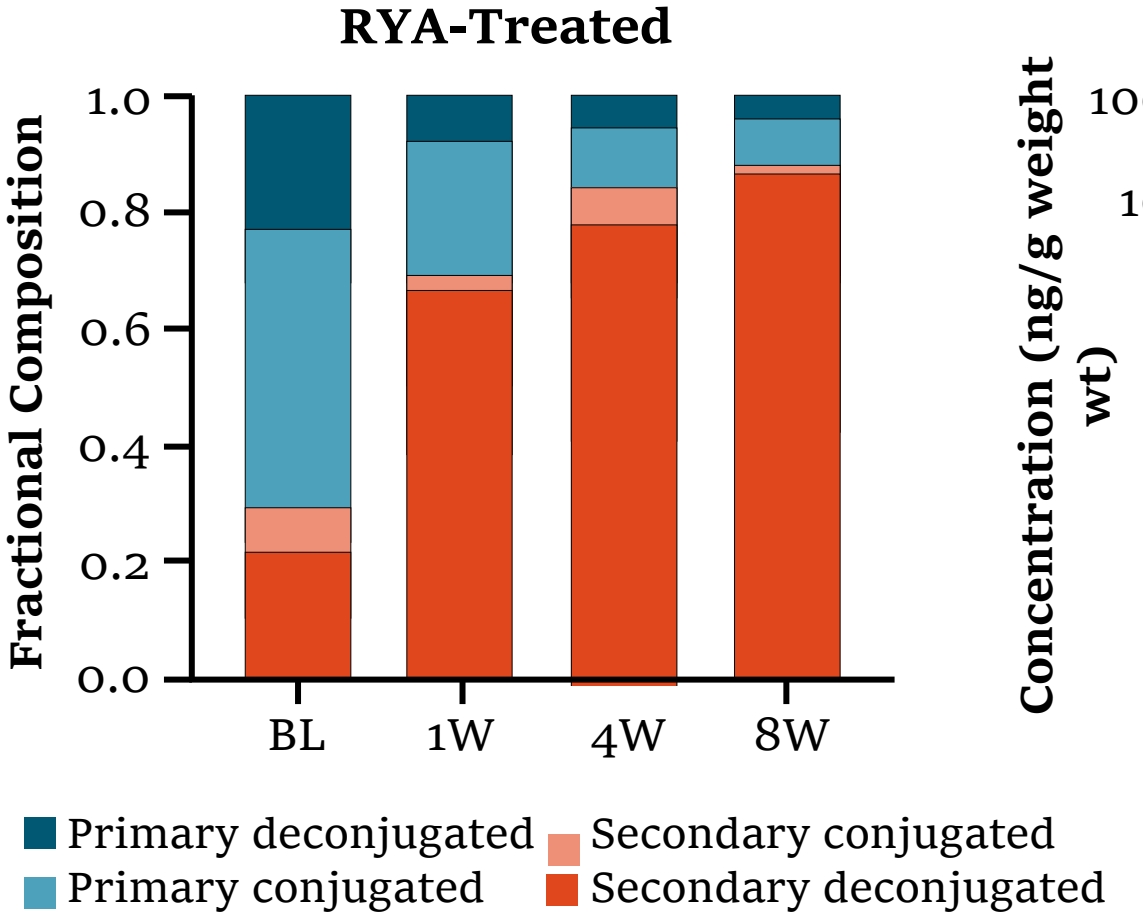
In an analysis of three trials (PUNCH CD2, PUNCH CD3, PUNCH OLS), baseline was characterized by predominance of *Gammaproteobacteria* and *Bacilli* whereas after treatment, microbiome composition shifted to predominance of *Clostridia* and *Bacteroidia* (healthy commensals), which occurred as early as week one. *Clostridium* species are Firmicutes.

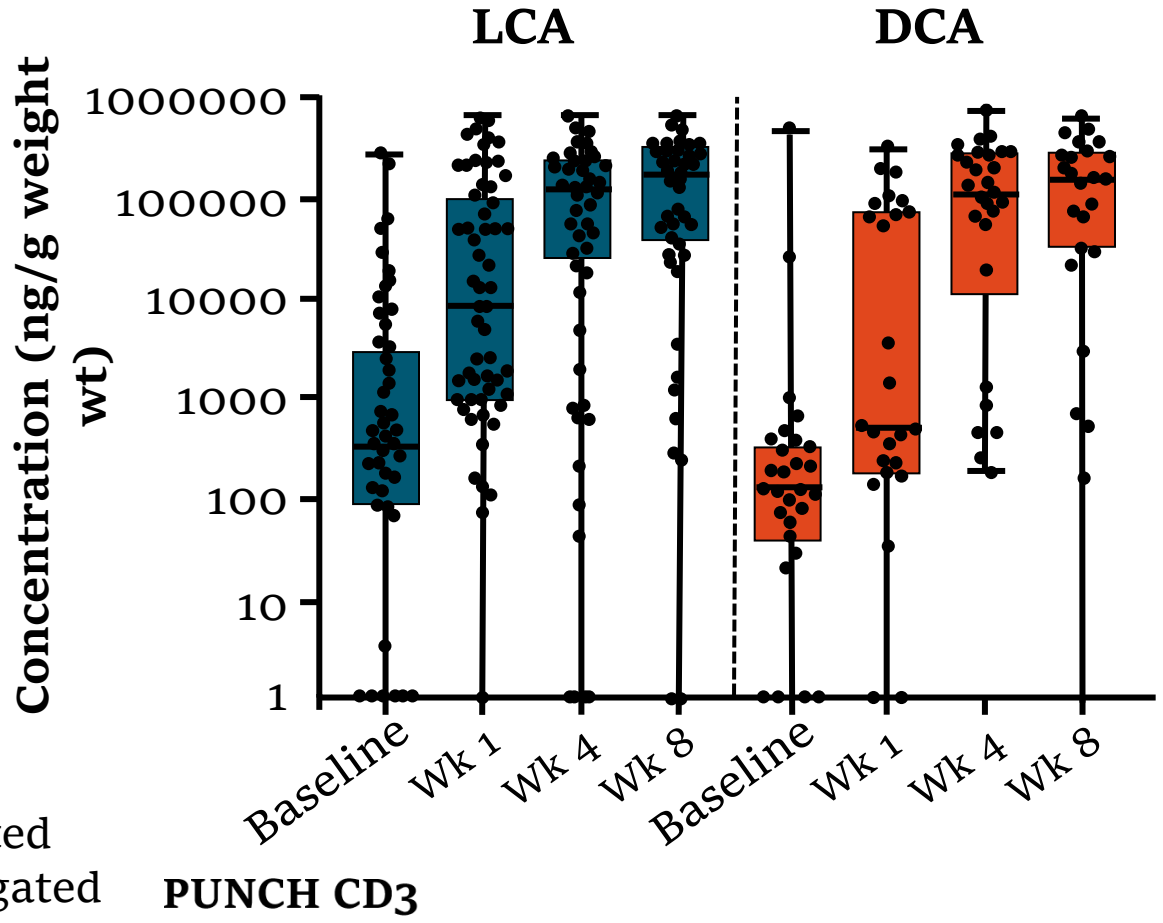
Abbreviations: **HG**, Healthy gut; **CD2**, PUNCH CD2; **CD3**, PUNCH CD3; **OLS**, PUNCH OLS

Open Forum Infectious Diseases 2023; 10: 11
doi: 10.1093/ofid/ofad529

Glenn Tillotson* [1], Gayatri Vedantam [2], Jae Hyun Shin [3], Cirle A. Warren [3]

RYA RESTORATION OF BILE SALT MILIEU



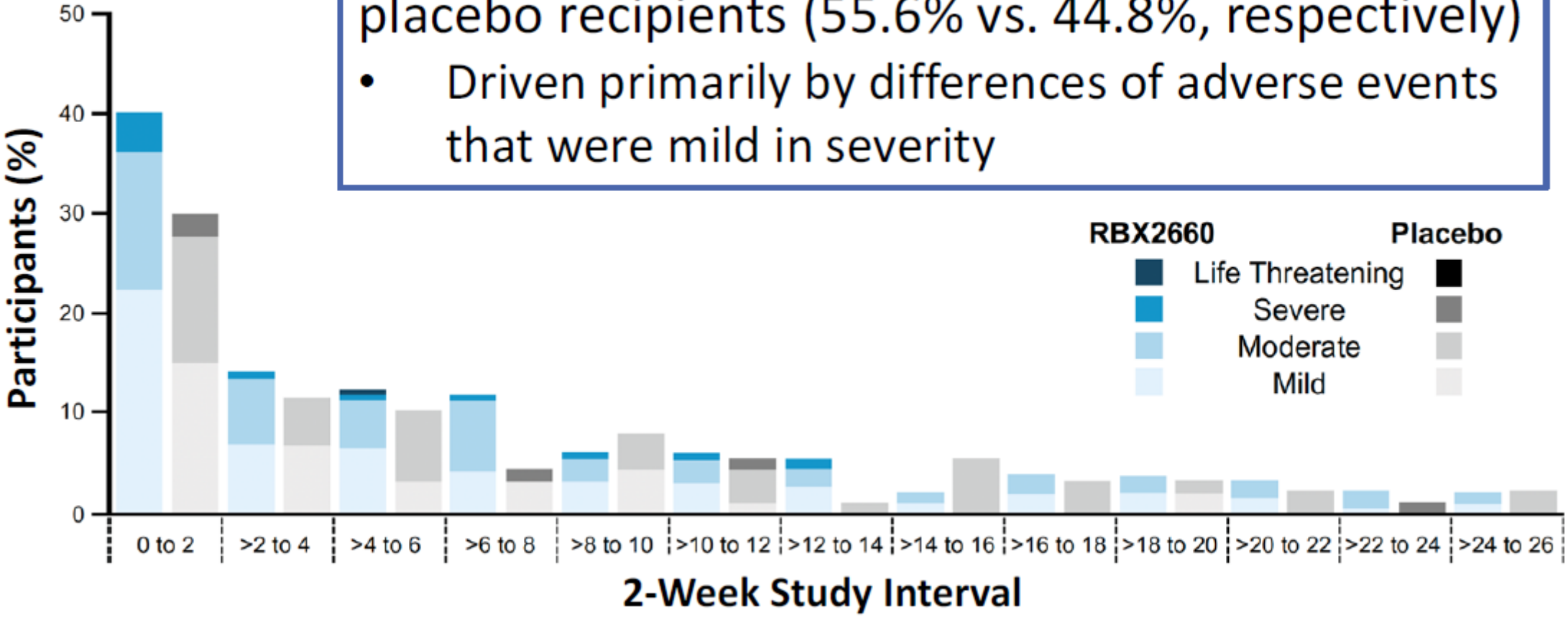


Papazyan. Open Forum Infect Dis. 2021;8(Suppl 1):S610.

RYA (RBX6220): SAFETY

Higher rate of adverse events in RBX2660 vs. placebo recipients (55.6% vs. 44.8%, respectively)

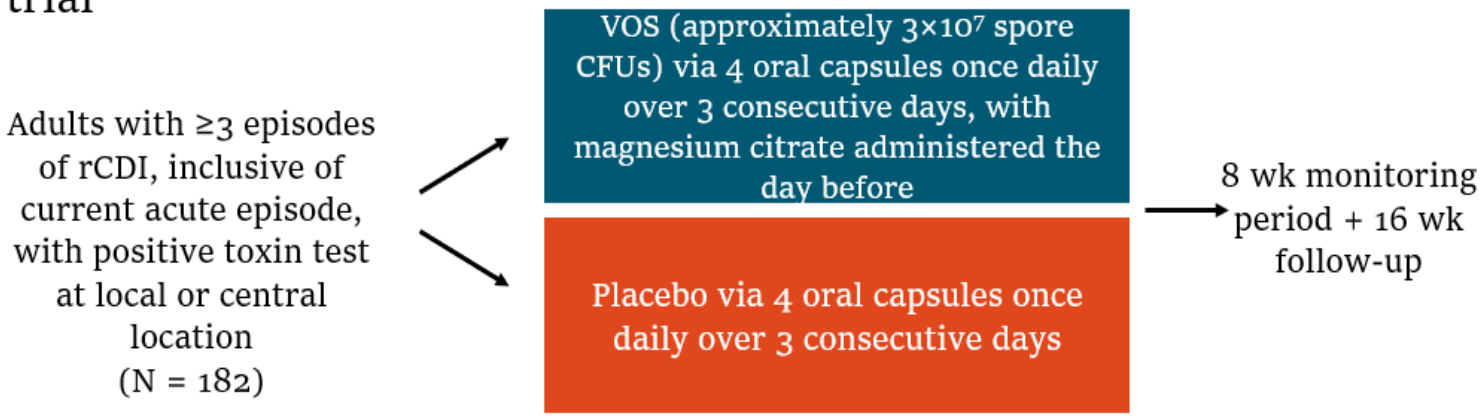
- Driven primarily by differences of adverse events that were mild in severity

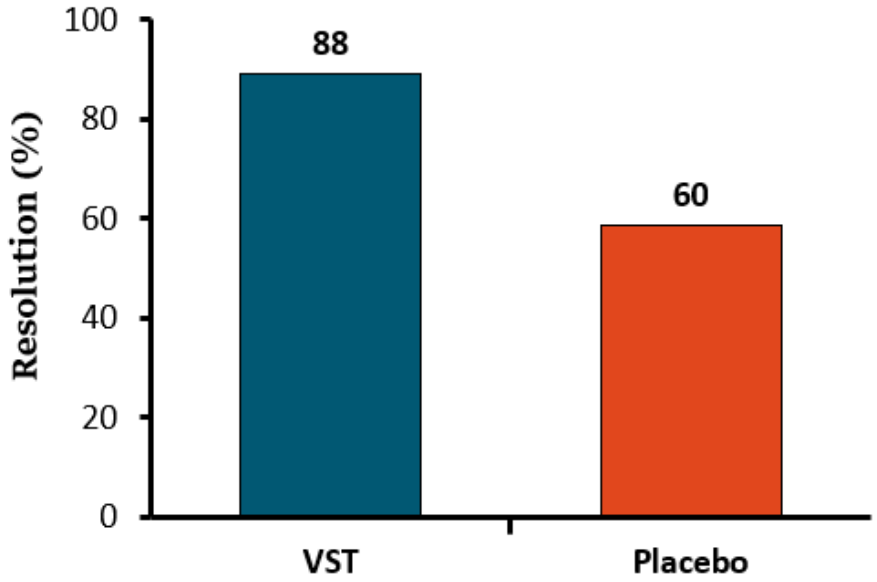


Khanna S et al. *Drugs*. 2022; 82:1527-38.

VST (SER-109): EFFICACY FROM ECOSPOR III

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

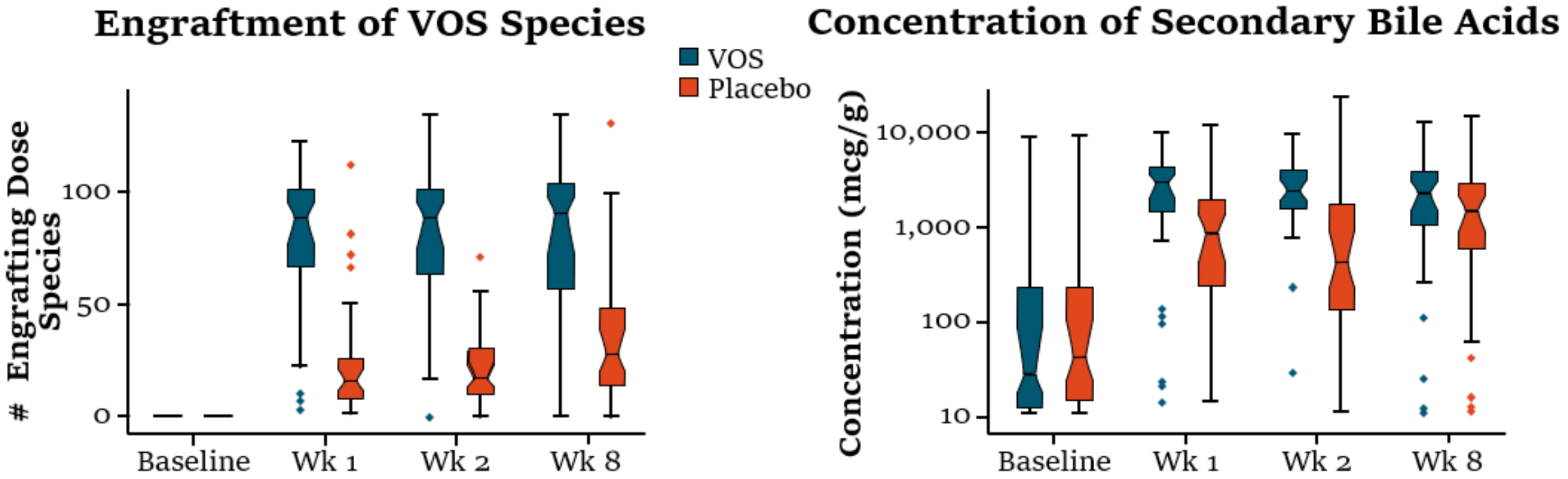




- **Primary endpoint:** resolution of diarrhea without need for further anti-CDI therapy within 8 wk of study treatment
  - Recurrences evaluated through Wk 24

Feuerstadt. NEJM. 2022;386:220.

VST: COMPOSITIONAL AND METABOLOMIC CHANGES



Feuerstadt. NEJM. 2022;386:220.

VST (SER-109): SAFETY

CONCLUSIONS

In patients with symptom resolution of *C. difficile* infection after treatment with standard-of-care antibiotics, oral administration of SER-109 was superior to placebo in reducing the risk of recurrent infection. The observed safety profile of SER-109 was similar to that of placebo. (Funded by Seres Therapeutics; ECOSPOR III ClinicalTrials.gov number, NCT03183128.)

SAFETY

No serious adverse events that were assessed by the site investigator as being related to SER-109 were observed through week 8 (Table S1). Adverse events that were related or possibly related to SER-109 or placebo occurred in slightly more than half of the patients in each group (Table 2). The most common adverse events were gastrointestinal disorders, the majority of which were mild to moderate in nature. Three deaths occurred in the SER-109 group, none of which were deemed by the investigators, who were unaware of the trial-group assignments, to be drug-related (Table 2 and the Supplementary Appendix).

Table 2. Adverse Events through 8 Weeks (Safety Population).*

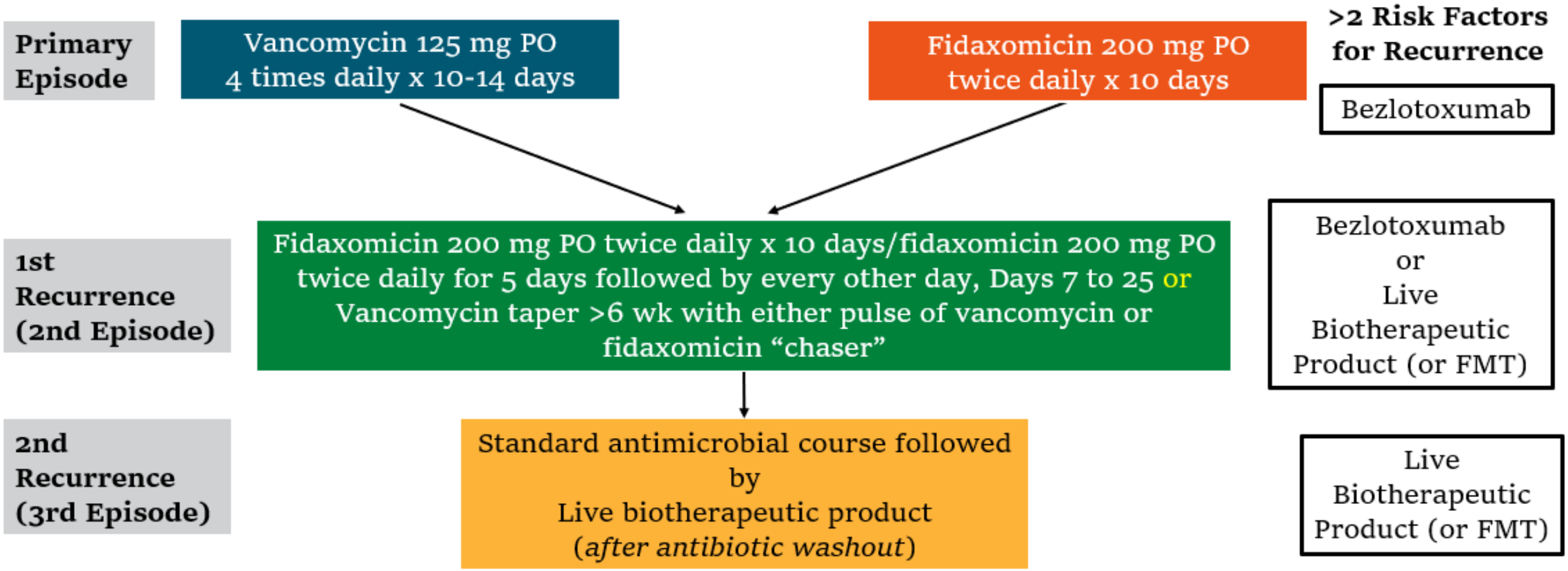
Adverse Event	SER-109 (N=90)	Placebo (N=92)
	no. of patients (%)	
Any adverse event	84 (93)	84 (91)
Adverse event related or possibly related to SER-109 or placebo	46 (51)	48 (52)
Serious adverse event†	7 (8)	15 (16)
Adverse event of special interest that occurred or worsened after initiation of SER-109 or placebo	1 (1)	1 (1)
Serious adverse event or an adverse event of special interest that occurred or worsened after initiation of SER-109 or placebo and was related or possibly related to SER-109 or placebo	0	0
Serious adverse event leading to withdrawal from the trial	0	1 (1)
Adverse event leading to death‡	2 (2)	0

Table 2. Adverse Events through 8 Weeks (Safety Population).*

Adverse Event	SER-109 (N=90)	Placebo (N=92)
	no. of patients (%)	
Adverse events reported in ≥5% of patients		
Gastrointestinal disorders	79 (88)	80 (87)
Flatulence	63 (70)	70 (76)
Abdominal distension	49 (54)	49 (53)
Abdominal pain	46 (51)	56 (61)
Constipation	28 (31)	22 (24)
Diarrhea	22 (24)	20 (22)
Nausea	16 (18)	30 (33)
Vomiting	3 (3)	10 (11)
General disorders and administration site conditions	57 (63)	65 (71)
Fatigue	53 (59)	58 (63)
Chills	21 (23)	22 (24)
Metabolism and nutrition disorders	28 (31)	36 (39)
Decreased appetite	26 (29)	34 (37)
Infections and infestations	18 (20)	14 (15)
Urinary tract infections	6 (7)	1 (1)
C. difficile colitis	1 (1)	7 (8)
Musculoskeletal and connective-tissue disorders	7 (8)	5 (5)
Nervous system disorders	7 (8)	4 (4)
Injury, poisoning, and procedural complications	4 (4)	6 (7)
Respiratory, thoracic, and mediastinal disorders	4 (4)	6 (7)
Renal and urinary disorders	3 (3)	5 (5)

Feuerstadt. NEJM. 2022;386:220.

A POTENTIAL ALGORITHM



Feuerstadt. NEJM. 2022;386:220. Johnson. Clin Infect Dis. 2021;73:e1029. Kelly. Am J Gastroenterol. 2021;116:1124. Khanna. Drugs 2022;82:1527. Louie. JAMA. 2023;329:1356. Orenstein. BMC Infect Dis. 2022;22:245.

AI AND CDI: THE FUTURE (THE PRESENT?)

A Generalizable, Data-Driven Approach to Predict Daily Risk of *Clostridium difficile* Infection at Two Large Academic Health Centers

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY APRIL 2018, VOL. 39, NO. 4

Jeeheh Oh, MS;[1,a] Maggie Makar, MS;[2,a] Christopher Fusco, BS;[3] Robert McCaffrey, BS;[3] Krishna Rao, MD, MS;[4] Erin E. Ryan, MPH, CCRP;[5,6] Laraine Washer, MD;[4,7] Lauren R. West, MPH;[5,6] Vincent B. Young, MD, PhD;[4,8] John Guttag, PhD;[2] David C. Hooper, MD;[5,6,9] Erica S. Shenoy, MD, PhD;[5,6,9,10,b] Jenna Wiens PhD[1,b]

METHODS. We utilized EHR data from 191,014 adult admissions to UM and 65,718 adult admissions to MGH. We extracted patient demographics, admission details, patient history, and daily hospitalization details, resulting in 4,836 features from patients at UM and 1,837 from patients at MGH. We used L2 regularized logistic regression to learn the models, and we measured the discriminative performance of the models on held-out data from each hospital.

RESULTS. Using the UM and MGH test data, the models achieved area under the receiver operating characteristic curve (AUROC) values of 0.82 (95% confidence interval [CI], 0.80–0.84) and 0.75 (95% CI, 0.73–0.78), respectively. Some predictive factors were shared between the 2 models, but many of the top predictive factors differed between facilities.

March 26 '18 MIT Computer Science & Artificial Intelligence Lab

Machine learning model predicts C. difficile infection risk

WRITTEN BY Sue McGreevey

Overall, the models were highly successful at predicting which patients would ultimately be diagnosed with C. difficile. In half of those who were infected, accurate predictions could have been made at least five days before diagnostic samples were collected, which would allow highest-risk patients to be the focus of targeted antimicrobial interventions. If validated in prospective studies, the risk prediction score could guide early screening for C. difficile. For patients diagnosed earlier in the course of disease, initiation of treatment could limit the severity of the illness, and patients with confirmed C. difficile could be isolated and contact precautions instituted to prevent transmission to other patients.

An integrated pipeline for prediction of *Clostridioides difficile* infection

Scientific Reports | (2023) 13:16532

Jiang Li[1], Durgesh Chaudhary[2,7], Vaibhav Sharma[3], Vishakha Sharma[4], Venkatesh Avula[1], Paddy Ssentongo[5], Donna M. Wolk[6], Ramin Zand[2,7] & Vida Abedi[1,5]✉

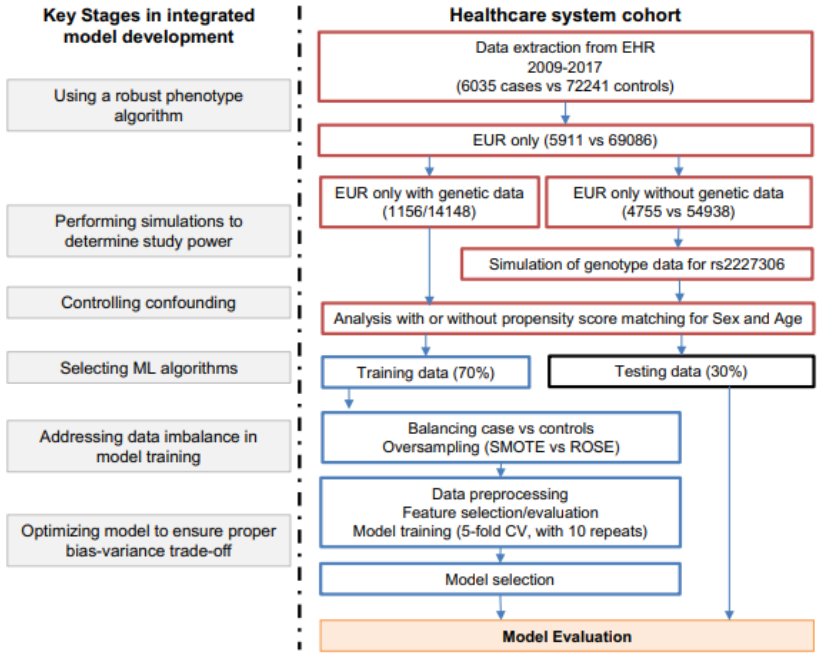


Figure 1. A flowchart illustrated the sample size and the pipeline for the prediction model development.

The generalizability of developed prediction models from a single healthcare system to others is debatable[37]. Since this study aims to utilize only common clinical risk factors readily available in most EHRs to build a prediction model, the conclusion made from this study could have better generalizability and may be easier to implement elsewhere. For these reasons, we propose that this integrated model is more transferable to EHR than complex models with manually curated variables and datasets.

UNRESOLVED ISSUES

SHEA/IDSA/APIC Practice Recommendation

Infection Control & Hospital Epidemiology (2023), **44**, 527–549
doi:10.1017/ice.2023.18

Strategies to prevent *Clostridioides difficile* infections in acute-care hospitals: 2022 Update

Larry K. Kociolek MD, MSCI[1], Dale N. Gerding MD[2], Ruth Carrico PhD, DNP, APRN, CIC[3], Philip Carling MD[4], Curtis J. Donskey MD[5], Ghinwa Dumyati MD[6], David T. Kuhar MD[7], Vivian G. Loo MD, MSc[8], Lisa L. Maragakis MD, MPH[9], Monika Pogorzelska-Maziarz PhD, MPH[10], Thomas J. Sandora MD, MPH[11], David J. Weber MD, MPH[12], Deborah Yokoe MD, MPH[13] and Erik R. Dubberke MD, MSPH[14]

Unresolved Issues
1. Identification of asymptomatic carriers of toxigenic *C. difficile* using rectal or perirectal swabs and NAAT testing and placing those who are positive on contact precautions.
2. Implementation of touchless disinfection technologies.
3. Use of probiotics as primary prophylaxis.
4. CDI antibiotic prophylaxis for certain very high-risk patients who are receiving systemic antibiotics.
5. Use of gowns and gloves by family members and other visitors.
6. Use of admission-based alert systems that notify infection preventionists and clinical personnel about readmitted or transferred patients with a history of CDI.
7. Ongoing assessment of CDI knowledge and intensified CDI education among HCP.
8. Restriction of gastric acid suppressants.

TAKE-HOME MESSAGES

- CDI prevention first rule: wise use of antibiotics (always)
- Nevertheless, dysbiosis has many causes
- Primary prophylaxis: the jury is still out (waiting for RCTs and AI)
- Secondary prophylaxis: several options (potentially) available

To explore further: cost-effectiveness, FDX extended-pulsed, combination of strategies

THANKS FOR YOUR ATTENTION

Optimize antibiotic use[a]
To minimize disruption of normal colonic microbiota and physically block the spread and acquisition of *C difficile*

Be prudent in initiating systemic antibiotics[b]
Ensure they are used for the shortest appropriate clinical duration

Reduce use of antibiotics commonly implicated as CDI-inciting agents[c]

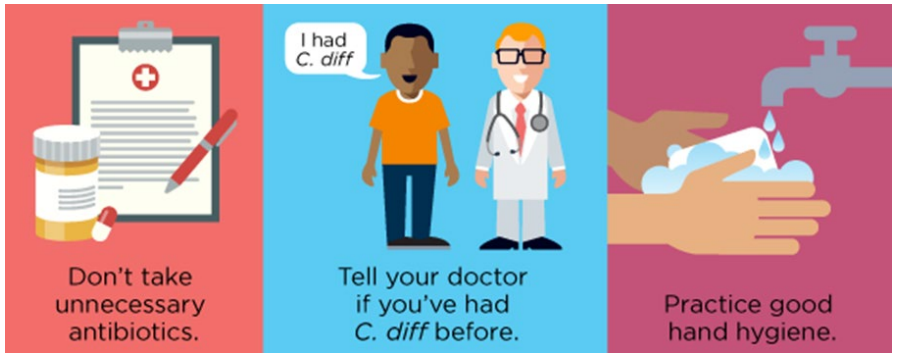
a. Aktories K. Naunyn Schmiedebergs Arch Pharmacol. 2023;396:173-190; b. Khanna S, et al. Therap Adv Gastroenterol. 2022;15:1-14; c. Barlam TF, et al. Clin Infect Dis. 2016;62:e51-e77.

Sistema nazionale linee guida - ISS

Diagnosi e terapia delle infezioni da microrganismi multiresistenti

Pubblicato 06/11/2023 - Modificato 06/11/2023

SIMIT Società Italiana di Malattie Infettive e Tropicali
GISA APS GRUPPO ITALIANO PER LA STEWARDSHIP ANTIMICROBICA
SITA Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina
AMCLI associazione microbiologi clinici italiani Ente del Terzo Settore
SIM SOCIETÀ ITALIANA DI MICROBIOLOGIA



Diagnosi e management delle infezioni causate da batteri multiresistenti: linee guida della Società Italiana di Malattie Infettive e Tropicali (SIMIT), Società Italiana di Terapia Antinfettiva (SITA), Gruppo Italiano per la Stewardship Antimicrobica (GISA), Associazione Microbiologi Clinici Italiani (AMCLI), Società Italiana di Microbiologia (SIM)

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