SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 23

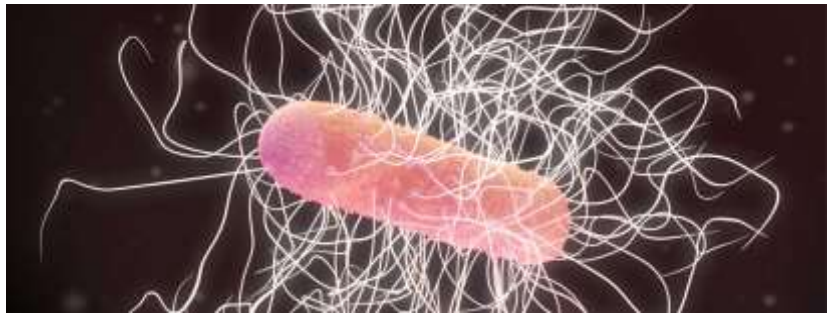
TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

AGGIORNAMENTI IN TEMA DI CLOSTRIDIOIDES DIFFICILE

18 Settembre 2023 – Ore 16.00-19.00

Responsabile scientifico Prof.ssa Alessandra Bandera



TERAPIA MEDICA E CHIRUGICA DELL'ENTERITE DA C. DIFFICILE

Alberto Enrico Maraolo, MD MSc FESCMID

@AlbertoEMaraolo

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

LEARNING OBJECTIVES

- *C. DIFFICILE* 101: NOTES ON DEFINITIONS, CLINICAL SPECTRUM, SCORES
- DIAGNOSIS: THE TOOLS, THE ALGORITHMS, THE NECESSITY OF A STEWARDSHIP
- MEDICAL THERAPY: THE DRUGS, THE GUIDELINES, THE APPROPRIATE STRATIFICATION ACCORDING TO CLINICAL SEVERITY
- SURGICAL TREATMENT: THE DIFFERENT APPROACHES WHEN DRUGS ARE NOT ENOUGH
- SOME FINAL CONSIDERATIONS

INFECTION BY C. DIFFICILE: DEFINITION

Stockholm, April 2017

Definition of *Clostridium difficile* infection (CDI)

A case of *Clostridium difficile* infection (CDI) (previously also referred to as *C. difficile*-associated diarrhoea or CDAD) must meet at least one of the following criteria [1]:

- diarrhoeal stools or toxic megacolon AND a positive laboratory assay for *C. difficile* toxin A and/or B in stools or a toxin-producing *C. difficile* organism detected in stool via culture or other means e.g. a positive PCR result;

OR

- pseudomembranous colitis revealed by lower gastro-intestinal endoscopy;

OR

- colonic histopathology characteristic of *C. difficile* infection (with or without diarrhoea) on a specimen obtained during endoscopy, colectomy or autopsy.

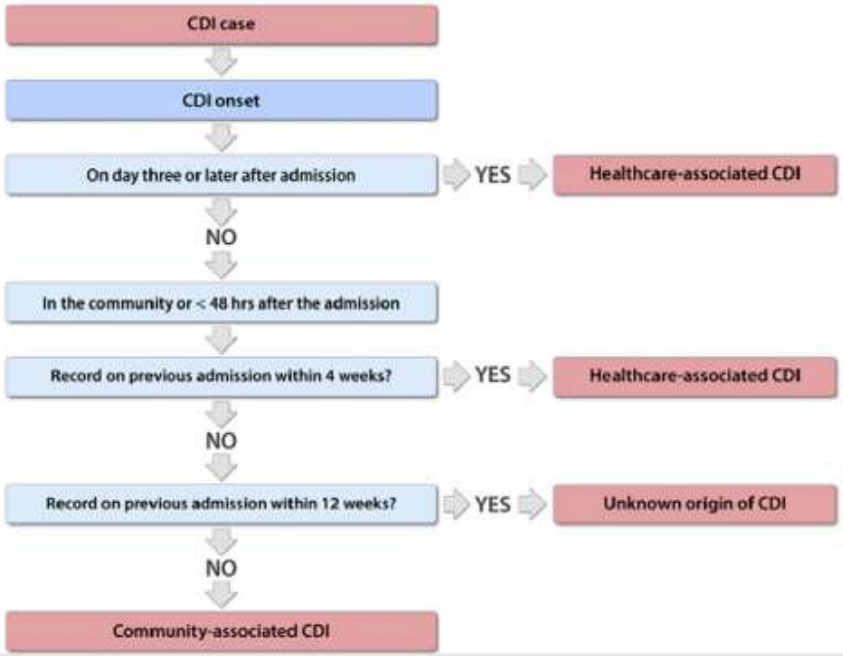
EPIDEMIOLOGICAL DEFINITIONS

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

How to: Surveillance of *Clostridium difficile* infections

M. Krutova [1,7,*], P. Kinross [2], F. Barbut [3,7], A. Hajdu [4], M.H. Wilcox [5,7], E.J. Kuijper [6,7], The survey contributors[†]

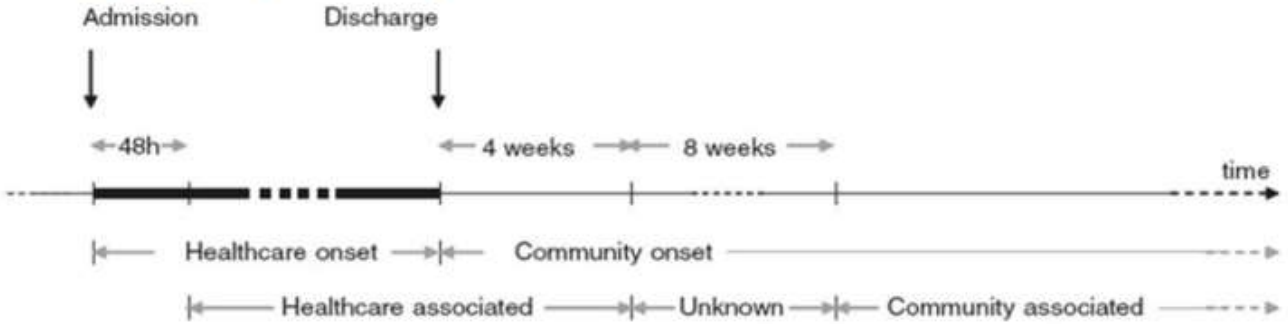
Clinical Microbiology and Infection xxx (2018) 1–7



CDI case origin

The origin of a CDI case can be healthcare-associated, community-associated or unknown (Figure 1).

Figure 1. Designation of CDI cases as healthcare-associated or community-associated based on location and time of onset of symptoms.



Source: [1]. *In practice, for this protocol, '48h' is interpreted as on the day of admission or on the following day.*

Healthcare-associated CDI (HA CDI) is defined as a case of CDI with onset of symptoms:

- on day three or later, following admission to a healthcare facility on day one,
  OR
- in the community within four weeks of discharge from a healthcare facility (including the current hospital or a previous stay in any other healthcare facility).

Community-associated CDI (CA CDI) is defined as a case of CDI with onset of symptoms:

- outside of healthcare facilities
  AND without discharge from a healthcare facility within the previous 12 weeks,
  OR
- on the day of admission to a healthcare facility or on the following day
  AND not resident in a healthcare facility within the previous 12 weeks.

Unknown association: the CDI case was discharged from a healthcare facility 4–12 weeks before the onset of symptoms.

RECURRENCE: DEFINITION

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION

Stockholm, April 2017

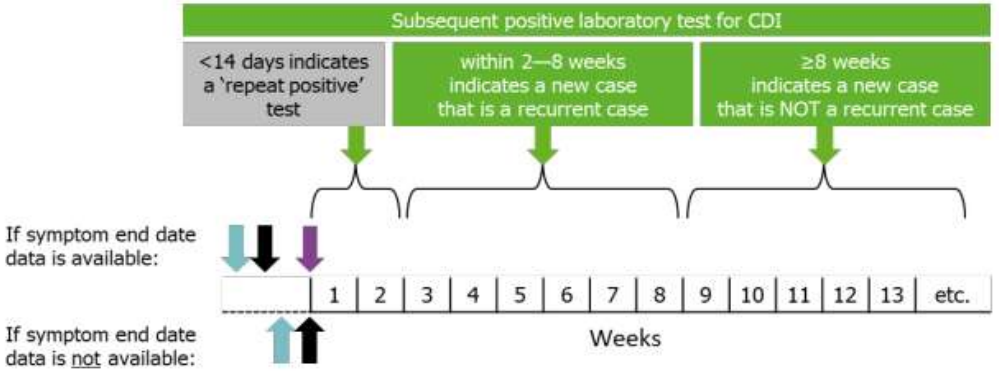
Repeat positives

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



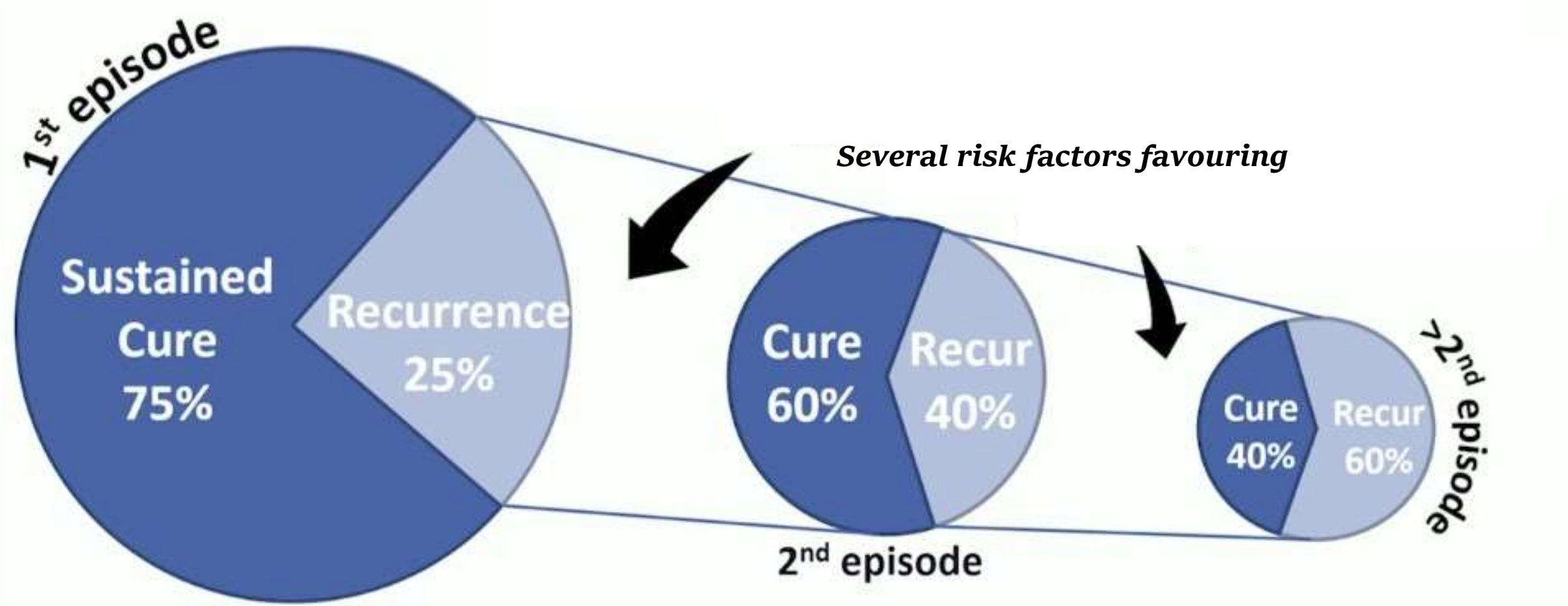
Recurrent CDI cases

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).

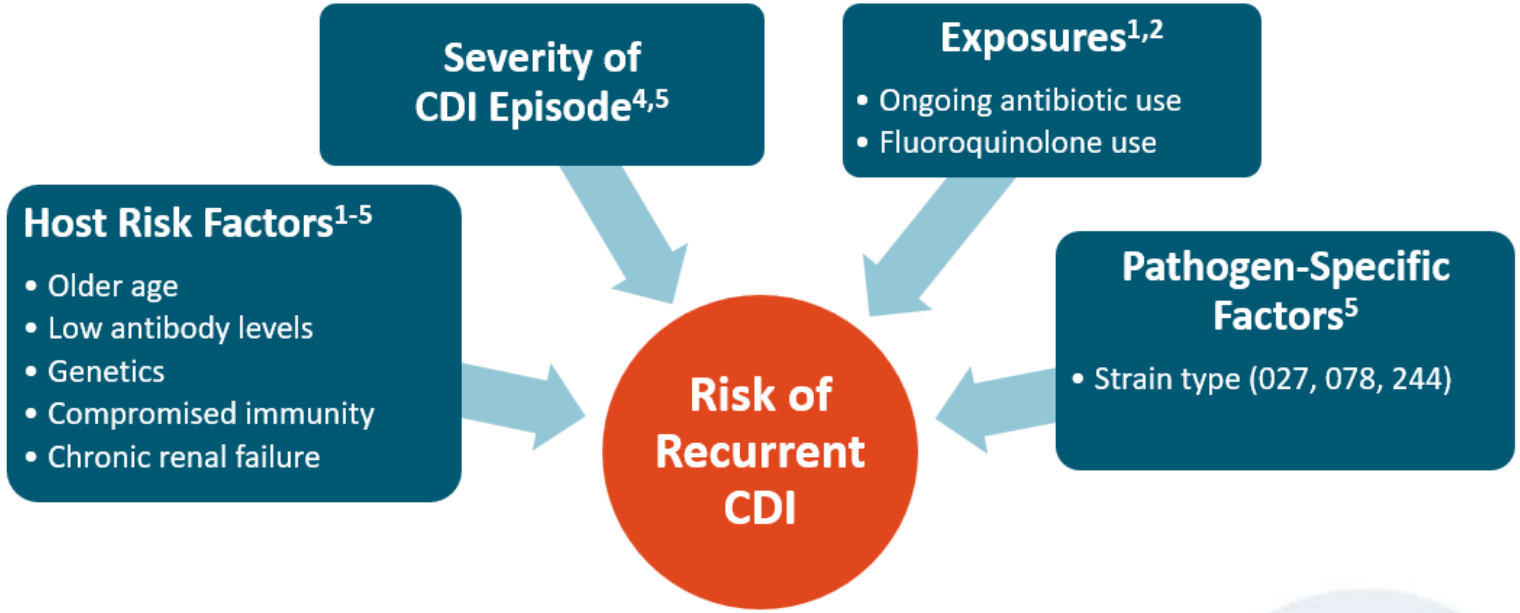
CDI cases with symptom onset more than eight weeks after the onset of a previous episode are included as new CDI cases. When evaluating the time window, the date of the return of the CDI symptoms should be considered. Only consider the date of sampling if the date of onset of symptoms is unknown.

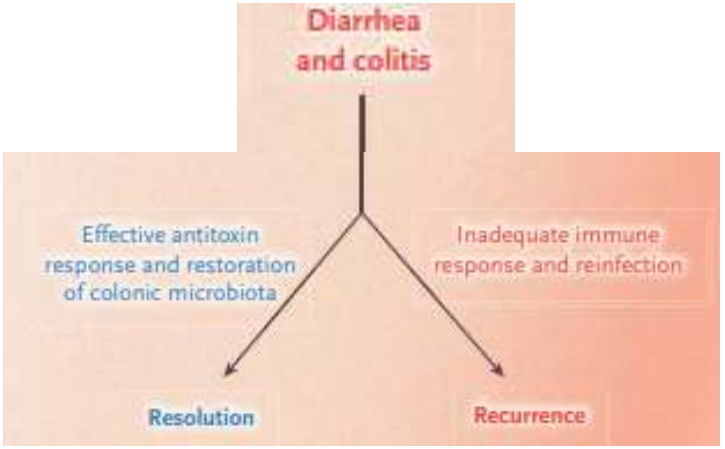
THE CYCLE OF RECURRENCE



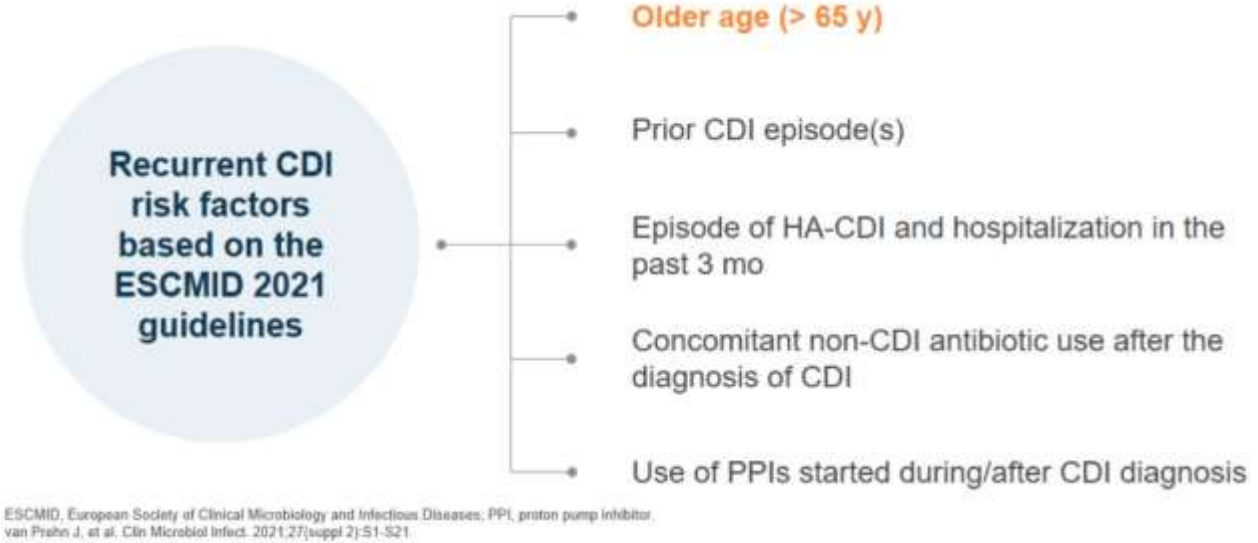
Cornely OA et al. *Clin Infect Dis.* 2012; 55(Suppl 2):S154-61.
McFarland LV et al. *Am J Gastroenterol.* 2002; 97:1769-75. Nair S et al. *Am J Gastroenterol.* 1998; 93:1873-6.

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.



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.

CLINICAL SPECTRUM

Annals of Internal Medicine®

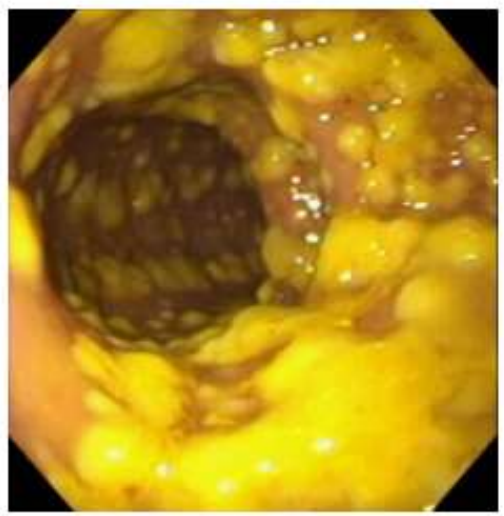
Physician Writers
Alice Y. Guh, MD, MPH
Preeta K. Kutty, MD, MPH
From the Centers for Disease Control and Prevention, Atlanta, Georgia.

In the Clinic®

Clostridioides difficile Infection

Table 1. **Clinical Features and Complications of *Clostridioides difficile* Infection**

Spectrum of Disease	*Diarrhea*	*Other Symptoms*	*Physical Examination*	*Colonoscopic and Other Findings*
Asymptomatic carrier	None	None	Normal	Normal
Simple antibiotic-associated diarrhea	Mild	Systemic symptoms usually absent	Usually normal	Normal
Early colitis	Profuse	Nausea, anorexia	Low-grade fever, with or without mild abdominal tenderness	Nonspecific patchy erythema
Pseudomembranous colitis	Profuse	Nausea, malaise, abdominal discomfort	Fever (sometimes high); abdominal tenderness, distention	Pseudomembranes (raised yellow plaques); leukocytosis (may be ≥50 × 10^9 cells/L, with left shift)
Fulminant colitis	Usually profuse and severe; may be absent in ileus or toxic megacolon	Nausea, abdominal discomfort or pain	Toxic appearance, fever (often high); abdominal distention, tenderness, and peritoneal signs	Endoscopy contraindicated in severely ill patients; leukemoid reaction common; radiographic studies may show colonic dilatation, mucosal thickening, or perforation



WHAT IS SEVERE ?

Table 1. Severity classification of *C. difficile* infection in the three guidelines

	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
Non-severe	WBC count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL.	WBC count of ≤15 000 cells/mL and a serum creatinine level ≤50% above baseline, and core body temperature at presentation ≤38.5°C. No imaging features of severity.	Absence of all features consistent with severe CDI.
Severe	One of the following factors at presentation: WBC count of >15 000 cells/mL or a serum creatinine level ≥1.5 mg/dL.	One of the following factors at presentation: WBC count of >15 000 cells/mL or a rise in serum creatinine level >50% above baseline or core body temperature >38.5°C. Additional supporting factors, when available, are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging.	Any of the following features if no other explanation can be provided: WBC count of >15 000 cells/mL or a rise in serum creatinine level >50% above baseline or core body temperature >38.5°C. Rigors, haemodynamic instability, peritonitis or evidence of bowel perforation, ileus or toxic megacolon, elevated lactate level, albumin level <25 mg/L, large intestine distension, colonic wall thickening, fat stranding, unexplained ascites (imaging) or pseudomembranous colitis on colonoscopy.
Severe-complicated 'fulminant'	Presence of hypotension or shock, ileus or megacolon.	Presence of one of the following factors that needs to be attributed to CDI: Hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of disease (i.e. rapid deterioration of the patient).	An episode of CDI complicated by: Toxic megacolon, admission to intensive care for severe sepsis, requirement for surgery or death due to CDI.

Bishop. JAC. 2023; 78: 21-30.

SEVERITY CRITERIA

TABLE 5. Prognostic markers that can be used to determine (increased risk of developing) severe *Clostridium difficile* infection

Characteristics	SoR[a]
Age (≥65 years)	A
Marked leucocytosis (leucocyte count > 15 × 10^9/L)	A
Decreased blood albumin (<30 g/L)	A
Rise in serum creatinine level (≥133 μM or ≥1.5 times the premorbid level)	A
Comorbidity (severe underlying disease and/or immunodeficiency)	B

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Comparison of 3 Severity Criteria for *Clostridium difficile* Infection

Angela Gomez-Simmonds, MD;[1]
Christine J. Kubin, PharmD, BCPS;[2]
E. Yoko Furuya, MD, MS[1]

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY FEBRUARY 2014, VOL. 35, NO. 2

Infection Control & Hospital Epidemiology

SHEA The Society for Healthcare Epidemiology of America

TABLE 1. Three Different Severity Criteria for *Clostridium difficile* Infection (CDI)

Severity criteria	Mild-moderate disease	Severe disease
Hospital-specific guidelines[9]	≥3 diarrheal stools/day; may be accompanied by mild or moderate abdominal discomfort, elevated WBC count, and fever	Mild-moderate criteria plus at least 1 of the following: At least 3 of the following: temperature >38.3°C, WBC count >20,000 cells/mm³, albumin level <2.5 g/dL, age ≥65 years, ICU admission; *OR* endoscopically or histologically confirmed pseudomembranous colitis; *OR* toxic megacolon, perforation, colectomy, or septic shock requiring ICU admission and pressors
SHEA/IDSA guidelines[8]	WBC count <15,000 cells/mm³ *AND* serum creatinine <1.5 × baseline	WBC count ≥15,000 cells/mm³ *OR* serum creatinine ≥1.5 × baseline; Severe, complicated CDI: hypotension or shock, ileus, or megacolon
Zar criteria[a]	<2 points	2 or more points

NOTE. ICU, intensive care unit; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America; WBC, white blood cell.

[a] Based on the clinical trial conducted by Zar et al.[7] One point is given for each of the following: age >60 years; temperature >38.3°C; albumin level <2.5 mg/dL; WBC count >15,000 cells/mm³. Two points are given for endoscopic evidence of pseudomembranous colitis and treatment in the ICU.

PROGNOSTIC SCORES

RESEARCH ARTICLE Open Access

Derivation and validation of a simple clinical bedside score (ATLAS) for *Clostridium difficile* infection which predicts response to therapy

Mark A Miller[1*], Thomas Louie[2], Kathleen Mullane[3], Karl Weiss[4], Arnold Lentnek[5], Yoav Golan[6], Yin Kean[7] and Pam Sears[7]

Miller *et al. BMC Infectious Diseases* 2013, **13**:148
http://www.biomedcentral.com/1471-2334/13/148

International Journal of Antimicrobial Agents 51 (2018) 393–398

Prediction of recurrent *clostridium difficile* infection at the bedside: the GEIH-CDI score

Javier Cobo [a,*], Esperanza Merino [b], Cristina Martínez [c], Alberto Cózar-Llistó [d], Evelyn Shaw [e], Teresa Marrodán [f], Esther Calbo [g], Elena Bereciartúa [h], Luis A. Sánchez-Muñoz [i], Miguel Salavert [j], M. Teresa Pérez-Rodríguez [k], Dácil García-Rosado [l], J. María Bravo-Ferrer [m], Juan Gálvez-Acebal [n], César Henríquez-Camacho [o], Jordi Cuquet [p], Berta Pino-Calm [q], Luis Torres [r], Antonio Sánchez-Porto [s], Borja M. Fernández-Félix [t,u] for the Nosocomial Infection Study Group

Response to therapy

Relapse

Mortality

SCORE

AP&T Alimentary Pharmacology and Therapeutics

Clostridium difficile associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with *C. difficile* infection

Aliment Pharmacol Ther 2016; **43**: 725–733

Z. Kassam*,†, C. Cribb Fabersunne‡,§, M. B. Smith*,†, E. J. Alm*, G. G. Kaplan¶, G. C. Nguyen** & A. N. Ananthakrishnan‡,††

PROGNOSTIC SCORES: SUBOPTIMAL PERFORMANCES

Antimicrobial Agents and Chemotherapy®
July 2022 Volume 66 Issue 7

Validation of Clinical Risk Models for *Clostridioides difficile*-Attributable Outcomes

Gregory R. Madden,[a] William A. Petri, Jr.,[a] Deiziane V. S. Costa,[a] Cirle A. Warren,[a] Jennie Z. Ma,[b] Costi D. Sifri[a,c]

ABSTRACT *Clostridioides difficile* is the leading health care-associated pathogen, leading to substantial morbidity and mortality; however, there is no widely accepted model to predict *C. difficile* infection severity. Most currently available models perform poorly or were calibrated to predict outcomes that are not clinically relevant. We sought to validate six of the leading risk models (Age Treatment Leukocyte Albumin Serum Creatinine (ATLAS), *C. difficile* Disease (CDD), Zar, Hensgens, Shivashankar, and *C. difficile* Severity Score (CDSS)), guideline severity criteria, and PCR cycle threshold for predicting *C. difficile*-attributable severe outcomes (inpatient mortality, colectomy/ileostomy, or intensive care due to sepsis). Models were calculated using electronic data available within ±48 h of diagnosis (unavailable laboratory measurements assigned zero points), calibrated using a large retrospective cohort of 3,327 inpatient infections spanning 10 years, and compared using receiver operating characteristic (ROC) and precision-recall curves. ATLAS achieved the highest area under the ROC curve (AuROC) of 0.781, significantly better than the next best performing model (Zar 0.745; 95% confidence interval of AuROC difference 0.0094–0.6222; $P = 0.008$), and highest area under the precision-recall curve of 0.232. Current IDSA/SHEA severity criteria demonstrated moderate performance (AuROC 0.738) and PCR cycle threshold performed the worst (0.531). The overall predictive value for all models was low, with a maximum positive predictive value of 37.9% (ATLAS cutoff ≥9). No dinical model performed well on external validation, but ATLAS did outperform other models for predicting clinically relevant *C. difficile*-attributable outcomes at diagnosis. Novel markers should be pursued to augment or replace underperforming dinical-only models.

Clinical Infectious Diseases® 2022;74(11):2028–35

External Validation and Comparison of *Clostridioides difficile* Severity Scoring Systems

D. Alexander Perry,[1,2,3] Daniel Shirley,[3] Dejan Micic,[4] Pratish C. Patel,[5] Rosemary Putler,[1,2] Anitha Menon,[2] Vincent B. Young,[1,2,6] and Krishna Rao[1,2]

Background. Many models have been developed to predict severe outcomes from *Clostridioides difficile* infection (CDI). These models are usually developed at a single institution and largely are not externally validated. Our aim in this study was to validate previously published risk scores in a multicenter cohort of patients with CDI.

Methods. This was a retrospective study on 4 inpatient cohorts with CDI from 3 distinct sites: the universities of Michigan (2010–2012 and 2016), Chicago (2012), and Wisconsin (2012). The primary composite outcome was admission to an intensive care unit, colectomy, and/or death attributed to CDI within 30 days of positive testing. Both within each cohort and combined across all cohorts, published CDI severity scores were assessed and compared to each other and the Infectious Diseases Society of America (IDSA) guideline definitions of severe and fulminant CDI.

Results. A total of 3646 patients were included for analysis. Including the 2 IDSA guideline definitions, 14 scores were assessed. Performance of scores varied within each cohort and in the combined set (mean area under the receiver operator characteristic curve [AuROC], 0.61; range, 0.53–0.66). Only half of the scores had performance at or better than IDSA severe and fulminant definitions (AuROCs of 0.64 and 0.63, respectively). Most of the scoring systems had more false than true positives in the combined set (mean, 81.5%; range, 0%–91.5%).

Conclusions. No published CDI severity score showed stable, good predictive ability for adverse outcomes across multiple cohorts/institutions or in a combined multicenter cohort.

ATLAS Bedside Scoring System

Parameter	0 points	1 point	2 points
Age (years)	< 60	60-79	> 80
Temperature (°C)	≤ 37.5	37.6-38.5	≥ 38.6
Leukocytosis	< 16,000	16,000-25,000	> 25,000
Albumin (g/L)	> 35	26-35	< 25
Systemic concomitant antibiotics during CDI Rx (=1 day)	No	—	Yes

Source: Dr. Miller

DIAGNOSIS: THE GUIDE FOR THE PERPLEXED

Original article

How to: diagnose infection caused by *Clostridium difficile*

Clinical Microbiology and Infection 24 (2018) 463–468

C. Gateau [1], J. Couturier [1, 2], J. Coia [3, 4], F. Barbut [1, 2, 4, *]

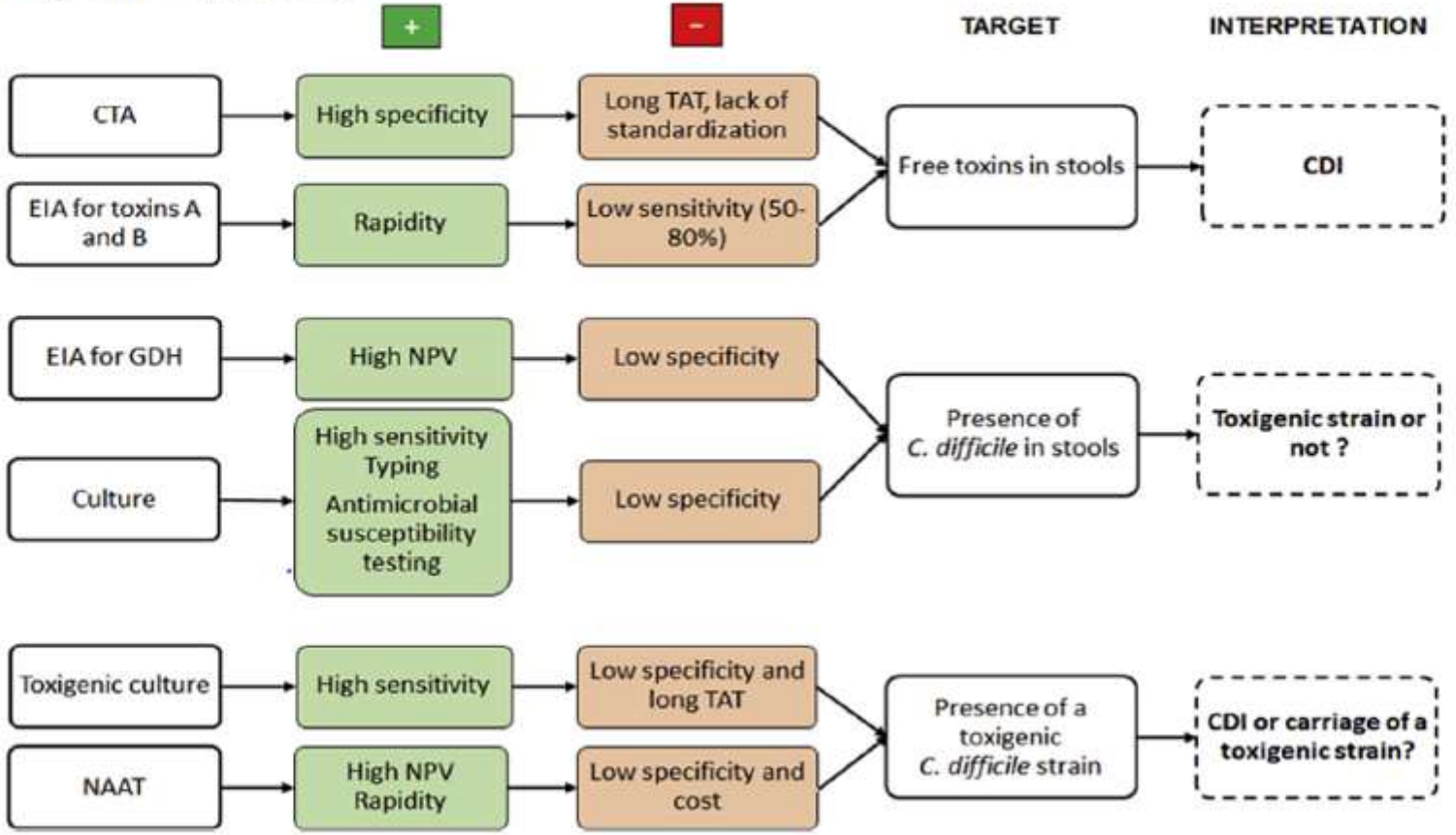


Fig. 1. Advantages, disadvantages and targets of the different methods used for the diagnosis of *Clostridium difficile* infection (CDI). Abbreviations: CTA, cytotoxicity assay; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; NPV, negative predictive value; TAT, turnaround time.

DIAGNOSIS: SOME USEFUL HINTS

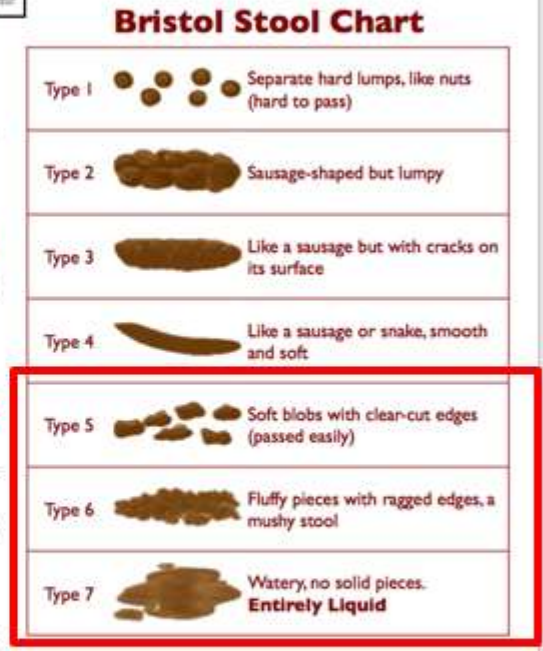
Original article

How to: diagnose infection caused by *Clostridium difficile*

Clinical Microbiology and Infection 24 (2018) 463–468

C. Gateau [1], J. Couturier [1, 2], J. Coia [3, 4], F. Barbut [1, 2, 4, *]

- Only **liquid or unformed stools**, i.e. specimens taking the shape of the container, should be processed **to avoid the identification of asymptomatic carriers**.
- Because of insufficient volume, **stool swabs cannot be used for toxin tests**. However, swabs can be analysed by culture or nucleic acid amplification tests (NAAT) for epidemiological studies or in case of a patient presenting with an ileus.
- For optimal recovery, **stool specimens should be cultured within 2 h after collection** and must be preserved in a leak-proof container. Beyond this time, even if some spores can survive at 4°C, the number of viable C. difficile vegetative cells will significantly decrease.
- For **toxin assay, stools can be stored at 4°C for a maximum of 3 days**. If testing is delayed, specimens have to be frozen **at -80°C**.
- **Stool samples from children <3 years old should only be tested in specific cases** (e.g. neonates with Hirschsprung disease or suspicion of an outbreak) **because asymptomatic carriage is common in this population**.



NO REPEAT TESTING

Original article

How to: diagnose infection caused by *Clostridium difficile*

Clinical Microbiology and Infection 24 (2018) 463–468

C. Gateau [1], J. Couturier [1, 2], J. Coia [3, 4], F. Barbut [1, 2, 4, *]

- **Repeated testing should be discouraged** because of a low diagnostic gain (defined as the rate of negative samples that convert to positive).
- This practice **increases the likelihood of false-positive results due to lack of specificity of the methods.** This practice was frequent when enzyme immunoassay (EIA) for toxins was used as a stand-alone test to overcome the lack of sensitivity of these tests.
- A **negative result with a screening test can reliably rule out the diagnosis of CDI** due to the **high negative predictive value (NPV)** at low disease prevalence.
- However, **in cases of outbreak situations where CDI prevalence is higher, the NPV of the algorithm will decrease**, and a **repeat sample** in cases of ongoing clinical suspicion **may be justified**.

$$\text{Negative predictive value, } \mathbf{NPV} = \frac{True\ Negatives}{True\ Negatives + False\ Negatives}$$

$$PPV = \frac{A}{(A + B)}$$

$$NPV = \frac{D}{(C + D)}$$

High prevalence = low NPV

Test	Disease +	Disease −
+	A True positive (TP)	B False positive (FP)
−	C False negative (FN)	D True negative (TN)

High disease prevalence

NO TEST OF CURE, TEST BEFORE TREATMENT

Original article

How to: diagnose infection caused by *Clostridium difficile*

C. Gateau [1], J. Couturier [1, 2], J. Coia [3, 4], F. Barbut [1, 2, 4, *]

Clinical Microbiology and Infection 24 (2018) 463–468

- Clinical cure is defined by the resolution of the symptoms. **A 'test of cure' is not recommended, since toxins and/or spores can persist in stools for up to 6 weeks**, despite symptom resolution.
- **Stool samples should be taken before initiation of treatment** to avoid false-negative results.
- Physicians should be aware that **any empirical therapy for suspected CDI started before stool collection can lead to a false negative test result**.

TOC

stands for

Test Of Cure

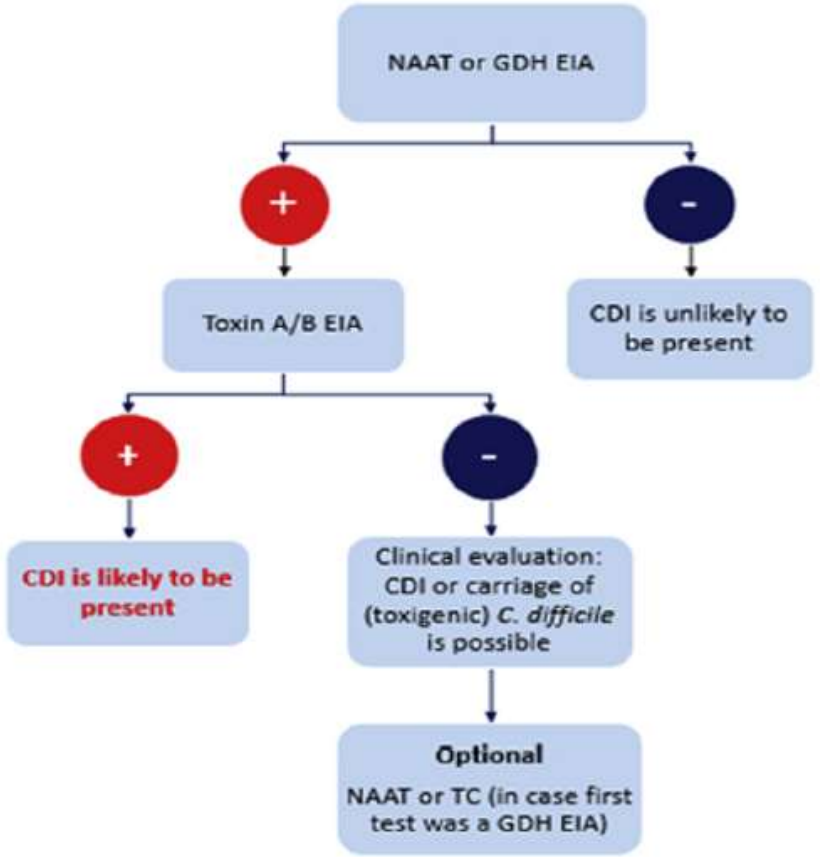
DIAGNOSIS: ALGORITHMS

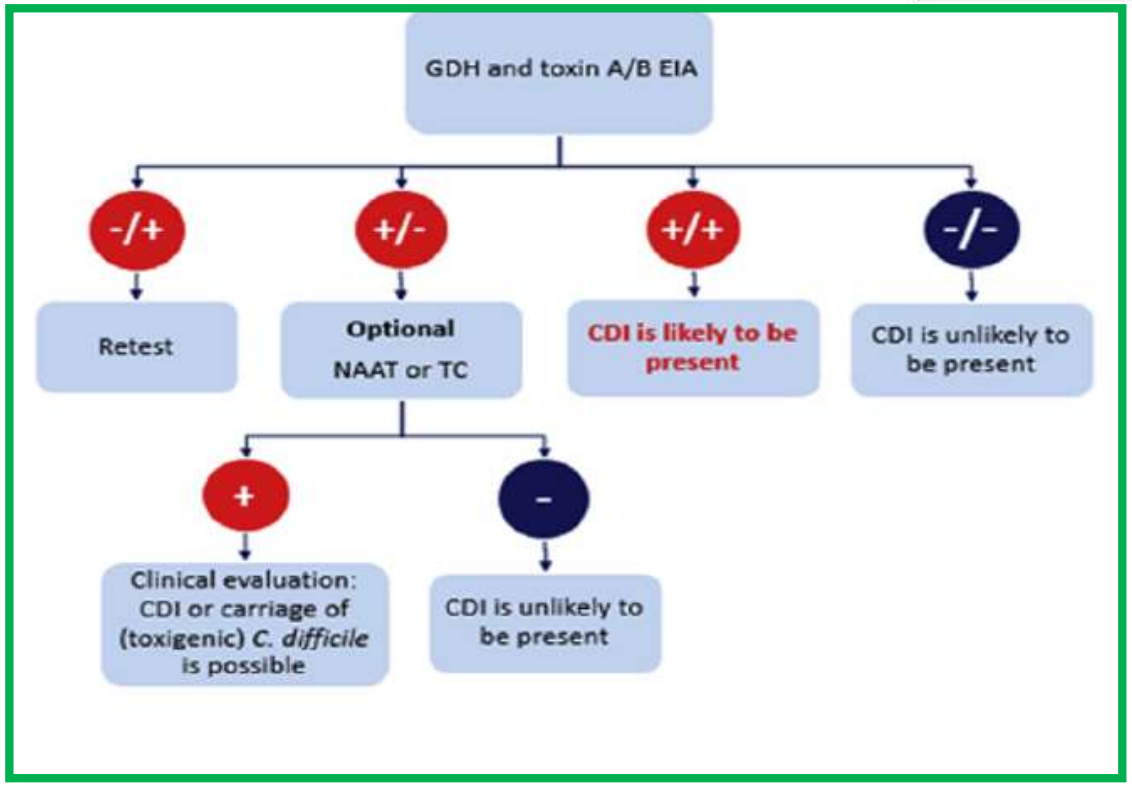
Original article

How to: diagnose infection caused by *Clostridium difficile*

C. Gateau [1], J. Couturier [1, 2], J. Coia [3, 4], F. Barbut [1, 2, 4, *]

Clinical Microbiology and Infection 24 (2018) 463–468





DIAGNOSTIC STEWARDSHIP OF CDI

- Diagnostic stewardship! Evaluate other potential causes of diarrhea prior to starting treatment:
  - **Laxatives**
  - Enteral tube feeding
  - Intensive cancer chemotherapy
  - Irritable bowel disease

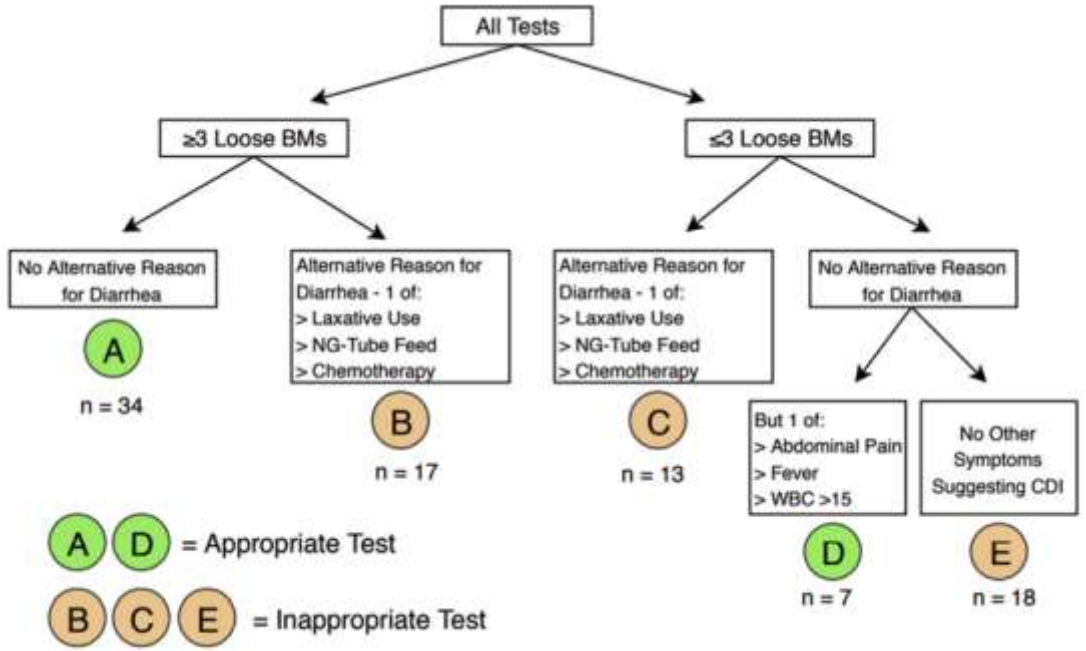


Figure 2. *Clostridioides difficile* test appropriateness categorization stratified by the presence of ≥3 loose bowel movements.

Reich. Infect Prev Pract. 2019; 1: 100017.

Open Forum Infectious Diseases

MAJOR ARTICLE

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

Open Forum Infectious Diseases, Volume 10, Issue 5, May 2023, ofad184

Syndromic Panel Testing Among Patients With Infectious Diarrhea: The Challenge of Interpreting *Clostridioides difficile* Positivity on a Multiplex Molecular Panel

Melissa Pender,[1,a] S. Kyle Throneberry,[2,a] Nancy Grisel,[2] Daniel T. Leung,[1] and Bert K. Lopansri[1,2]

[1]Division of Infectious Diseases, Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA, and [2]Division of Infectious Diseases and Clinical Epidemiology, Intermountain Health, Murray, Utah, USA

Background. Including *Clostridioides difficile* (CD) in gastrointestinal multiplex molecular panels (GIPCR) presents a diagnostic challenge. Incidental detection by polymerase chain reaction (PCR) without consideration of pretest probability (PTP) may inadvertently delay diagnoses of other treatable causes of diarrhea and lead to prescription of unnecessary antibiotics.

Methods. We conducted a retrospective study to determine the frequency at which clinicians characterize PTP and disease severity in adult patients who test positive for CD by GIPCR. We organized subjects into cohorts based on the status of their CD PCR, glutamate dehydrogenase enzyme immunoassay (GDH), and toxin A/B detection, as well as by high, moderate, or low CD PTP. We used multivariable regression models to describe predictors of toxin positivity.

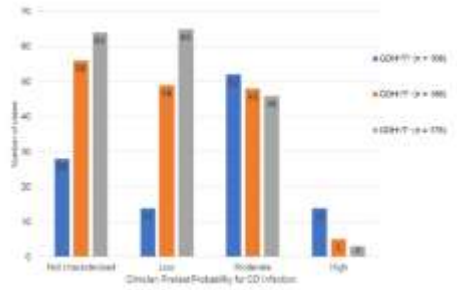
Results. We identified 483 patients with positive CD PCR targets. Only 22% were positive for both GDH and CD toxin. Among patients with a low PTP for CDI, 11% demonstrated a positive CD toxin result compared to 63% of patients with a high PTP. A low clinician PTP for CD infection (CDI) correlated with a negative CD toxin result compared to cases of moderate-to-high PTP for CDI (odds ratio, 0.19 [95% confidence interval, .10–.36]). Up to 64% of patients with negative GDH and CD toxin received CD treatment. Only receipt of prior antibiotics, fever, and a moderate-to-high clinician PTP were statistically significant predictors of toxin positivity.

Conclusions. Patients with a positive CD PCR were likely to receive treatment regardless of PTP or CD toxin results. We recommend that CD positivity on GIPCR be interpreted with caution, particularly in the setting of a low PTP.

Keywords. *Clostridioides difficile* infection; molecular panel; pretest probability.

We subsequently reviewed patient records to describe CD PTP at the time GIPCR was ordered. We classified PTP as follows:

1. Not done: clinician did not document clinical decision making regarding CDI.
2. Low: Clinician mentioned CD in assessment and documented low clinical suspicion.
3. Moderate: Clinician discussed risk for CD in the assessment along with suspicion of disease but did not initiate empiric antibiotic therapy.
4. High: Clinician described antibiotic exposure in the admission documentation, documented suspicion for CDI, and initiated empiric antibiotic therapy.



DIAGNOSIS: THE ROLE OF ID CONSULTANT

Impact of Mandatory Infectious Disease Specialist Approval on Hospital-Onset Clostridioides difficile Infection (HO-CDI) Rates and Testing Appropriateness

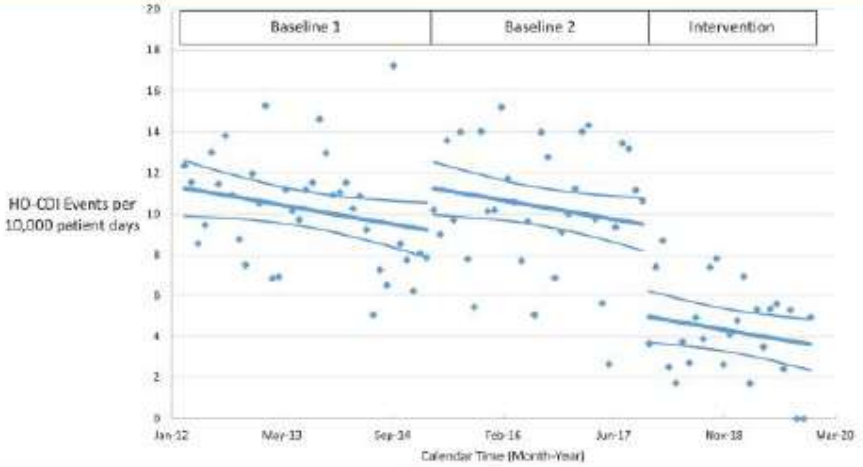
Lin et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

The potential role and impact of infectious diseases specialists in enforcing appropriate *C. difficile* testing is unclear.

During an intervention period, all *C. difficile* testing on hospital day 4 or later required infectious diseases specialist approval.

The HO-CDI event rate per 10,000 patient days decreased from 10.2 and 10.4 during the first two baseline periods respectively to 4.3 during the intervention period ($P < .001$).



An infectious disease–led *C. difficile* testing approval process was feasible and associated with a >50% decrease in HO-CDI rates, due to enforcement of appropriate testing.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad250

Michael Y. Lin,[1] Brian D. Stein,[1] Sonya M. Kothadia,[1,a] Samantha Blank,[1,b] Michael E. Schoeny,[2] Alexander Tomich,[3] Mary K. Hayden,[4] and John Segreti[1]

Published: 09 May 2023

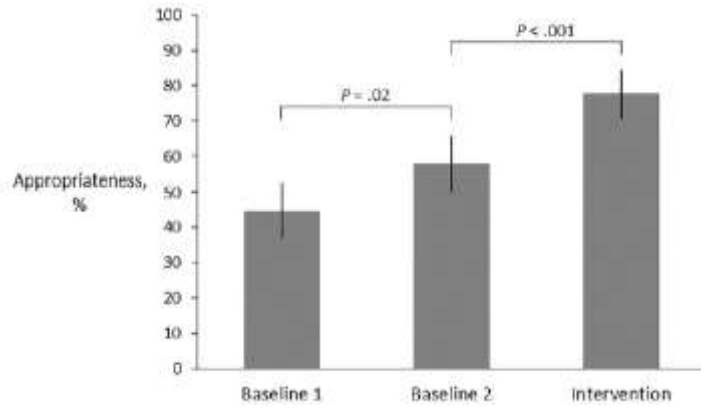


Figure 2. Appropriateness of hospital-onset *Clostridioides difficile* testing, by study period. Baseline 1 = no decision support. Baseline 2 = computerized decision support. Intervention = mandatory infectious diseases approval. Vertical line represents the 95% confidence interval.

Table 2. Reasons for Inappropriate Hospital-Onset *Clostridioides difficile* Testing During Each Time Period

Reason for Testing	Baseline 1	Baseline 2	Intervention	*P* Value
<3 documented stools, no./No. (%)	62/83 (75)	41/63 (65)	21/32 (65)	.39
No diarrheal stools charted in prior 24 h, no./No. (%)	9/74 (12)	2/60 (3)	1/30 (3)	.10
Laxative use in prior 24 h, no./No. (%)	38/83 (46)	34/63 (54)	15/33 (45)	.57

P value tests the null hypothesis that the proportions are equal across the 3 time periods. Baseline 1 = no decision support. Baseline 2 = computerized decision support. Intervention = mandatory infectious diseases specialist approval.

THERAPY: TENETS

Antibiotic administration based on infection severity[a]

3

Isolation of the patient to control the infection[a]

1

Asymptomatic patients do not require treatment, despite having a positive stool toxin test[a]

4

2

Discontinuation of unnecessary inciting antibiotics[a,b]

Closely monitor the patient for 48 h[b]

Clinical Infectious Diseases

IDSA GUIDELINE

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)*.

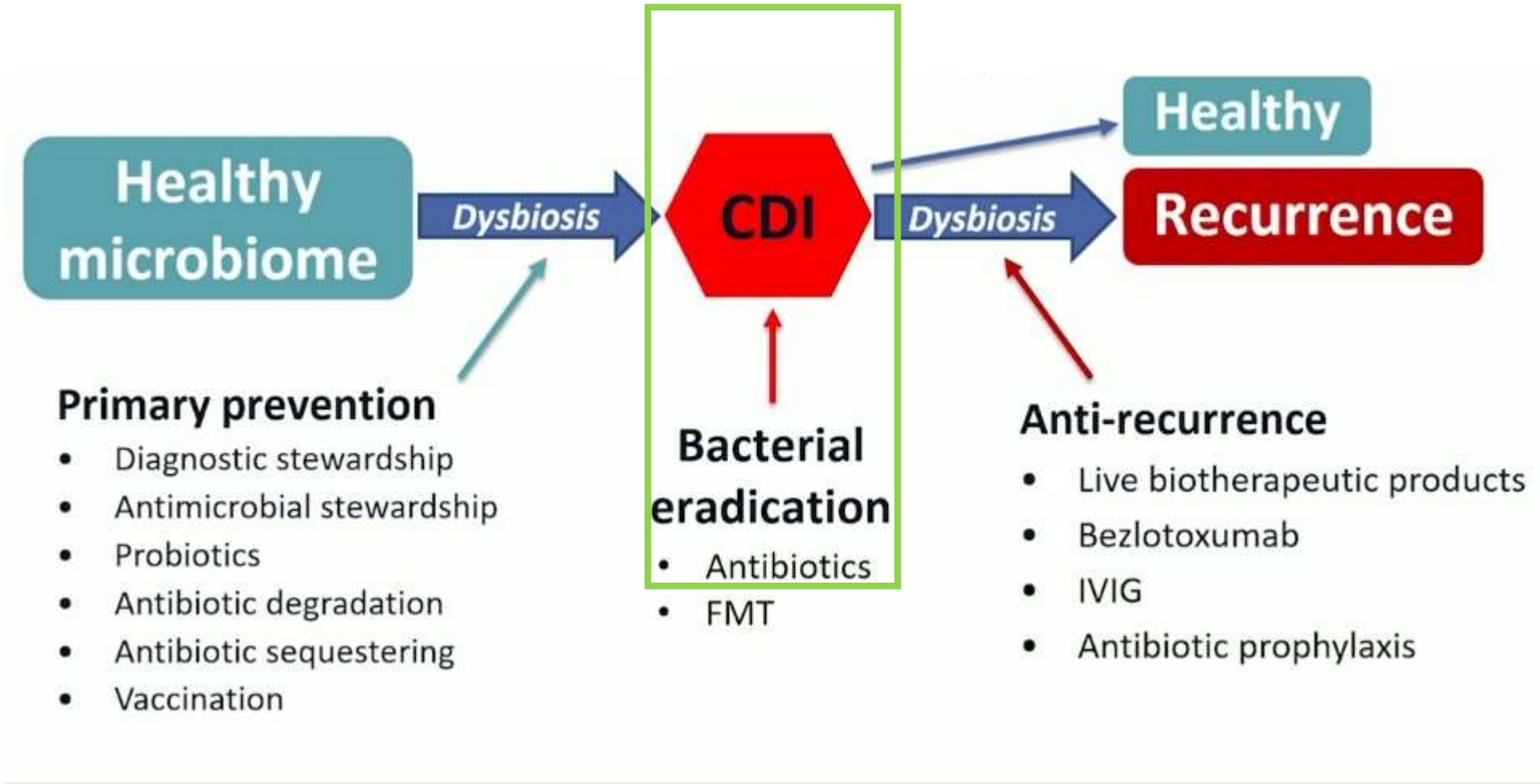
a. Mada PK, et al. *Clostridioides difficile*. In: StatPearls. StatPearls Publishing; 2022. Updated May 1, 2022. Accessed February 9, 2023. https://www.ncbi.nlm.nih.gov/books/NBK431054/; b. van Prehn J, et al. Clin Microbiol Infect. 2021;27(suppl 2):S1-S21.

CDI RISK STRATIFICATION CHALLENGES

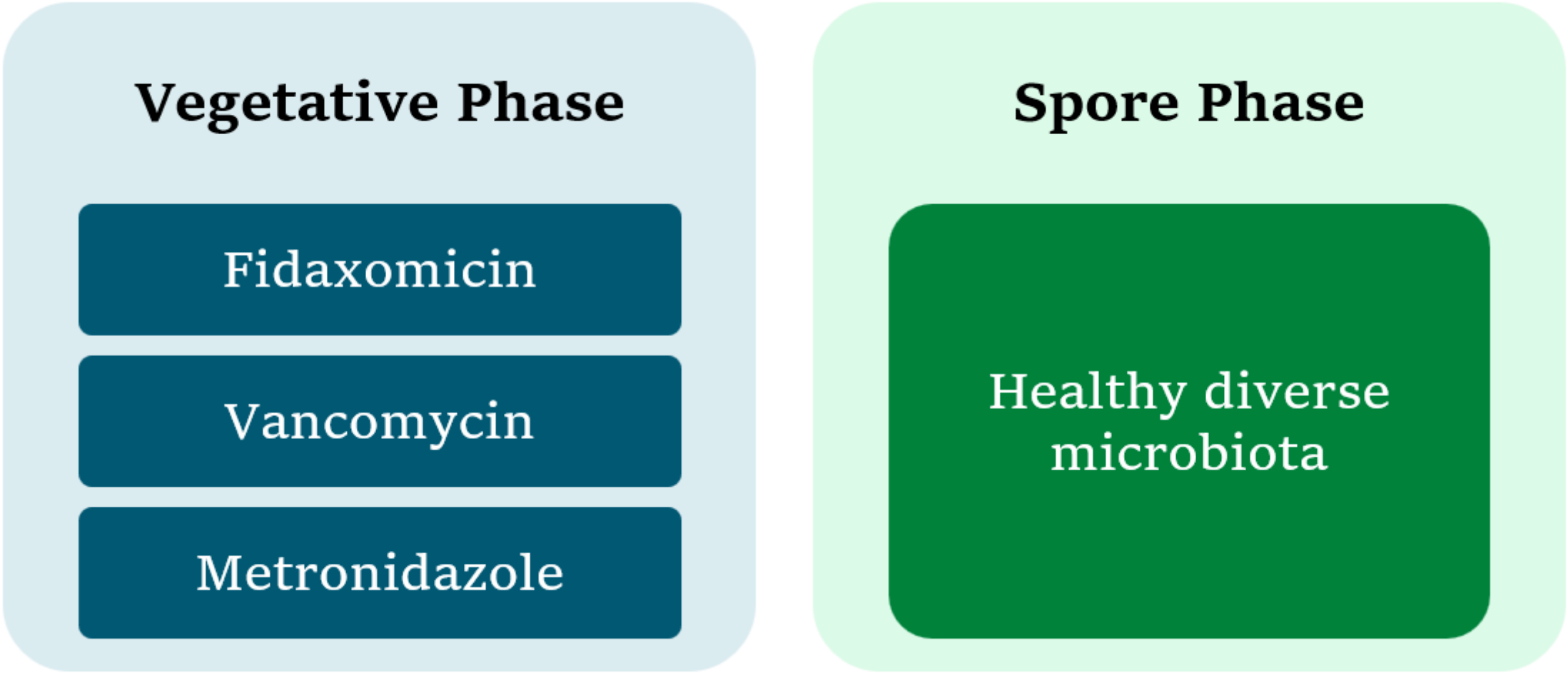
- Address **modifiable risk factors** (eg, discontinuation of unnecessary antibiotics, PPIs)[1]
- **Stratify treatment** according to severity (eg, nonsevere/severe vs fulminant)[1]
- Determine **CDI episode number** (eg, primary vs recurrent)[1]
- Identify patients at highest risk for recurrence who may benefit from **adjunctive comedications** (eg, bezlotoxumab) and **microbiome-sparing agents** (eg, fidaxomicin)[2]
  - Consider: age >65 yr, prior history of CDI, immunocompromised, severe CDI, infection with certain ribotypes (eg, 027/078)

Cost and **drug availability** remain a challenge in some areas of the country[3]

MANAGEMENT APPROACH



PHARMACOTHERAPY: PRINCIPLES



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

PHARMACOTHERAPY: HISTORY

1970s
- Vancomycin established as effective treatment for pseudomembranous colitis

1980s
- Metronidazole shown to be effective for CDI

1995
- HICPAC: reduce vancomycin use in hospitals (concerns about emergence of resistance to vancomycin in other pathogens)
- SHEA position paper on CDI: vancomycin or metronidazole for 10 days is effective; metronidazole may be preferred

2010
- SHEA/IDSA CDI guidelines: vancomycin is the drug of choice for severe disease, metronidazole is drug of choice for mild-to-moderate CDI. 10 to 14-day course recommended (concern for slow response to metronidazole)

2018
- IDSA/SHEA CDI guidelines: vancomycin or fidaxomicin is the drug of choice for CDI.
- 10-day course of metronidazole is only recommended when VAN and FDX are not available and only for mild-to-moderate CDI

2021
- 2021 IDSA/SHEA, ACOG, & ESCMID guidelines: Fidaxomicin is now preferred for initial episodes of CDI and bezlotoxumab is recommended for high-risk patients.

1. *Lancet*. 1978; 2:226-8, tedesco, F; 2. *Lancet*. 1983; 2:1043-6, Teasley DG; 3. *MMWR Recomm Rep*. 1995; 44(RR-12):1-13, Favero MS; 4. *Infect Control Hosp Epidemiol*. 1995; 16:459-77, Gerding DN; 5. *Infect Control Hosp Epidemiol*. 2010; 31:431-55, Cohen, SH;6. *Clin Infect Dis*. 2018; 66:e41-48, Barker, AK.

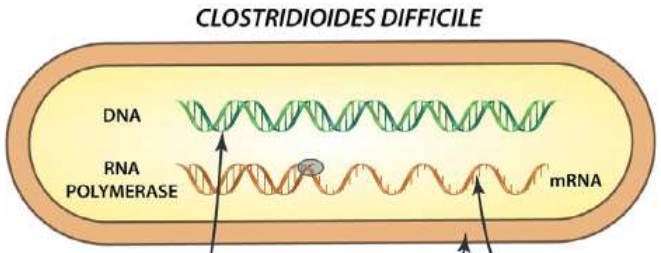
THERAPY: DIFFERENCES ACROSS DRUGS

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

Review

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]



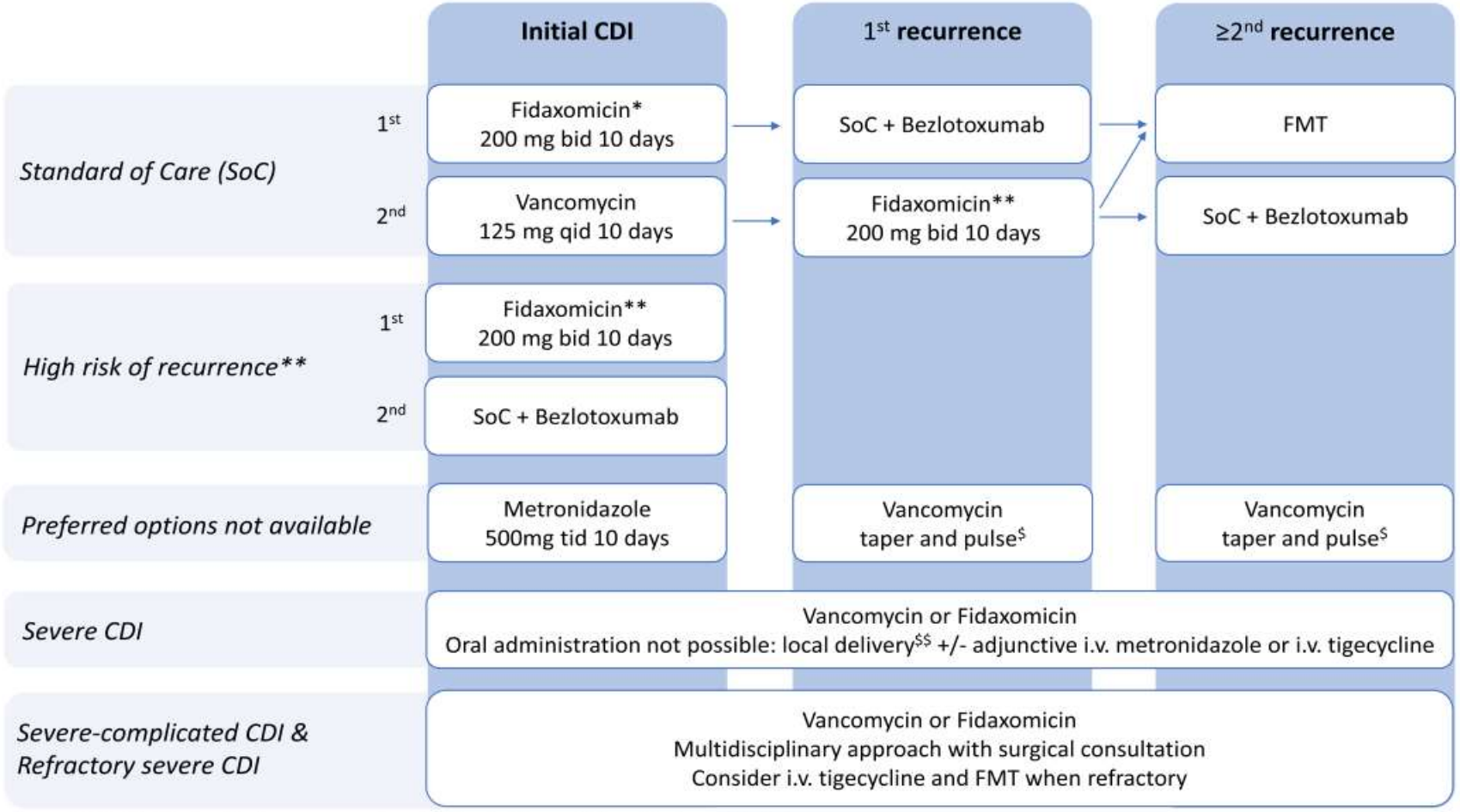
	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST	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.

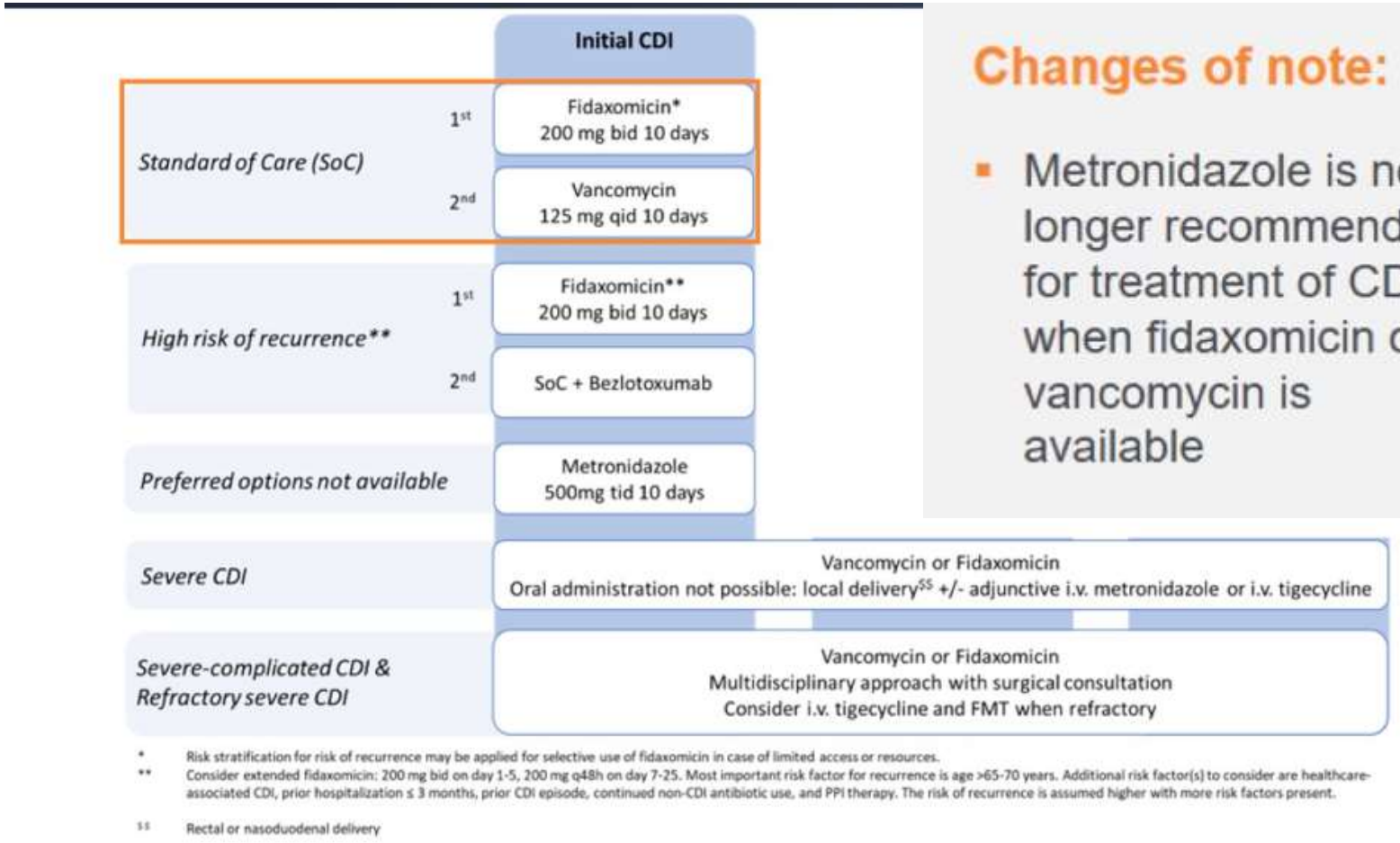
** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use,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

THERAPY: INITIAL CDI – IDSA/SHEA

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative
	Alternative for nonsevere CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of nonsevere CDI is supported by the following laboratory parameters: White blood cell count of 15 000 cells/μL or lower and a serum creatinine level <1.5 mg/dL

Like the ESCMID guidelines, the 2021 IDSA/SHEA guidelines also recommend fidaxomicin as the first-line treatment over vancomycin for primary CDI

Johnson S, et al. Clin Infect Dis. 2021;73:755-757.

THERAPY: INITIAL CDI – ACG

Recommendations:

- Fidaxomicin and vancomycin are equally preferred for nonsevere CDI
- Metronidazole may be considered for initial nonsevere CDI in low-risk patients

4. We recommend that oral vancomycin 125 mg 4 times daily for 10 d be used to treat an initial episode of nonsevere CDI (strong recommendation, low quality of evidence).
5. We recommend that oral fidaxomicin 200 mg twice daily for 10 d be used for an initial episode of nonsevere CDI (strong recommendation, moderate quality of evidence).
6. Oral metronidazole 500 mg 3 times daily for 10 d may be considered for treatment of an initial nonsevere CDI in low-risk patients (strong recommendation/ moderate quality of evidence).

Kelly CR, et al. Am J Gastroenterol. 2021;116:1124-1147.

THERAPY: PRIMARY NOT SEVERE CDI

Fidaxomicin is recommended for first CDI episode

If access to fidaxomicin is limited, it should be recommended to patients with high risk of recurrence

When fidaxomicin is not available or feasible, oral vancomycin is a suitable alternative

Oral metronidazole should be used only when vancomycin and fidaxomicin are not available or feasible

Prolonged administration of fidaxomicin (extended)
200 mg twice daily on days 1 to 5, and 200 mg once daily on alternate days on days 7 to 25 can be considered in patients with CDI with increased risk of recurrence, especially in older adult hospitalized patients (evidence: weak, low)*

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

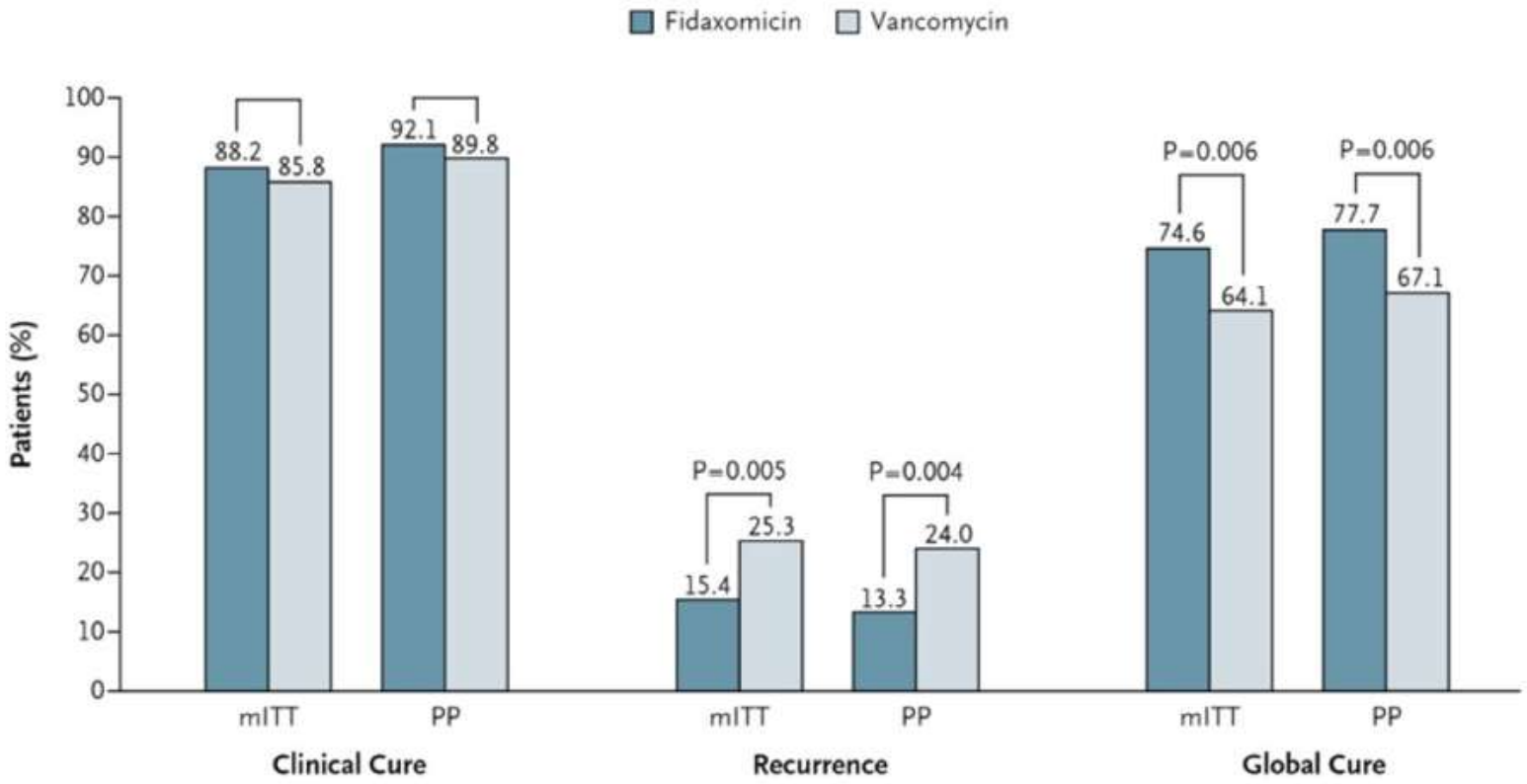
GOODBYE METRONIDAZOLE

- 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.

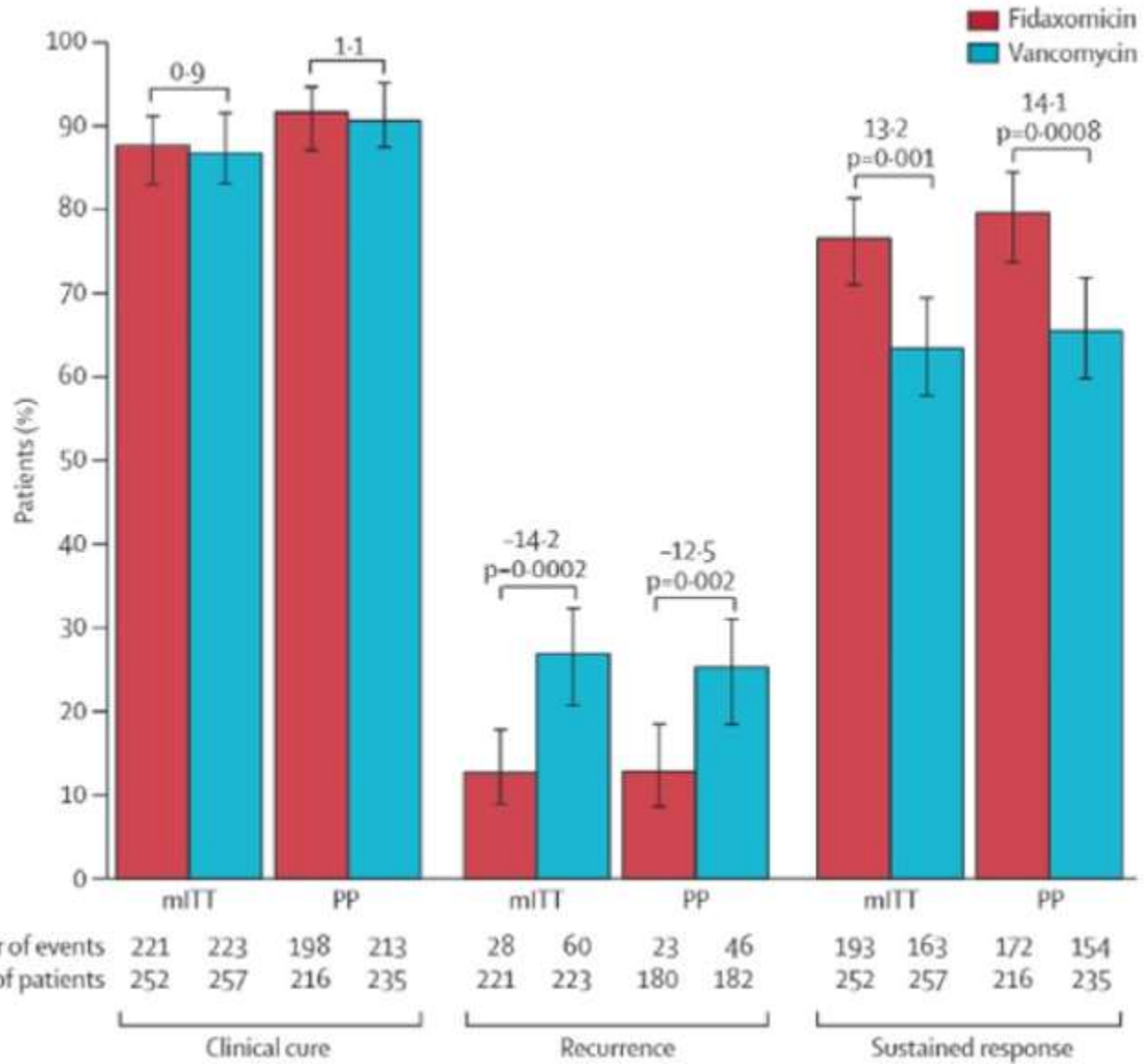
FIDAXOMICIN VS VANCOMYCIN: 2011 RCT

Phase 3 RCT evaluated the efficacy and safety of FDX (200 mg orally twice daily for 10 d) vs VAN (125 mg orally 4 times daily for 10 d) in adult patients with acute, toxin-positive CDI



mITT, modified intention-to-treat; PP, per protocol.
Louie TJ, et al. N Engl J Med. 2011;364:422-431.

FIDAXOMICIN VS VANCOMYCIN: 2012 RCT



Cornely OA, et al. Lancet Infect Dis. 2012;12:281-289.

FIDAXOMICIN VS VANCOMYCIN: RCTs

OPT-80-003 Study[a]

- Median time to resolution of diarrhea: 58 h in FDX vs 78 h in VAN group
  - Inpatients: 91 h vs 120 h
  - Outpatients: 47 h vs 61 h
- No significant differences between groups in the rates of AEs or serious AEs

OPT-80-004 Study[b]

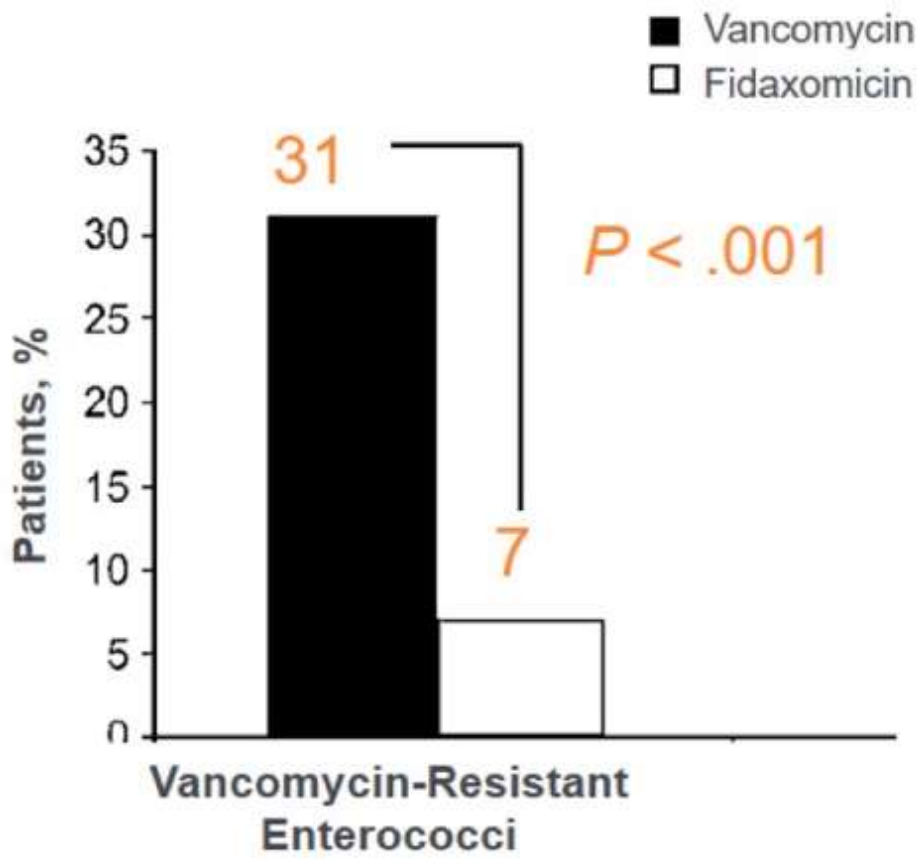
- Time to resolution of diarrhea: 56 h in FDX vs 58 h in VAN group
- Similar trends were recorded for inpatient and outpatient visits
- Occurrence of TEAEs did not differ between groups

AE, adverse event; TEAE, treatment-emergent AE.
a. Louie TJ, et al. N Engl J Med. 2011;364:422-431; b. Cornely OA, et al. Lancet Infect Dis. 2012;12:281-289.

FIDAXOMICIN VS VANCOMYCIN: VRE

OPT-80-003 Study

Phase 3 RCT of patients treated with FDX vs VAN for CDI



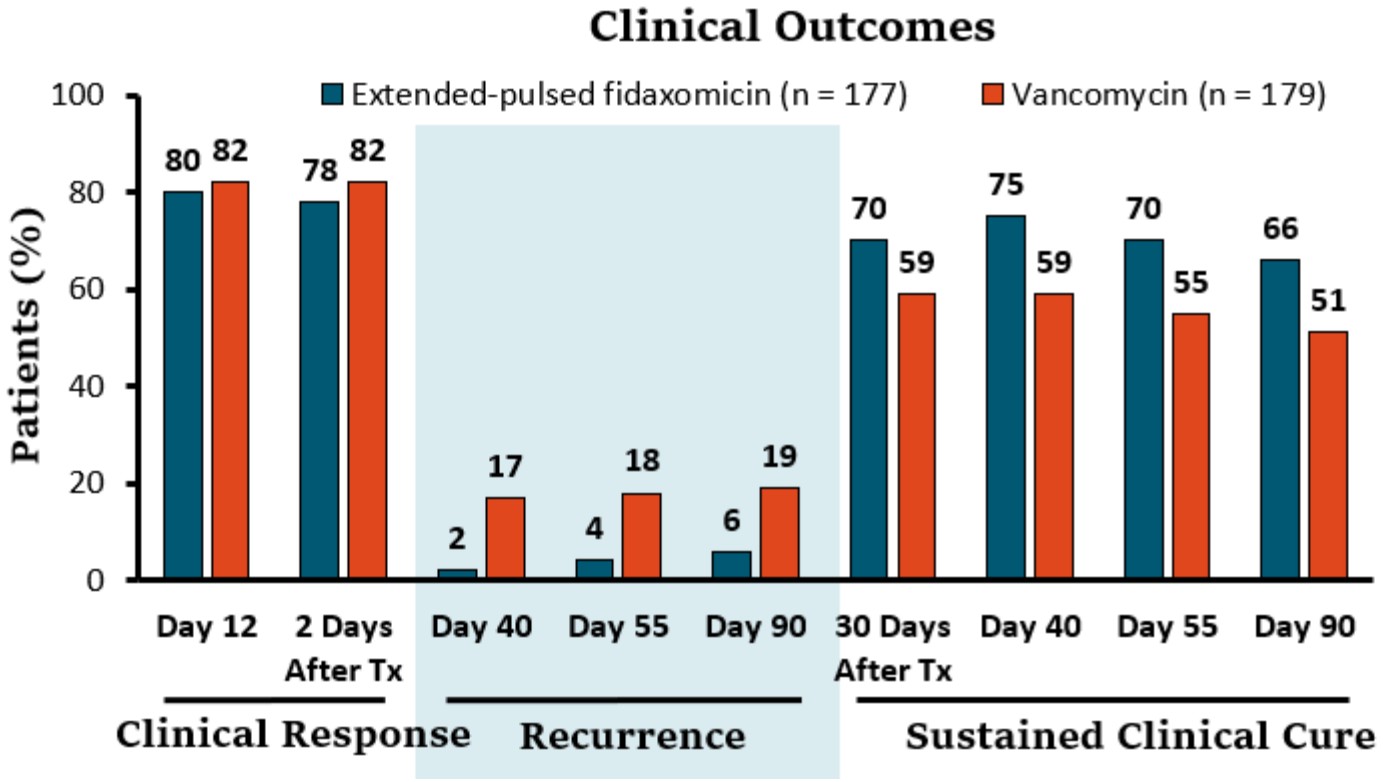
Result

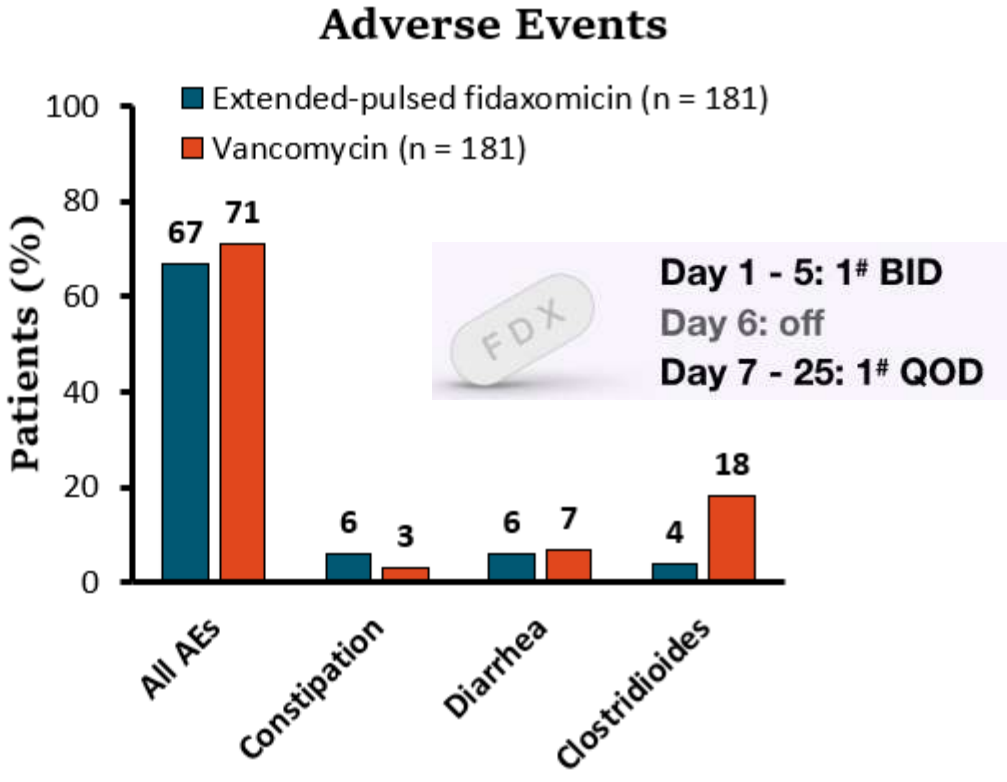
FDX treatment reduced frequency of novel stool culture positivity for VRE among 247 patients with negative pretreatment stool cultures

VRE, vancomycin-resistant enterococci.
Nerandzic MM. Clin Infect Dis. 2012;55(suppl 2):S121-S126.

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





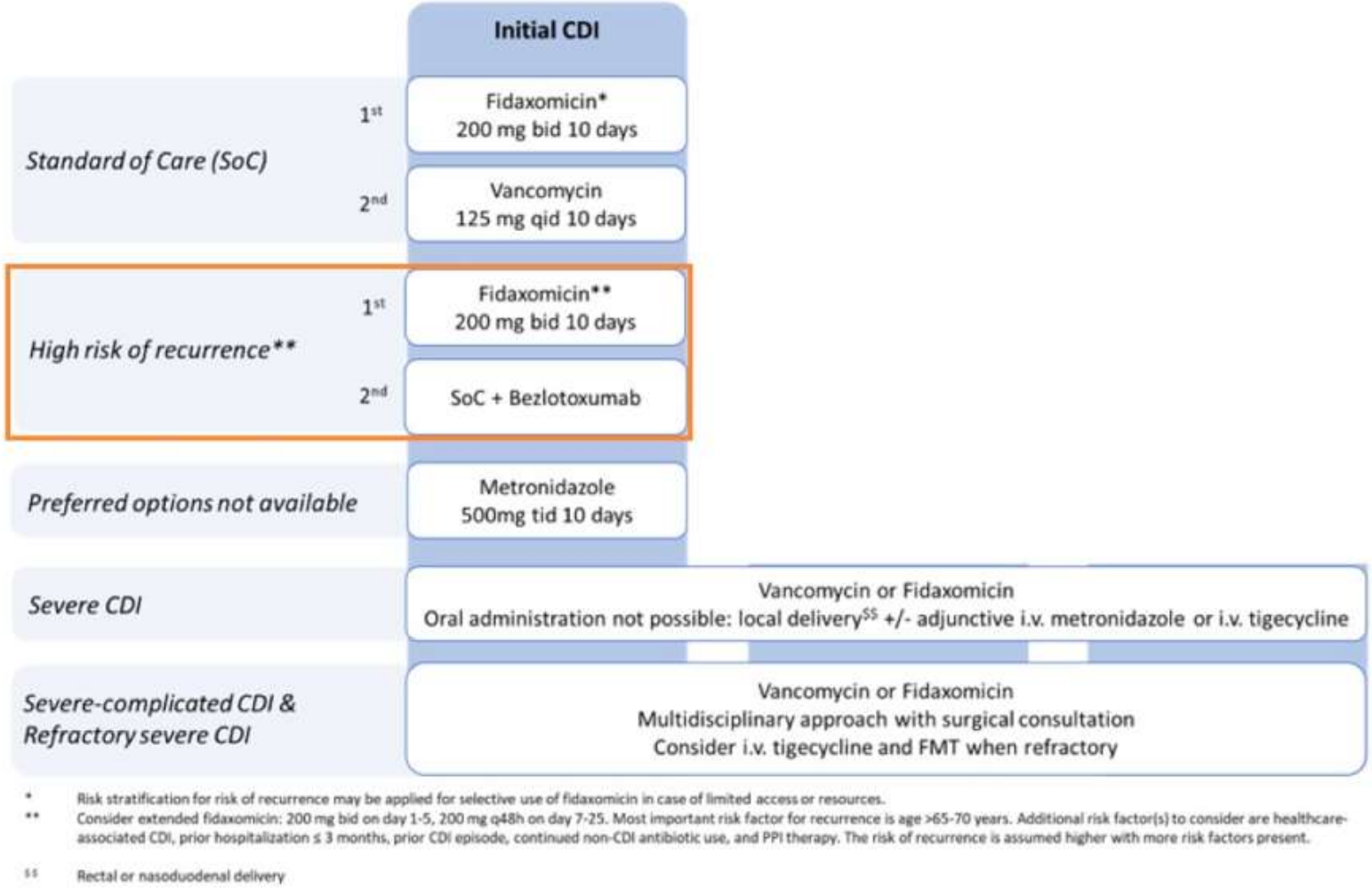
Guery. Lancet Infect Dis. 2018; 18: 296.

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: FIRST LINE/RISK OF RELAPSE- 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.

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

FIRST LINE/RISK OF RELAPSE - LGs DIFFERENCES

	ESCMID 2021	IDSA/SHEA 2021	ACG 2021
Initial episode, nonsevere	Fidaxomicin STD* **preferred** **OR** vancomycin 125 mg PO 6 hourly for 10 d (alternative) **If above agents are unavailable:** metronidazole 500 mg PO 8 hourly for 10 d **If high risk of recurrence:** consider EPFX† or adjunctive bezlotoxumab if fidaxomicin is unavailable	Fidaxomicin STD* **preferred** **OR** vancomycin 125 mg PO 6 hourly for 10 d (alternative) **If above agents are unavailable:** metronidazole 500 mg PO 8 hourly for 10-14 d	Vancomycin 125 mg PO 6 hourly for 10 d **OR** fidaxomicin STD* For initial nonsevere CDI in low-risk patients, consider metronidazole 500 mg PO 8 hourly for 10 d
Severe	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d If PO administration not possible, use rectal or nasoduodenal delivery Consider adjunctive IV metronidazole or IV tigecycline	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d and adjunctive bezlotoxumab for primary CDI if other risk factors for recurrence (age ≥ 65 y, immunocompromised host) or if episode in prior 6 mo	Vancomycin 125 mg PO 6 hourly for 10 d **OR** fidaxomicin STD* Consider bezlotoxumab if high risk of recurrence
Severe-complicated "fulminant"	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d and consider IV tigecycline 100 mg load, then 50 mg 12 hourly Consult a surgeon Consider FMT when refractory	Vancomycin 500 mg 6 hourly PO or by nasogastric tube and metronidazole 500 mg IV 8 hourly **AND** consider vancomycin per rectum if ileus present	Vancomycin 500 mg 6 hourly PO or by nasogastric tube Consider metronidazole 500 mg IV 8 hourly **AND** consider vancomycin per rectum if ileus present Consider FMT when refractory

EPFX, extended-pulse fidaxomicin; PO, by mouth; STD, standard.
*Fidaxomicin STD regimen: 200 mg PO 12 hourly for 10 d; †EPFX: 200 mg PO 12 hourly for 5 d, followed by 200 mg PO every other day for 20 d; not FDA-approved as of February 20, 2023.
Bishop J, et al. J Antimicrob Chemother. 2023;78:21-30; Kelly CR, et al. Am J Gastroenterol. 2021;116:1124-1147.

AIFA – BEZLOTOXUMAB NOT AS FIRST LINE

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

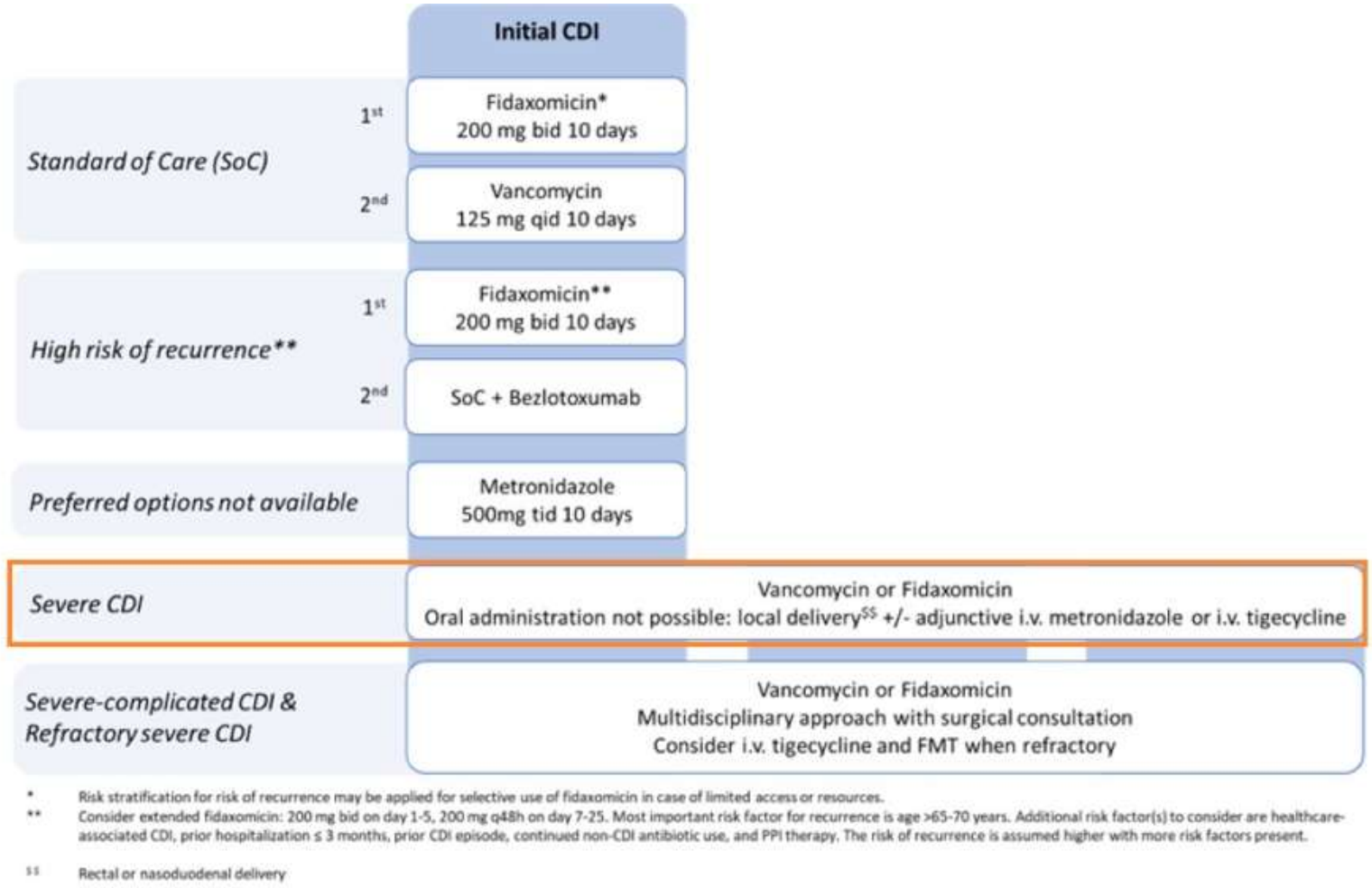
PROGRAMMA TERAPEUTICO

	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.

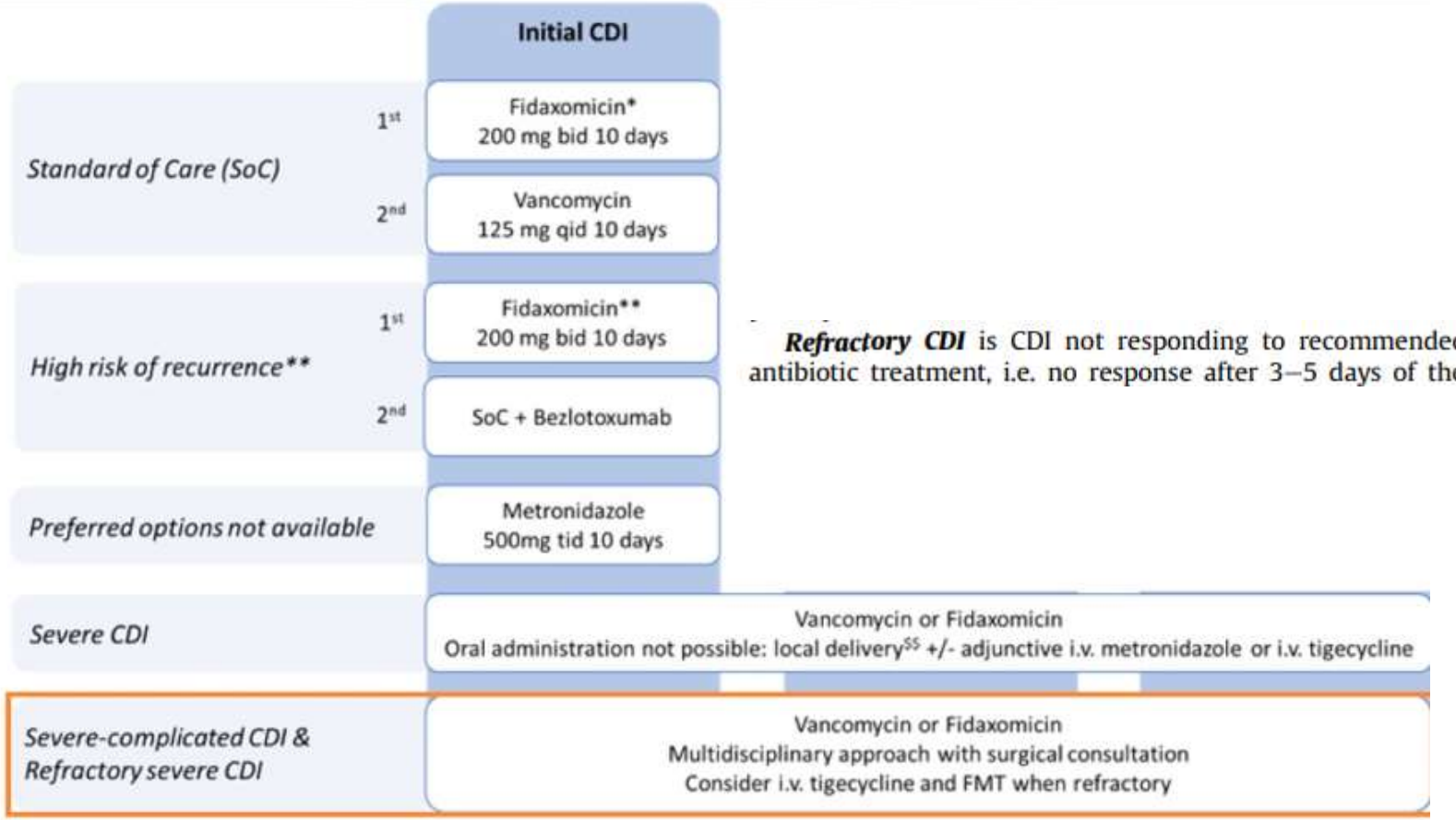
THERAPY: SEVERE CDI - ESCMID



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.

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

THERAPY: COMPLICATED/REFRACTORY CDI - ESCMID



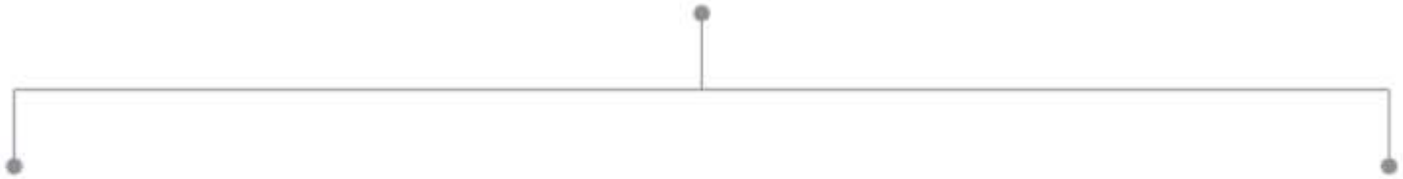
Refractory CDI is CDI not responding to recommended CDI antibiotic treatment, i.e. no response after 3–5 days of therapy.

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.

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

SEVERE CDI

Options for treatment of any severe and severe-complicated CDI episode include:



Vancomycin

125 mg 4 times daily for 10 d

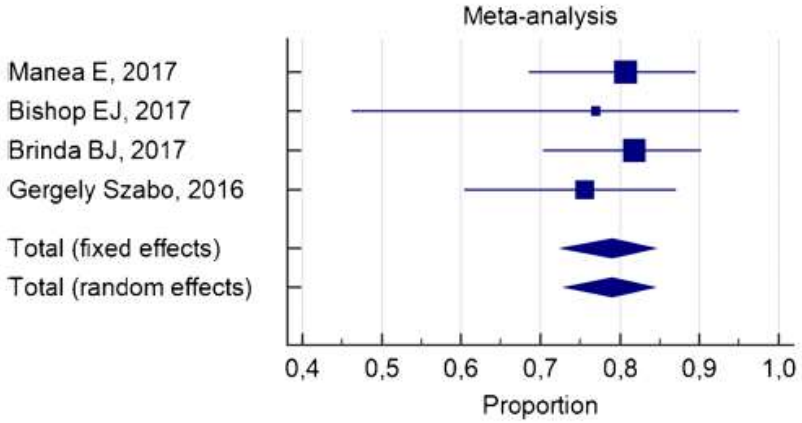
Fidaxomicin

200 mg twice daily for 10 d

Consult a surgeon for any severe-complicated cases of CDI

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

SEVERE CDI: ROLE OF TIGECYCLINE



Test for heterogeneity	
Q	0,8215
DF	3
Significance level	P = 0,8443
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 52,85

Fig. 2 Pooled analysis of clinical cure among patients with severe *C. difficile* infections treated with tigecycline. (Squares = proportion in each study; horizontal lines = 95% CI; diamonds = pooled proportion for all studies)

European Journal of Clinical Microbiology & Infectious Diseases (2020) 39:1053–1058
https://doi.org/10.1007/s10096-019-03756-z

REVIEW

Tigecycline for the treatment of patients with *Clostridium difficile* infection: an update of the clinical evidence

Konstantinos S. Kechagias[1] · Stamatia Chorepsima[1] · Nikolaos A. Triarides[1,2] · Matthew E. Falagas[1,2,3]

Abstract

Purpose *Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea in adult patients and is associated with considerable morbidity and mortality. Apart from the standard treatment regimens, tigecycline has shown significant in vitro activity against *C. difficile* but data regarding its clinical impact remains controversial. The aim of this article is to update the evidence related to the clinical role of tigecycline against *C. difficile*.

Methods PubMed and Scopus databases were searched for relevant literature published from January 2015 to July 2018.

Results Six retrospective cohort studies, 1 prospective study, 1 case series, and 2 case reports provided data regarding the effectiveness of tigecycline against *C. difficile* and were included in our evaluation. Also, we performed a meta-analysis based on 186 patients (from 4 studies) that showed clinical cure 79% (95% CI 73.0–84.5%).

Conclusion Despite the heterogeneity of the included studies and the small number of patients, the available evidence suggests that tigecycline might be considered as a potential therapeutic option for patients with CDIs, especially in severe cases.

SEVERE CDI: ROLE OF IV METRONIDAZOLE

Letter to the Editor Clinical Microbiology and Infection 29 (2023) 656–657

Intravenous metronidazole for fulminant *Clostridioides difficile* infection

Giuseppe Pipitone [1,*], Guido Granata [2], Massimo Sartelli [3], Andrea Gizzi [1,4], Claudia Imburgia [1], Antonio Cascio [4], Chiara Iaria [1]

To the editor,

Recently, van Prehn et al. [1] rev
infection (CDI) guidelines of the E
Microbiology and Infectious Disease (E
for severe-complicated or fulminant
fidaxomicin alone (the latter being s
with no comparison to 'standard of ca
In the Infectious Disease Society
guidelines [2], the treatment of choic
bination therapy with vancomycin plu
Among the four observational stud
its guidelines to discourage the rou
metronidazole for CDI (panellists appr
only as adjunctive therapy if no oral t

them [3–5] evaluated the efficacy
versus vancomycin plus metronidazo
three antibiotic regimens (oral metronidazole, intravenous metronidazole, and oral vancomycin), but no comparison was made between vancomycin alone and vancomycin plus metronidazole.

The other three studies are as follows.

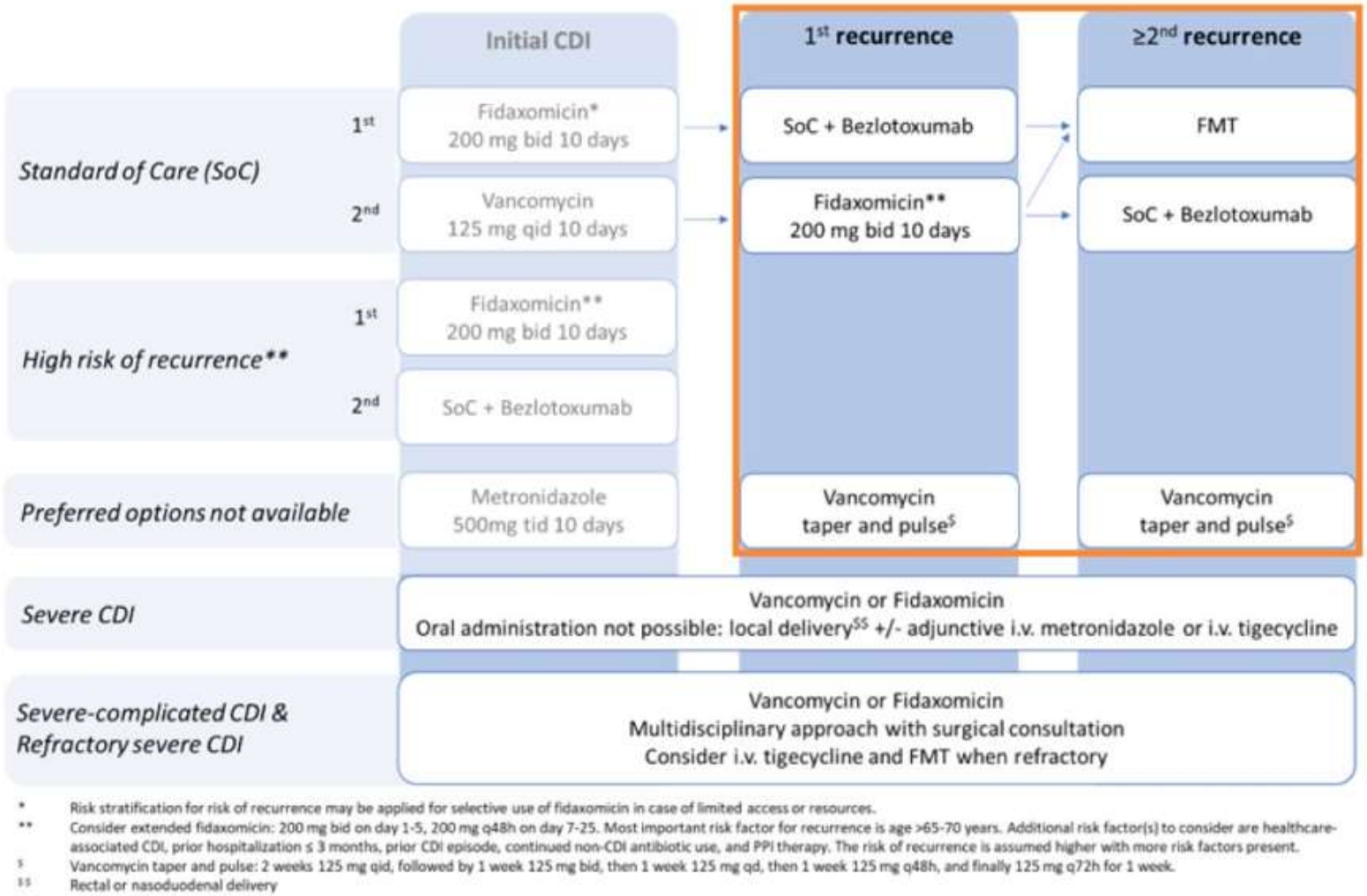
The first study cited by the ESCMID guidelines, a retrospective study by Rokas et al. [3], suggested that the addition of metronidazole to vancomycin could reduce mortality compared with vancomycin alone. Patients were enrolled if they had severe or fulminant CDI. The study included 88 patients, 44 in the combination group and 44 in the vancomycin alone group. The mortality in the combination group was significantly lower, despite the fact that the number of patients with high white blood cell count, low mean arterial pressure, and moderate-to-severe renal disease was higher in the combination group. However, the analysis did not take into
pital mortality,
e of disease.
nal retrospec-
al vancomycin
cin alone. The
114) with CDI:
s in the inten-
This study did
sted OR of 1.07
or colectomy
evere patients
be that the lo-
not account for

ational study by
nts treated with
r, the severity of the disease was much higher in patients treated with combination therapy. It is doubtful whether the statistical analysis could account for that.

All studies were observational and retrospective. The level of evidence should be 'very low'. All these studies have many biases: allocation, misclassification, performance, and detection biases should be noted.

We should be cautious when approaching a patient with severe/fulminant CDI. Suggesting the removal of a drug from the treatment of severely ill patients (intravenous metronidazole added to vancomycin), a combination used in clinical practice, should not be based only on a few retrospective studies with multiple biases.

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

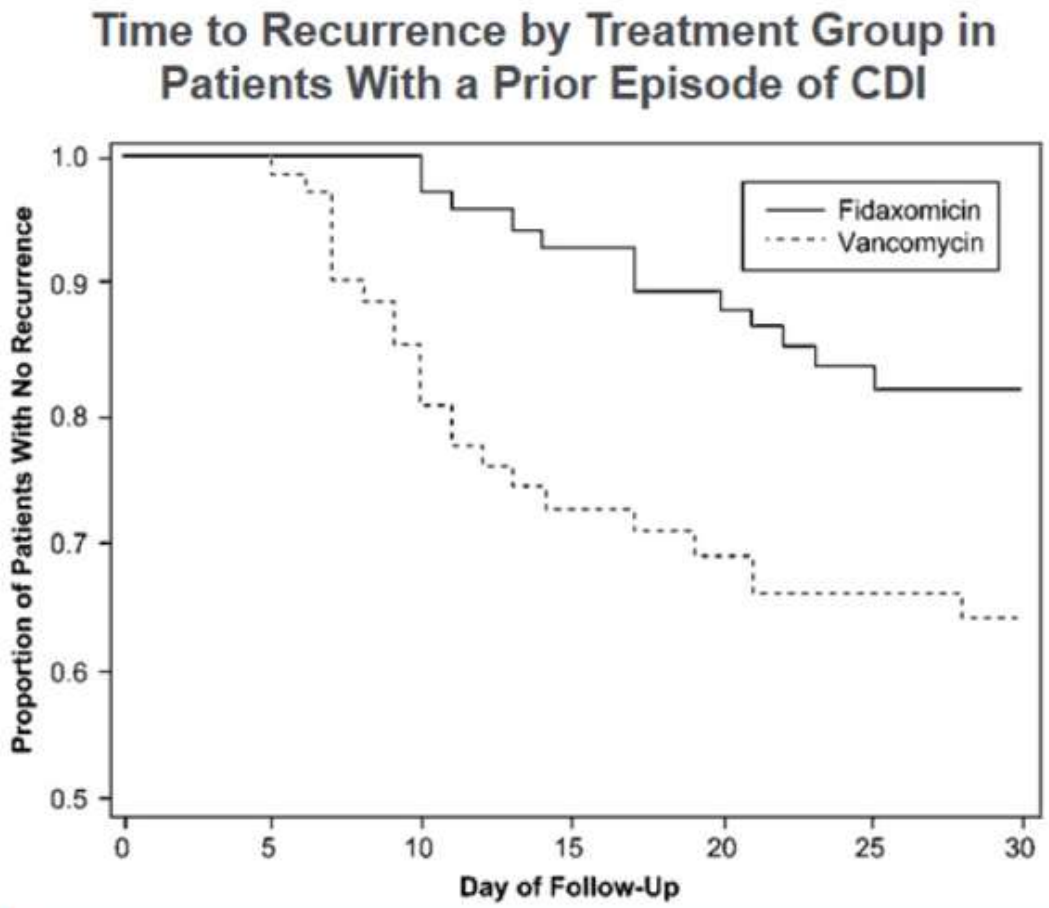
In 2 phase 3 RCTs conducted in US, Canada, and Europe, patients with CDI received FDX 200 mg twice daily or VAN 125 mg 4 times daily for 10 d

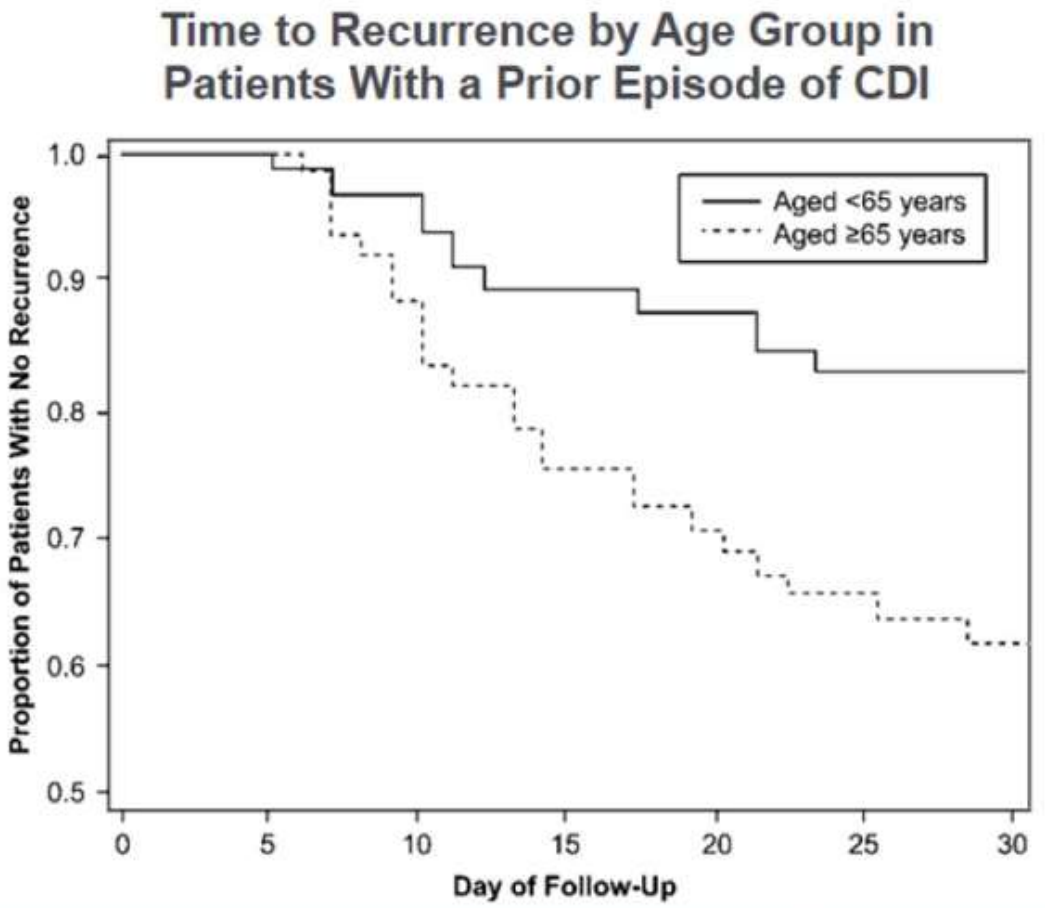
***Clostridium difficile* Infection Recurrence Following Successful Fidaxomicin or Vancomycin Treatment**

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.

THERAPY: FIRST RECURRENCE (FDX VS VAN)



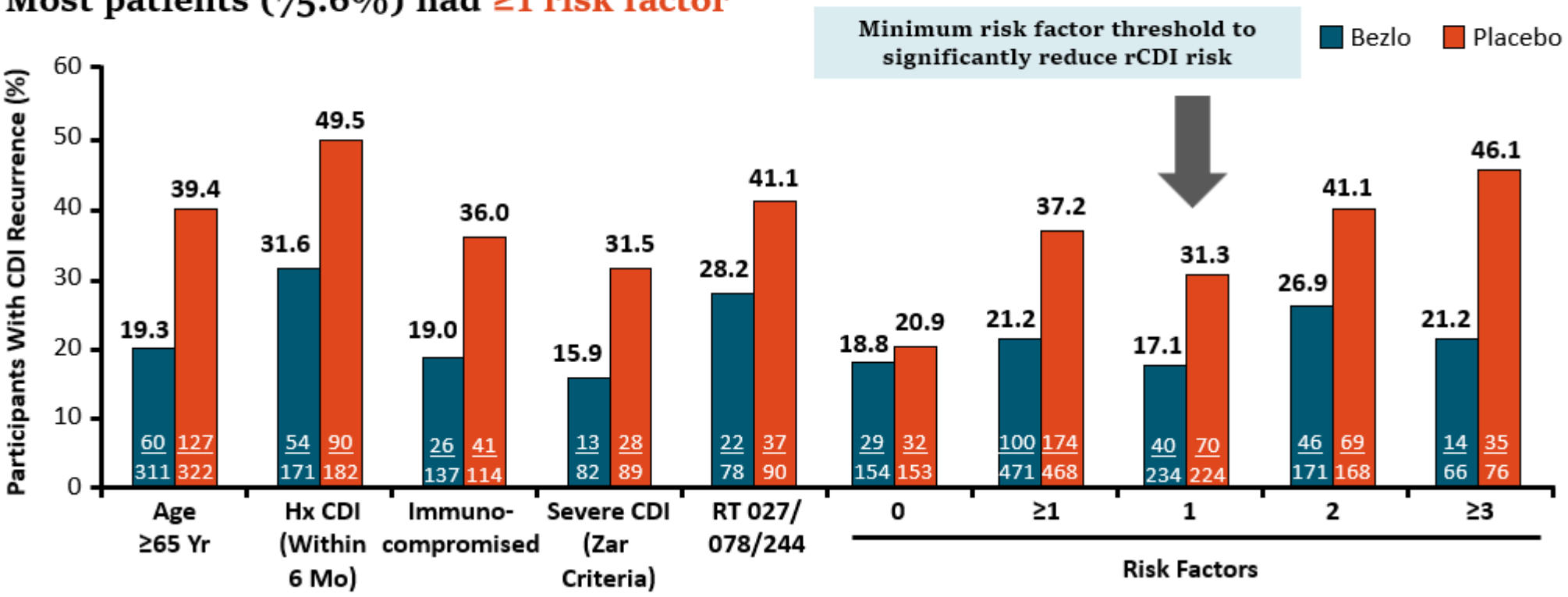


FDX was associated with a lower risk of and longer time to recurrence than with VAN; age was associated with risk of recurrence

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

GOING FOR BEZLOTOXUMAB

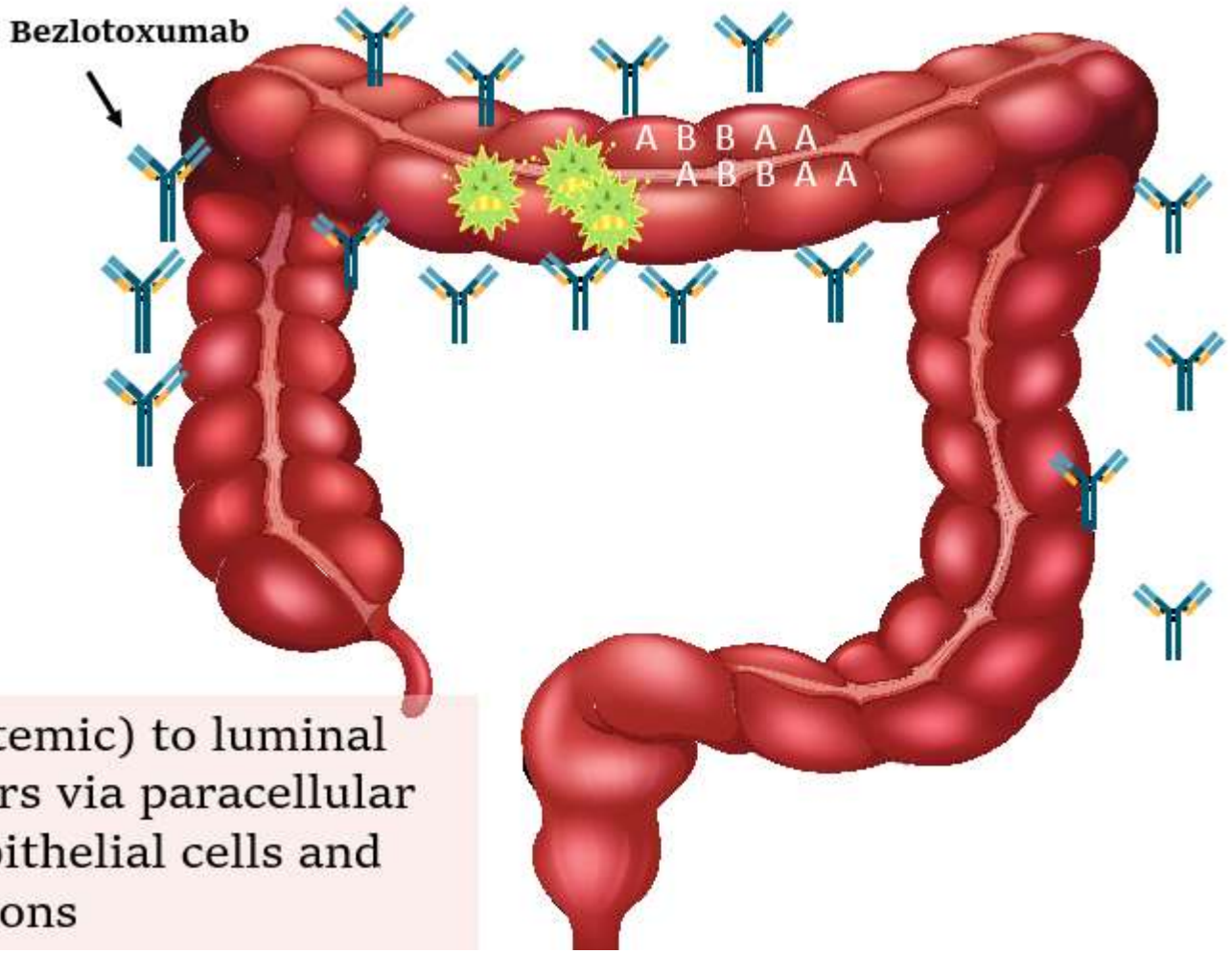
- Analysis using 2 double-blind, randomized, placebo-controlled phase III trials (N = 1554) and prespecified rCDI risk factors (age ≥65 yr, history of CDI in past 6 mo, compromised immunity, severe CDI [Zar score ≥2 points], and ribotypes 027/078/244)
- **Most patients (75.6%) had ≥1 risk factor**



Gerding. Clin Infect Dis. 2018; 67: 649

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

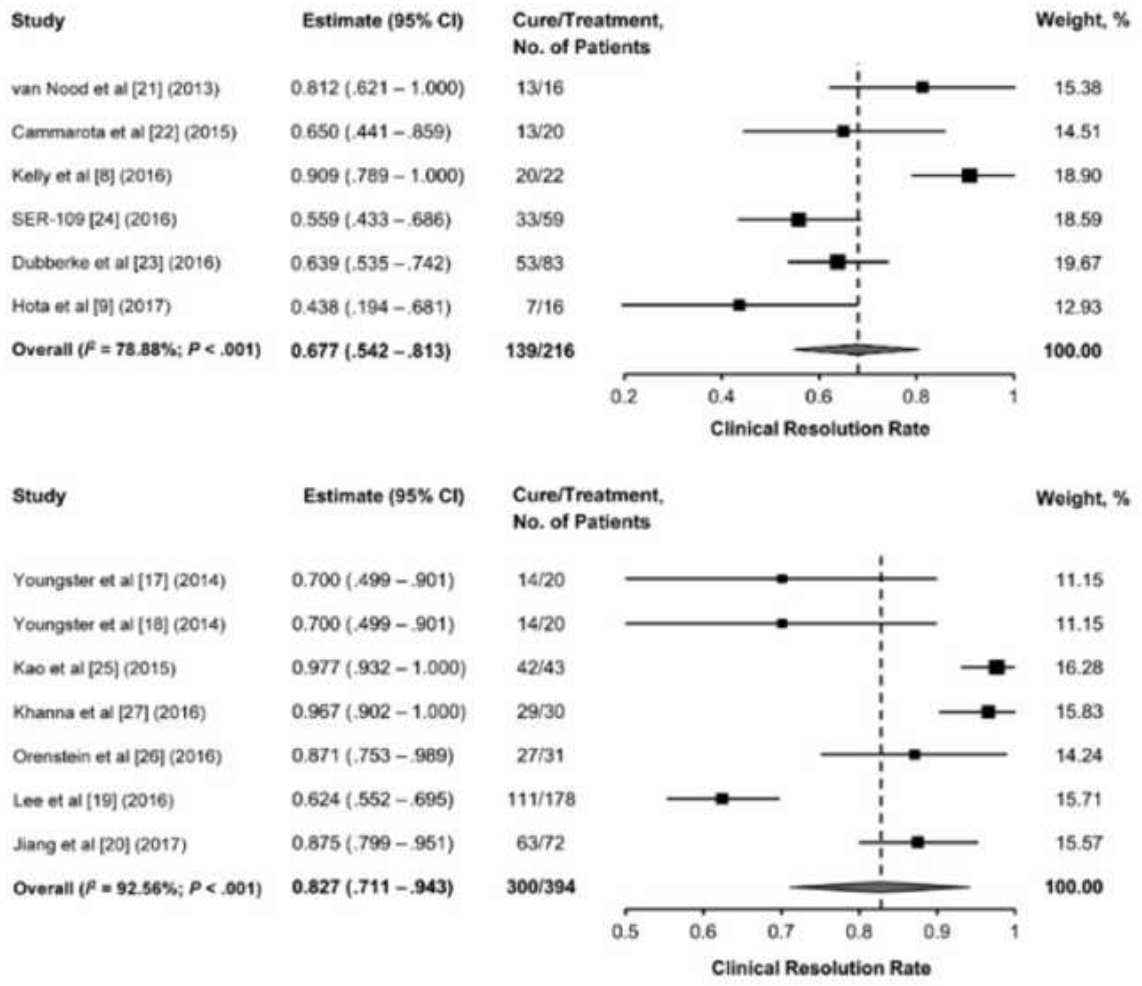


Transport from basolateral (systemic) to luminal compartment of colonocytes occurs via paracellular path after toxin disruption of epithelial cells and intercellular junctions

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

FMT FOR RECURRENT CDI

Forest Plots Showing Weighted Clinical Resolution Rates of FMT in Patients With CDI in Trials With a Non-FMT Comparator Group (Top) and in Open-Label Trials (Bottom)



Tariq R, et al. Clin Infect Dis. 2019;68:1351-1358.

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)

FMT FOR RECURRENT CDI: ROUTES

Delivery of FMT by colonoscopy or oral routes (eg, nasoduodenal infusion) was more effective than by enema

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)

Tariq R, et al. Clin Infect Dis. 2019;68:1351-1358.

THE FIRST APPROVED FECAL MICROBIOTA PRODUCT

FDA NEWS RELEASE

FDA Approves First Fecal Microbiota Product

Approved for the Prevention of Recurrence of Clostridioides difficile Infection in Adults

RBX2660 was approved to prevent recurrent *Clostridioides difficile infection* (CDI) in adult patients who have already completed an antibiotics regimen for recurrent CDI.

RBX2660: Intestinal Fecal Microbiota Suspension that is Standardized, Stabilized, and Quality Controlled CO-5

- Standardized for potency with controlled formula
- Stabilized for extended shelf life
- Pre-packaged single-dose: 150 mL microbiota suspension from individual human stool donation

FDA U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety Fecal Microbiota, Live (RBX2660)

September 22, 2022

Omolara Adewuni, MD, MPH
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

Zhong Gao, Ph.D.
Therapeutics Evaluation Branch 2
Division of Biostatistics
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research

Clear Benefits of A Regulated, FDA Approved Microbiome Restoration Therapy

- **Well-studied, consistent process to product**
- **Established, positive benefit-risk profile**
- **Approval of a standardized product**
  - Reduce variability and heterogeneity of the processes and preparation
  - Uniform and iterative donor screening to improve safety outcomes
  - Improve access for patients
- **Address the cycle of CDI recurrence**

RBX2660

Drugs | Peer-Reviewed Feature

Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection

Khanna S, Assi M, Lee C, Yoho D, Louie T, Knapple W, Aguilar H, Garcia-Diaz J, Wang GP, Berry SM, Marion J, Su X, Braun T, Bancke L, Feuerstadt P. *Drugs* 82, 1527–1538 (2022). https://doi.org/10.1007/s40265-022-01797-x

Recurrent ***Clostridioides difficile*** infection (CDI) is a major health problem worldwide –especially among older adults

RBX2660 is a microbiota-based live biotherapeutic that is rectally administered for the prevention of recurrence of CDI

The microbiota suspension contains a broad consortium of **live microbes** sourced from **healthy donors**

The PUNCH CD3 trial found RBX2660 superior to placebo in patients with recurrent CDI

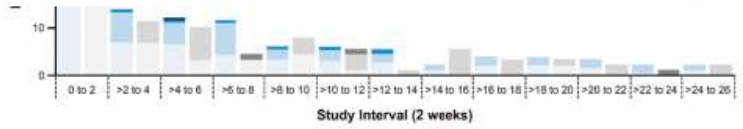
PUNCH CD3

- A randomized, double-blind, placebo-controlled, phase 3 study
- Patients enrolled had either ≥1 recurrence of CDI after a primary episode and completed ≥1 round of antibiotic therapy or ≥2 episodes of severe CDI that resulted in hospitalization in the past year
- Treatment arms: single-dose RBX2660 (n = 180) or placebo (n = 87)
- Primary endpoint: Treatment success, absence of CDI-related diarrhea at 8 weeks
- Patients were followed up for 6 months

SAFETY & TOLERABILITY

Incidence and Severity of AEs

- Most AEs occurred within 2 weeks of treatment
- AEs ≥5% in both groups were GI-related
- Favorable safety profile may be partially due to rigorous screening of donors and samples against pathogens



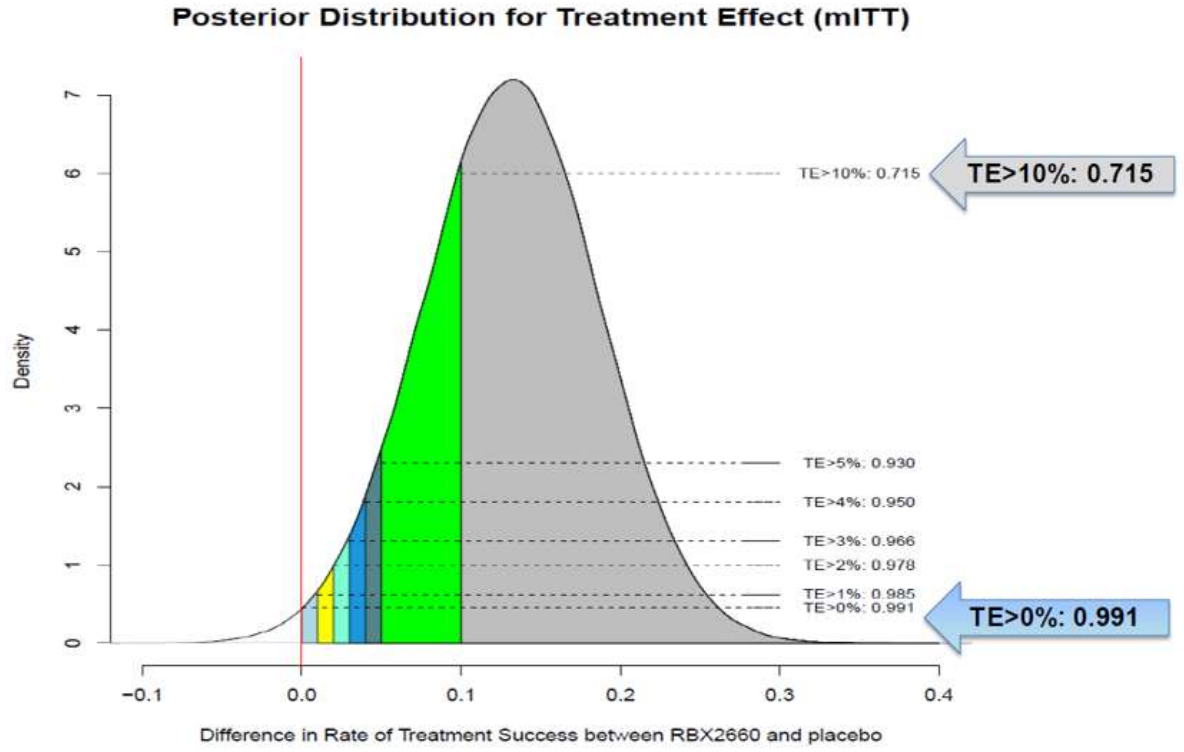
Limitations, potentially leading to high placebo response rate:

- PCR assay used in >70% of patients
- 1/3 of patients enrolled after one rCDI occurrence

RBX2660 is administered rectally in 1 dose.

Posterior Probability for Different Treatment Effect Levels

FDA



THERAPY: COMPARISON BETWEEN GLs

	ESCMID 2021	IDSA/SHEA 2021	ACG 2021
Initial episode, nonsevere	Fidaxomicin STD* **preferred** **OR** vancomycin 125 mg PO 6 hourly for 10 d (alternative) **If above agents are unavailable:** metronidazole 500 mg PO 8 hourly for 10 d **If high risk of recurrence:** consider EPFX† or adjunctive bezlotoxumab if fidaxomicin is unavailable	Fidaxomicin STD* **preferred** **OR** vancomycin 125 mg PO 6 hourly for 10 d (alternative) **If above agents are unavailable:** metronidazole 500 mg PO 8 hourly for 10-14 d	Vancomycin 125 mg PO 6 hourly for 10 d **OR** fidaxomicin STD* For initial nonsevere CDI in low-risk patients, consider metronidazole 500 mg PO 8 hourly for 10 d
Severe	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d If PO administration not possible, use rectal or nasoduodenal delivery Consider adjunctive IV metronidazole or IV tigecycline	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d and adjunctive bezlotoxumab for primary CDI if other risk factors for recurrence (age ≥ 65 y, immunocompromised host) or if episode in prior 6 mo	Vancomycin 125 mg PO 6 hourly for 10 d **OR** fidaxomicin STD* Consider bezlotoxumab if high risk of recurrence
Severe-complicated "fulminant"	Fidaxomicin STD* **OR** vancomycin 125 mg PO 6 hourly for 10 d and consider IV tigecycline 100 mg load, then 50 mg 12 hourly Consult a surgeon Consider FMT when refractory	Vancomycin 500 mg 6 hourly PO or by nasogastric tube and metronidazole 500 mg IV 8 hourly **AND** consider vancomycin per rectum if ileus present	Vancomycin 500 mg 6 hourly PO or by nasogastric tube Consider metronidazole 500 mg IV 8 hourly **AND** consider vancomycin per rectum if ileus present Consider FMT when refractory

EPFX, extended-pulse fidaxomicin; PO, by mouth; STD, standard.
*Fidaxomicin STD regimen: 200 mg PO 12 hourly for 10 d; †EPFX: 200 mg PO 12 hourly for 5 d, followed by 200 mg PO every other day for 20 d; not FDA-approved as of February 20, 2023.

Jones. Antibiotics. 2022; 11: 1247.

WHY GUIDELINES DIFFER

Assessment of costs

- ESCMID guidelines noted higher acquisition costs of fidaxomicin and other agents, but based their evaluation on evidence of clinical effectiveness only
- ISDA/SHEA and ACG guidelines chose to include healthcare economics studies, eg, noting that fidaxomicin may be cost effective because of lower recurrence risk and thus lower overall healthcare costs

Availability and access

- Some drugs, such as fidaxomicin and bezlotoxumab, are not available in some countries
- Some drugs may only be available on specialist prescription or in hospitals

Scope

- The 2021 IDSA/SHEA guidelines are a focused update on treatment of primary CDI, recurrent CDI, and use of bezlotoxumab in conjunction with standard-of-care antibiotics

Jones. Antibiotics. 2022; 11: 1247.

CDI: SURGICAL THERAPY

CLINICAL PRACTICE GUIDELINES

The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of *Clostridioides difficile* Infection

Vitaliy Poylin, M.D.[1] • Alexander T. Hawkins, M.D., M.P.H.[2] • Anuradha R. Bhama, M.D.[3]
Marylise Boutros, M.D.[4] • Amy L. Lightner, M.D.[5] • Sahil Khanna, M.B.B.S., M.S.[6]
Ian M. Paquette, M.D.[7] • Daniel L. Feingold, M.D.[8]
Prepared by the Clinical Practice Guidelines Committee of The American Society of Colon and Rectal Surgeons

1 Division of Gastrointestinal Surgery, Northwestern Medicine, Chicago, Illinois
2 Department of Surgery, Section of Colon & Rectal Surgery, Vanderbilt University Medical Center, Nashville, Tennessee
3 Department of Surgery, Division of Colon & Rectal Surgery, Rush University Medical Center, Chicago, Illinois
4 Jewish General Hospital, McGill University, Montreal, Quebec, Canada
5 Department of Colorectal Surgery, Digestive Disease Surgery Institute, Cleveland Clinic, Cleveland, Ohio
6 Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota
7 Department of Surgery, University of Cincinnati, Cincinnati, Ohio
8 Section of Colorectal Surgery, Rutgers University, New Brunswick, New Jersey

DISEASES OF THE COLON & RECTUM VOLUME 64: 6 (2021)

Surgical Therapy

10. Surgery for *C difficile* colitis should typically be reserved for patients with colonic perforation or severe colitis who do not improve with medical therapy. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

11. Subtotal colectomy with end ileostomy is typically the operative procedure recommended for severe-complicated or fulminant *C difficile* colitis. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

12. A diverting loop ileostomy with antegrade colonic lavage may be an alternative to subtotal colectomy for the treatment of severe-complicated or fulminant CDI. Grade of recommendation: Weak recommendation based on low-quality evidence, 2C.

In general, the most obvious indication for operation in the setting of CDI is in rare cases of colonic perforation; otherwise, the decision to proceed with surgery is difficult to standardize because there is no clear algorithm to determine which patients will ultimately respond to medical management and avoid surgery.

IS COLECTOMY LIFE SAVING?

Colorectal Disease © 2013 The Association of Coloproctology of Great Britain and Ireland. **15,** 798–804

Systematic review

doi:10.1111/codi.12134

Is colectomy for fulminant *Clostridium difficile* colitis life saving? A systematic review

D. B. Stewart*, C. S. Hollenbeak† and M. Z. Wilson‡

*Department of Surgery, Division of Colon and Rectal Surgery, †Departments of Surgery and Public Health Sciences and ‡Department of Surgery, Division of General Surgery, The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania, USA

Received 5 September 2012; accepted 15 November 2012; Accepted Article online 25 January 2013

Abstract

Aim It is unclear whether colectomy for fulminant *Clostridium difficile* colitis (FCDC) leads to a improvement in survival compared with continued medical therapy for this moribund population.

Method Selected studies from 1994–2010 were identified through a comprehensive search theme applied to MEDLINE (OvidSP and PubMed), EMBASE and by hand searching. Data regarding mortality rates between medically and surgically treated patients were extracted. Risk of bias was assessed using a Newcastle–Ottawa Scale score. A meta-analysis of the odds ratios for mortality between surgical and medical treatment for FCDC was conducted using the Mantel–Haenszel method and fixed-effects modelling.

Results Five hundred and ten patients with FCDC were identified in six studies. The pooled adjusted odds ratio of mortality comparing surgery with medical therapy was 0.70 (0.49–0.99), suggesting that surgery provided a survival benefit.

Conclusion Emergent colectomy for patients with FCDC provides a survival advantage compared with continuing antibiotics. Though there is selection bias of patients having surgery, the results of this systematic review suggest that colectomy has a therapeutic role in treating severe forms of *C. difficile* colitis.

Keywords *Clostridium difficile*, colitis, fulminant, mortality, colectomy

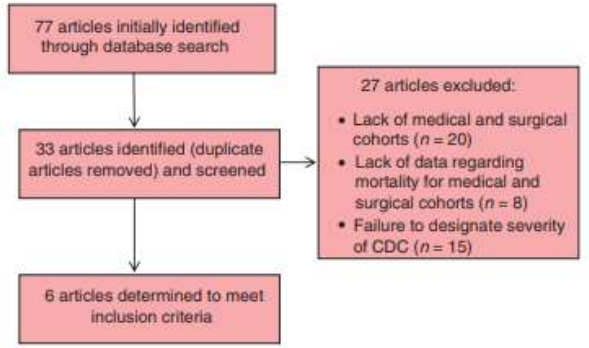


Figure 1 Flow chart of the study.

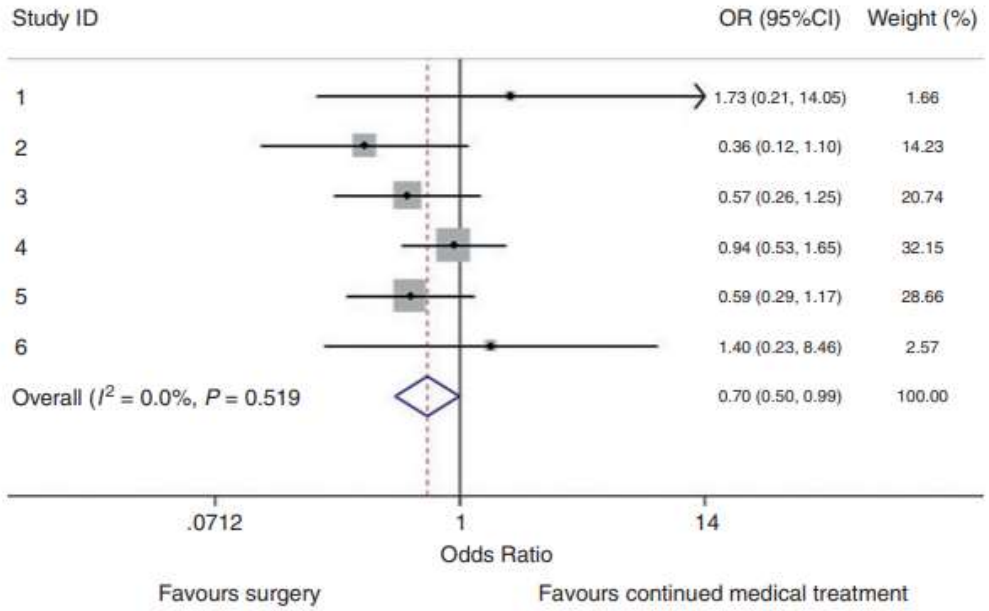


Figure 2 Fixed-effects model of the odds of mortality comparing colectomy with medical therapy for fulminant *Clostridium difficile* colitis.

(SUB)TOTAL COLECTOMY: FOCUS

Clinics in Colon and Rectal Surgery Vol. 33 No. 2/2020

Role of Surgery in *Clostridium difficile* Infection

Aela Vely, MD[1] Paula Ferrada, MD, FACS[1]

The patient can be placed either supine or in lithotomy position to allow for endoscopy intraoperatively as needed. In the case of CDI, the colon has the possibility of being significantly distended and good exposure is essential. Hence, a long–midline incision is recommended.

Once the abdominal cavity is entered, quickly examine all four quadrants for any purulence, feculence or gross perforation, run, and palpate the bowel for any lesions or injuries.

The colon is often so distended than mobilization is easier than with other colonic diseases. Since this is not an oncological resection, the operator can leave all the mesentery behind. Staying close to the colon can expedite this procedure and avoid further complications.

After the ileum and rectum are stapled off, the operator can decide to finalize the procedure with an ostomy.

If other risk factors, such as over resuscitation are placing the patient at risk of abdominal compartment syndrome, it is reasonable to perform damage control surgery and leave the bowel in discontinuity with an abdominal vacuum-assisted closure system and return to the operating room (OR) 24 to 48 hours later for further washout and reestablishment of continuity. On the other hand, if the patient is stable enough and the contamination was minimal, and end ileostomy can be performed with abdominal closure (►**Fig. 1**).

The standard of care is the subtotal colectomy. This operation leaves the patient with a permanent ostomy, and carries some blood loss and operative time; these factors can add to morbidity and mortality on a patient who is already physiologically compromised.

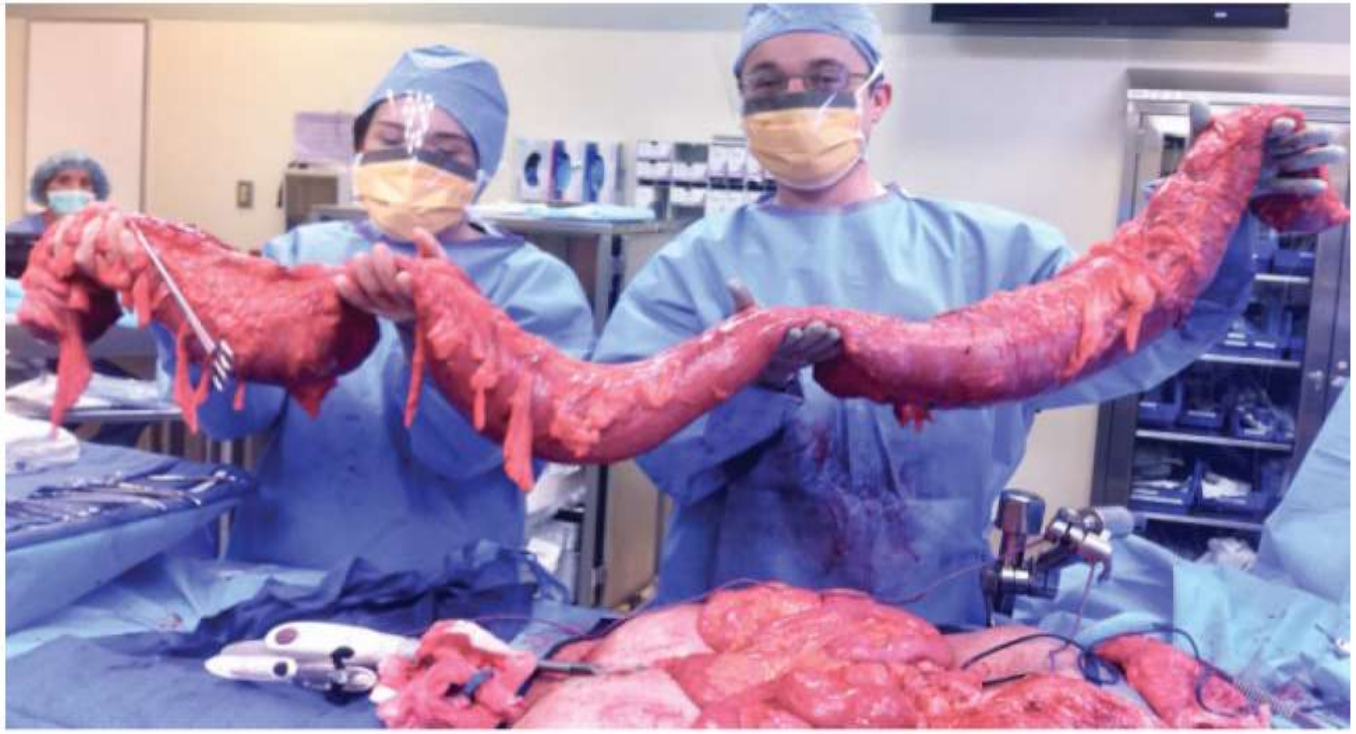


Fig. 1 Fulminant CDI sp. total colectomy. In the picture Dr. Levi Procter. CDI, *Clostridium difficile* infection.

DIVERTING LOOP ILEOSTOMY

PAPERS OF THE 131ST ASA ANNUAL MEETING

(*Ann Surg* 2011;254:423–429)

Diverting Loop Ileostomy and Colonic Lavage

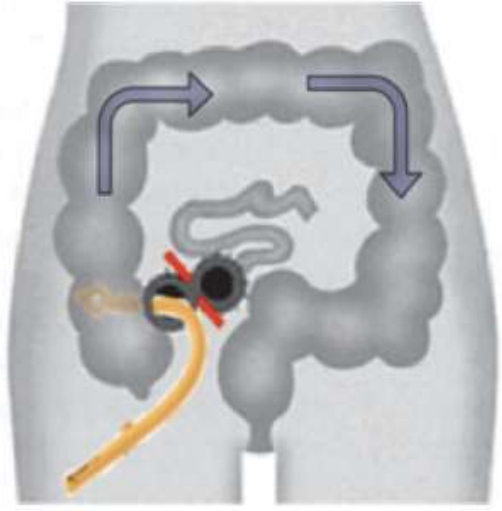
An Alternative to Total Abdominal Colectomy for the Treatment of Severe, Complicated Clostridium difficile *Associated Disease*

Matthew D. Neal, MD, John C. Alverdy, MD,† Daniel E. Hall, MD,*‡ Richard L. Simmons, MD,* and Brian S. Zuckerbraun, MD*‡*

Methods: All patients who were diagnosed with severe, complicated ("fulminant") CDAD and were treated at the University of Pittsburgh Medical Center or VA Pittsburgh Healthcare System between June 2009 and January 2011 were treated with this novel approach. The surgical approach involved creation of a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy and postoperative antegrade instillation of vancomycin flushes via the ileostomy. The primary end point for the study was resolution of CDAD. The matching number of patients treated with colectomy for CDAD preceding the initiation of this current treatment strategy was analyzed for historical comparison.

Results: Forty-two patients were treated during this time period. There was no significant difference in age, sex, pharmacologic immunosuppression, and Acute Physiology and Chronic Health Evaluation-II scores between our current cohort and historical controls. The operation was accomplished laparoscopically in 35 patients (83%). This treatment strategy resulted in reduced mortality compared to our historical population (19% vs 50%; odds ratio, 0.24; $P = 0.006$). Preservation of the colon was achieved in 39 of 42 patients (93%).

Conclusions: Loop ileostomy and colonic lavage are an alternative to colectomy in the treatment of severe, complicated CDAD resulting in reduced morbidity and preservation of the colon.



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

FIGURE 1. Operative treatment strategy for loop ileostomy and colonic lavage for severe, complicated *C. difficile*-associated disease. When possible laparoscopic exploration of the colon and abdominal cavity is performed and a diverting loop ileostomy is created. The colon is then lavaged in an antegrade fashion through the ileostomy with a high volume (8 L) of polyethylene glycol 3350 or balanced electrolyte solution and the effluent is collected via a rectal drainage tube. A catheter is placed in the efferent limb of the ileostomy to deliver vancomycin flushes in an antegrade fashion in the postoperative period.

DIVERTING LOOP ILEOSTOMY: EVIDENCE SYNTHESIS

International Journal of Colorectal Disease
https://doi.org/10.1007/s00384-019-03447-3

Published online: 21 November 2019

REVIEW

Diverting loop ileostomy with colonic lavage as an alternative to colectomy for fulminant *Clostridioides difficile*: a systematic review and meta-analysis

Tyler McKechnie[1,2] · Yung Lee[1,2] · Jeremy E. Springer[2] · Aristithes G. Doumouras[2,3] · Dennis Hong[2,3] · Cagla Eskicioglu[2,3]

Southern California Chapter of American College of Surgeons Annual Scientific Meeting

Diverting Loop Ileostomy for *Clostridium Difficile* Colitis: A Systematic Review and Meta-analysis

The American Surgeon
2020, Vol. 86(10) 1269–1276
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0003134820964213
journals.sagepub.com/home/tas
SAGE

Adam D. Shellito, MD[1], and Marcia M. Russell, MD[2]

Table 1. Study Characteristics.

Author	Year published	Years studied	Study type	Total # patients	#TAC, n	#DLI, n	Laparoscopic, %	Female, %	Age DLI vs. TAC	MINORS score
Juo et al	2019	2011-2015	Retrospective (NIS)	3021	2408	613	NR	57	60.4 vs. 68.2* (mean)	17
Hall et al	2018	2011-2016	Retrospective (ACS NSQIP)	457	410	47	64	57	64.8 vs. 65.4 (mean)	18
Ferrada et al	2017	2011-2014	Retrospective (multi-institutional)	98	77	21	NR	40	60.0 vs 65.0 (median)	16
Fashandi et al	2017	2011-2015	Retrospective (single institution)	23	13	10	70	61	59.7 vs. 63.2 (median)	15
Neal et al	2011	2009-2011	Prospective (single institution matched cohort)	84	42	42	83	45	65.3 vs. 62.1 (mean)	16

Abbreviations: NIS, National Inpatient Sample; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; NR, not reported; DLI, diverting loop ileostomy; TAC, total abdominal colectomy; MINORS, Methodological Index for Non-randomized Studies.
*Indicates where reported significant difference.

Fig. 2 Mortality. Random-effects meta-analysis comparing the 30-day mortality rate between diverting LI with colonic lavage and TAC

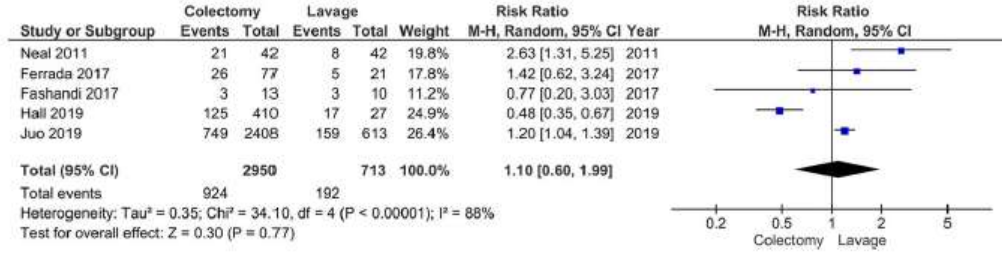


Fig. 3 Overall complication rate. Random-effects meta-analysis comparing the rate of overall postoperative complication between diverting LI with colonic lavage and TAC

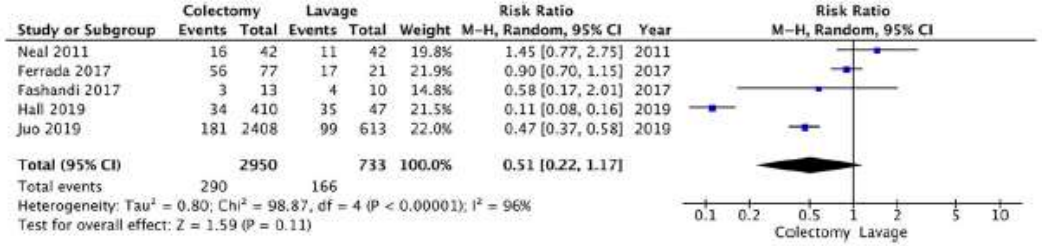
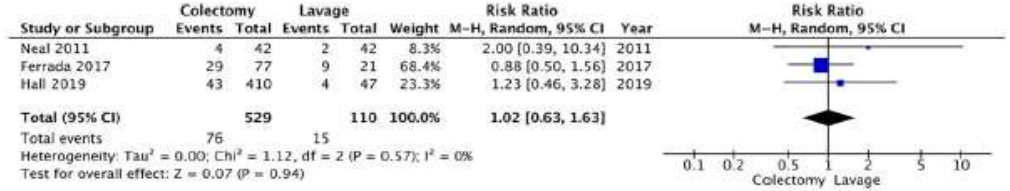


Fig. 4 Reoperation rate. Random-effects meta-analysis comparing the rate of required reoperation for diverting LI with colonic lavage



Conclusion There does not appear to be a survival advantage with the use of diverting loop ileostomy with colonic lavage compared to TAC for fulminant CDI. However, diverting loop ileostomy with colonic lavage results in increased rates of colonic preservation, restoration of intestinal continuity, and laparoscopic surgery. This review is limited by the small number of included studies.

DIVERTING LOOP ILEOSTOMY: FOCUS

Role of Surgery in *Clostridium difficile* Infection

Clinics in Colon and Rectal Surgery Vol. 33 No. 2/2020

Aela Vely, MD[1] Paula Ferrada, MD, FACS[1]

Who Is Not a Candidate for This Approach?

Patients with fulminant CDI and perforation or colon necrosis are not a candidate for LI since the entire point of this surgery is to preserve the colon. The presence of transmural necrosis and/or perforation indicates the infectious process is too advanced to offer colon presentation. These patients have an extremely high mortality and should undergo a subtotal colectomy.

It is also important to ensure the patient does not have a distal obstruction, since this would not allow the vancomycin to reach the entire colon. Patients with intra-abdominal hypertension should undergo an exploratory laparotomy and total colectomy and are not candidates for colon preservation.[24,25]

The approach can be either laparoscopic or open based on surgeon's preference and patient's capacity to tolerate insufflation. Hypovolemic patients or patients in shock can have further hypotension after the creation of pneumoperitoneum since the acute collapse of the inferior vena cava, decreased venous return, and acute decreased cardiac output. This can result in imminent cardiovascular deterioration. Each case needs to be considered separately.

Another anatomical consideration is the distention of the colon and the small bowel in severe cases. This can displace the location of the terminal ileum adding difficulty in doing the loop ileostomy via a small incision.

If colonic ischemia, obstruction, or perforation are noted, or if the patient's clinical status worsens, the procedure should be converted to a subtotal colectomy.

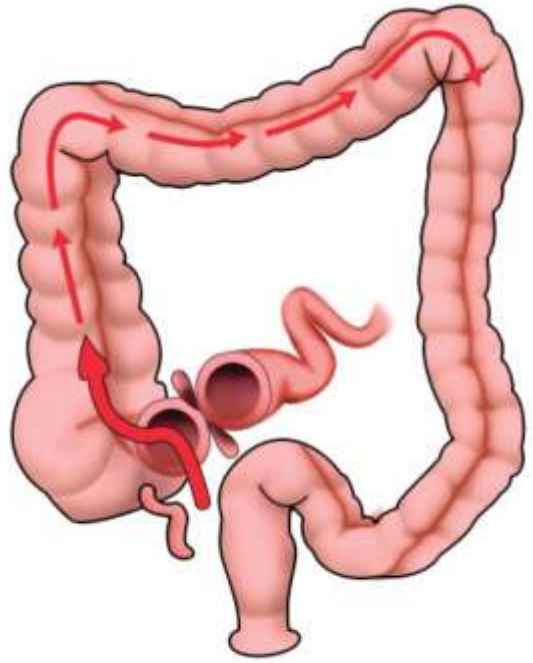


Fig. 2 Drawing showing the loop ileostomy and direction of the vancomycin enemas (By Paula Ferrada).

Failure of Loop Ileostomy

Several factors can be attributed to the failure of this procedure. Lack of adherence to the protocol or the prescience of a distal obstruction are two factors that can be corrected by the treating team.[26,27]

Hypervirulent strains of *Clostridium* and resistance to the treatment are other considerations.[28]

In our experience, when this procedure is performed patients start improving within 48 hours. If the patient is not responding to treatment considering an urgent total colectomy.

When to Reverse the Loop Ileostomy?

Ideally, the patient needs to be completely recovered from the initial physiological insult, tolerating regular diet and back to normal daily activities. It is important to discuss with the patient the risk of recurrence for fulminant CDI and, if this occurs, they could require a total colectomy. Some recurrences of CDI or reinfections can be seen when the continuity of the bowel is reestablished.[26–28] Fecal transplant could be a consideration before reanastomosis in these patients to help prevent recurrence.[29–31]

ROLE OF PROBIOTICS

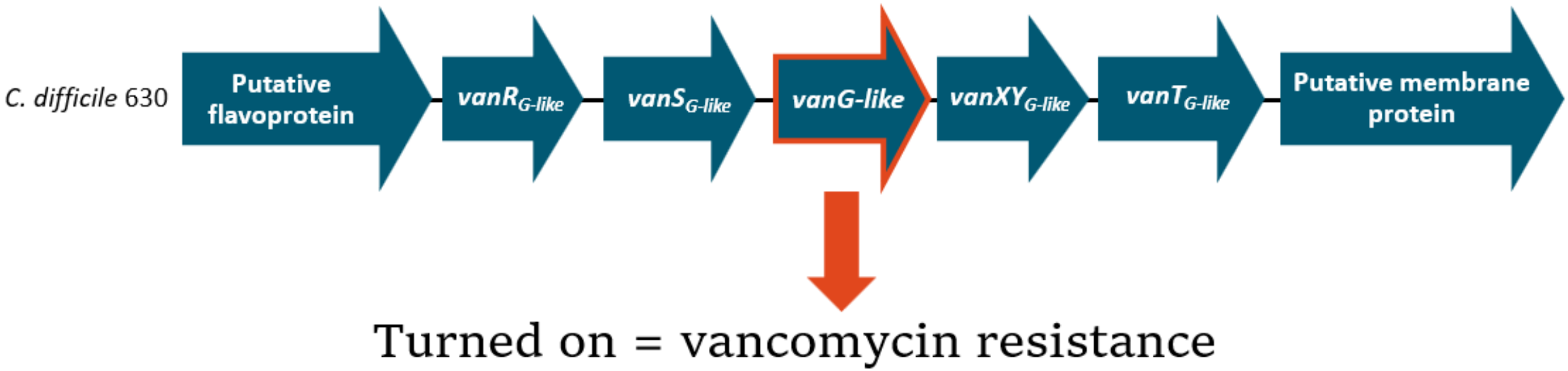
- Both ESCMID and ACG recommend against probiotic use to prevent CDI
- Probiotic use was not in the scope of the IDSA/SHEA focused update in 2021

ESCMID 2021	Strength/Quality	IDSA/SHEA 2021	Strength/Quality	ACG 2021	Strength/Quality
Recommend against	Strong/Low	No recommendation	No update from 2017 guidance, when there was insufficient evidence found	Recommend against	Conditional/moderate

Jones J, et al. Antibiotics (Basel). 2022;11:1247; Kelly CR, et al. Am J Gastroenterol. 2021;116:1124-1147.

RESISTANCE ISSUES: VANCOMYCIN

Approximately 85% of all *C. difficile* isolates have *vanG* gene cluster, usually silent (cryptic)



Shen. J Antimicrob Chemother. 2020;75:859. Ammam. Can J Microbiol. 2012;58:547.

VANCOMYCIN RESISTANCE: EXAMPLE

Clinical Infectious Diseases® 2022;74(1):120–6

Clinical Infectious Diseases

MAJOR ARTICLE

Emergence of Clinical *Clostridioides difficile* Isolates With Decreased Susceptibility to Vancomycin

Charles Darkoh,[1,2] Kadiatou Keita,[3] Chioma Odo,[2] Micah Oyaro,[4] Eric L. Brown,[1] Cesar A. Arias,[1,2,5] Blake M. Hanson,[1,5] and Herbert L. DuPont[1,2,6]

Methods. Stool samples from patients with CDI were collected from 438 and 98 patients at a large university hospital in Houston, Texas, and Nairobi, Kenya, respectively. The stools were examined for the presence of vancomycin and metronidazole nonsusceptible *C. difficile* using broth dilution culture, Etest (BioMérieux, France), polymerase chain reaction (PCR), whole-genome sequencing, and *in vivo* testing in a CDI mouse model.

Results. Of the Houston stool samples, 114/438 (26%) had vancomycin nonsusceptible *C. difficile* isolates and 128/438 (29%) were metronidazole nonsusceptible. Similarly, 66 out of 98 (67%) and 83/98 (85%) of the Nairobi patients harbored vancomycin and metronidazole nonsusceptible isolates, respectively. Vancomycin treatment of a CDI mouse model infected with a vancomycin nonsusceptible isolate failed to eradicate the infection. Whole-genome sequencing analyses did not identify *vanA* genes, suggesting a different mechanism of resistance.

Conclusions. *C. difficile* strains exhibiting reduced susceptibility to vancomycin are currently circulating in patient populations. The spread of strains resistance to vancomycin, a first-line antibiotic for CDI, poses a serious therapeutic challenge. Routine susceptibility testing may be necessary.

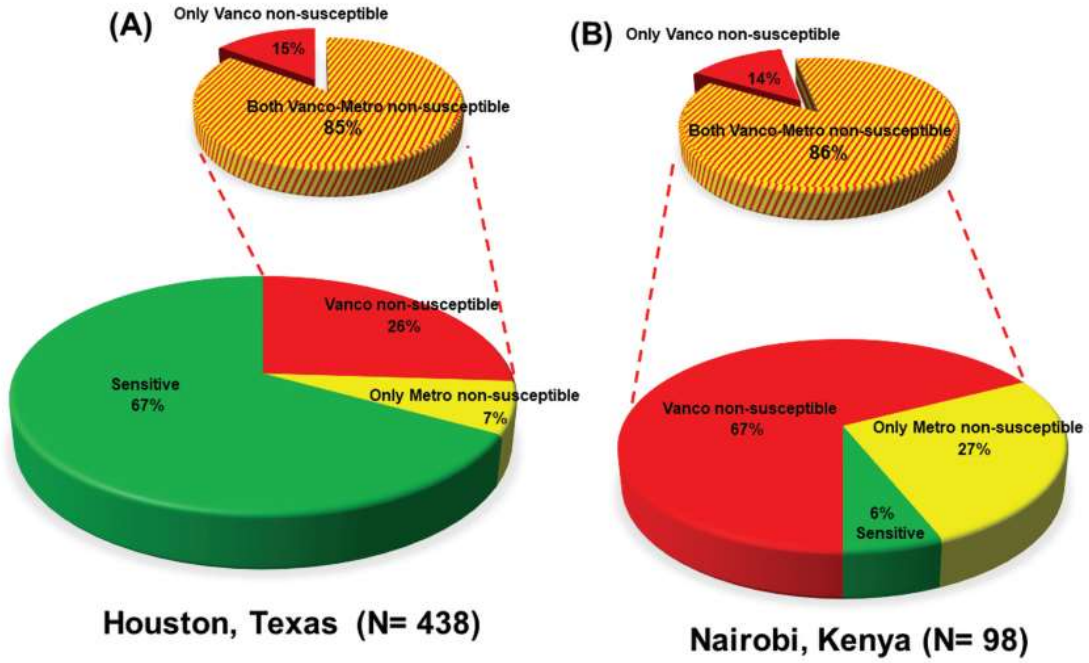


Figure 1. Emergence of metronidazole- and vancomycin nonsusceptible *Clostridioides difficile* isolates in patients from Houston, Texas (*A*), and Nairobi, Kenya (*B*). *Clostridioides difficile*–positive stools from patients with diarrhea were streaked on *C. difficile* medium containing either 8 µg/mL metronidazole or 4 µg/mL vancomycin based on published CLSI break-point concentrations [14–16]. The plates were incubated anaerobically at 37°C for 48 hours and stools that grew colonies were enumerated. Only Metro non-susceptible = stools that only grew metronidazole nonsusceptible isolates; Vanco non-susceptible = stools that grew vancomycin nonsusceptible isolates; Only Vanco non-susceptible = stools that grew only vancomycin nonsusceptible isolates; Both Vanco-Metro non-susceptible = stools that grew both metronidazole and vancomycin nonsusceptible isolates. Abbreviation: CLSI, Clinical and Laboratory Standards Institute.

RESISTANCE ISSUES: FIDAXOMICIN

- In vitro activities of 234 *C. difficile* isolates from 6 common or emerging ribotypes[1]
  - 4 isolates had fidaxomicin MIC of ≥4 µg/mL

MIC (µg/mL)	Eravacycline	Fidaxomicin	Metronidazole	Vancomycin
MIC_{50}	≤0.0078	0.016	0.25	2
MIC_{90}	0.016	0.0625	1	4

- Goldstein and colleagues reported single strain isolated from cured patient found to have elevated fidaxomicin MIC of 16 µg/mL[2]

Shen. J Antimicrob Chemother. 2020;75:859. Ammam. Can J Microbiol. 2012;58:547.

CDI STEP-DOWN THERAPY

- **Little guidance from current guidelines in determining treatment response**[1-3]
  - **ACG guidelines**: dose reduce oral vancomycin to 125 mg every 6 hr in case of "clinical improvement" after 48-72 hr and continue for 10 days[4]

Treatment Response (ESCMID Guidelines)[4]

- Resolution of diarrhea, with formed stool or "normal" stool at least 48 hr after EOT, ***and***
- No further CDI therapy, ***and***
- Parameters of severity have improved with no new signs of severe disease

- Assessing when patients meet criteria for step-down therapy is arbitrary[4]
- Consider evaluation of clinical, laboratory, and radiographic signs when determining timing of de-escalation of CDI therapies[4]

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

REDEFINING OUTCOMES IN CDI STUDIES

Redefining *Clostridioides difficile* infection antibiotic response and clinical outcomes

Anne J Gonzales-Luna, Andrew M Skinner, Carolyn D Alonso, Emilio Bouza, Oliver A Cornely, Tim G J de Meij, Richard J Drew, Kevin W Garey, Dale N Gerding, Stuart Johnson, Stacy A Kahn, Haru Kato, Ciaran P Kelly, Colleen R Kelly, Larry K Kociolek, Ed J Kuijper, Thomas Louie, Thomas V Riley, Thomas J Sandora, Maria J G T Vehreschild, Mark H Wilcox, Erik R Dubberke, The EXPAND Cdiff group

With the approval and development of narrow-spectrum antibiotics for the treatment of *Clostridioides difficile* infection (CDI), the primary endpoint for treatment success of CDI antibiotic treatment trials has shifted from treatment response at end of therapy to sustained response 30 days after completed therapy. The current definition of a successful response to treatment (three or fewer unformed bowel movements [UBMs] per day for 1–2 days) has not been validated, does not reflect CDI management, and could impair assessments for successful treatment at 30 days.

Lancet Infect Dis 2023
Published Online
April 13, 2023

Panel: Proposed outcome definitions for *Clostridioides difficile* infection (CDI) clinical trials

Initial response

- Any significant improvement in diarrhoea by day 2 after completion of primary CDI therapy plus investigator determination that CDI treatment can be stopped
- Improvement in diarrhoea measured as any one or more of the following: three or fewer unformed bowel movements per day; more than 50% reduction in number of stools; more than 75% decrease in stool volume (ostomy or rectal collection device); or attainment of bowel movements of Bristol Stool Form Scale types 1–4, on average

Sustained response

- Attained if initial response present with no need to retreat for CDI by day 30 after completion of primary CDI therapy

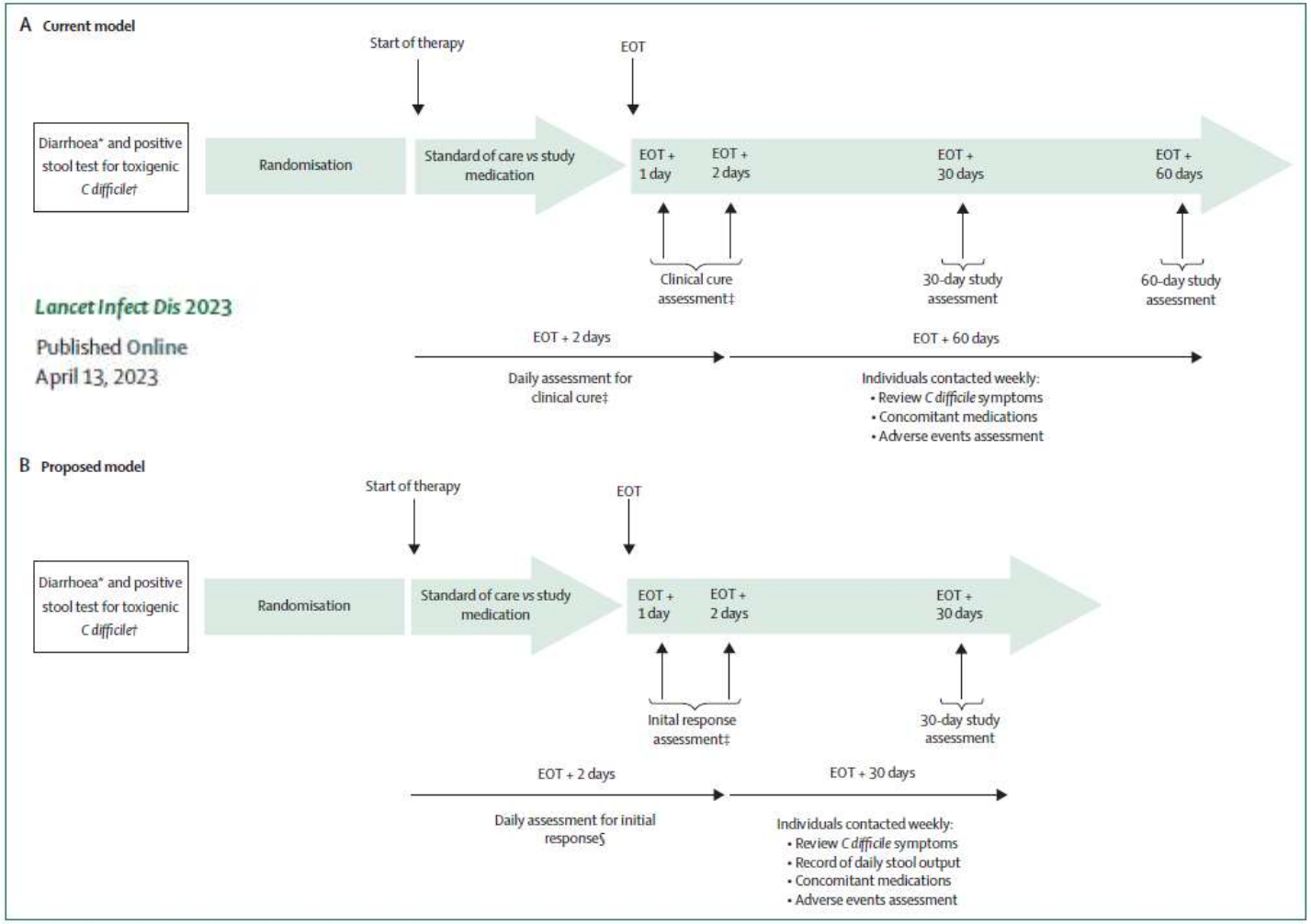


Figure: **Timeline of *Clostridioides difficile* infection outcome assessments for clinical trials**
CDI=*Clostridioides difficile* infection. EOT=end of treatment. *Diarrhoea defined as three or more loose stools in 24 h or fewer. †Diarrhoeal stool testing positive for toxigenic *C difficile*. Specimen collected within 48 h of randomisation and before anti-CDI treatment. ‡Clinical cure defined as resolution of diarrhoea (ie, three or fewer stools for 2 consecutive days) and maintenance of resolution requiring no further treatment for CDI within 2 days after completion of therapy. §Initial response defined as any significant improvement in diarrhoea (three or fewer unformed bowel movements per day, >50% reduction in unformed bowel movements per day, >75% decrease in stool volume for those with an ostomy, or attainment of bowel movements of Bristol Stool Form Scale types 1–4 on average) by day 2 after completion of CDI therapy.

WHEN CONSIDERING OTHER OUTCOMES

SYSTEMATIC REVIEW | ARTICLES IN PRESS

The Effect of Antibiotic Therapy for *Clostridioides difficile* Infection on Mortality and Other Patient-Relevant Outcomes: a Systematic Review and Meta-analysis

Yoav Stabholz • Mical Paul

Published: September 07, 2023 • DOI: https://doi.org/10.1016/j.cmi.2023.09.002

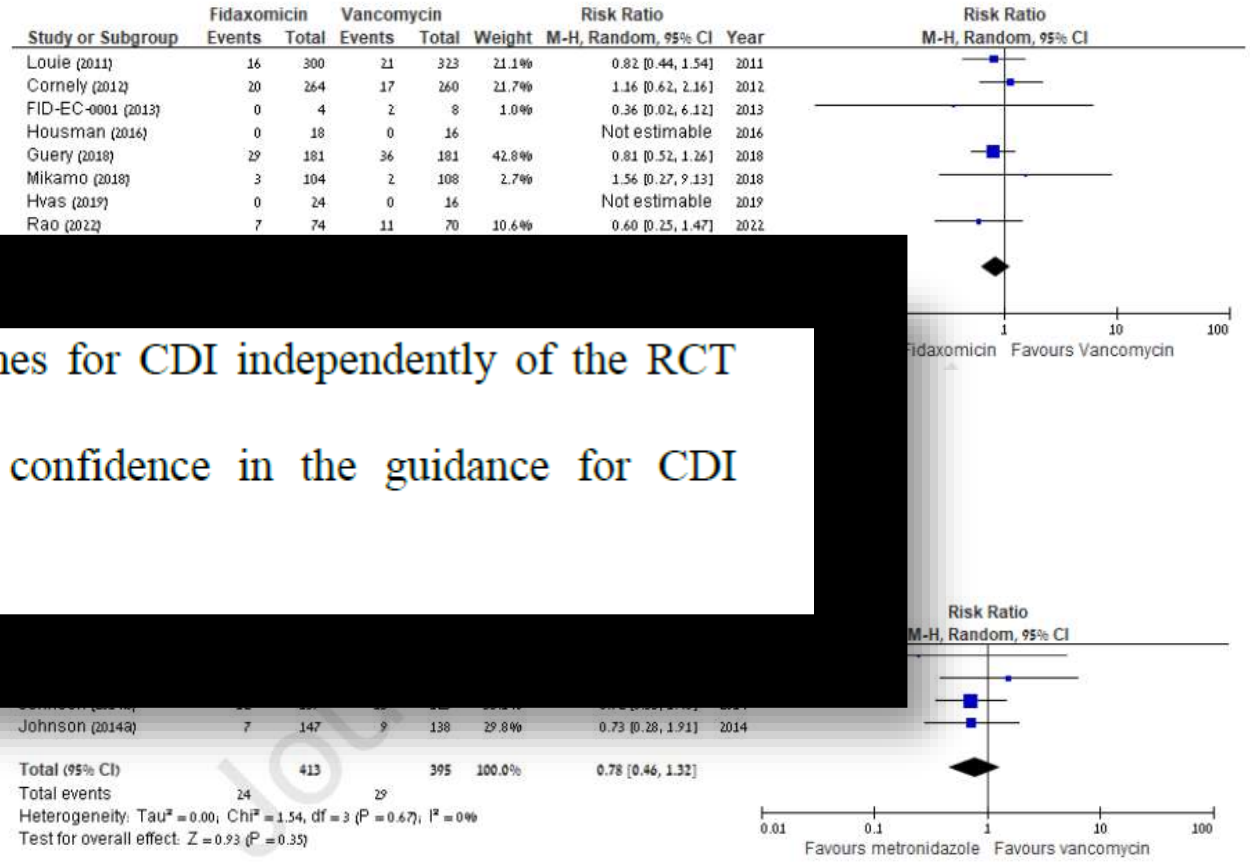
CMI CLINICAL MICROBIOLOGY AND INFECTION

Results: Thirteen trials were included. There was no significant difference in all-cause mortality (RR<1 fa
0.86, 95% CI 0.64
0.46 to 1.32, 4 R
respectively. No si
and vancomycin
metronidazole (RR
on symptomatic re
Among initially-cured patients, symptomatic recurrence necessitating re-treatment was lower with fidaxomicin than with vancomycin (RR 0.54, 95% CI 0.42 to 0.71, 6 RCTs, 1617 patients). None of the studies reported on other CDI complications or the burden of infection on daily activities.

Conclusions: Setting patient-relevant outcomes for CDI independently of the RCT definitions and results might lead to less confidence in the guidance for CDI management.

Figure 2: Forest plot of all-cause mortality

A. Fidaxomicin versus vancomycin



FOOD FOR THOUGHT

- Diagnostic stewardship: beware the abuse of molecular testing, especially syndromic panel testing.
- Future (or present?) nightmare: resistance to vancomycin and also fidaxomicin.
- Risk of VRE selection by vancomycin.
- Cost-effectiveness of fidaxomicin and bezlotoxumab.
- How to implement FMT therapy in routine practice.
- Use of artificial intelligence (e.g. machine learning) for prediction models.
- New drugs.

Table 5. Traditional antibacterials in clinical development for the treatment of CDIs

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Innovation			
					NCR	CC	T	MoA
Ridinilazole	3	Bis-benzimidazole	oral, not absorbed	Summit Therapeutics	✓	✓	✓	✓
CRS3123	2	Diaryldiamine	oral	Crestone/NIAID	✓	✓	✓	✓
DNV3837 (MCB-3837)	2	Oxazolidinone-quinolone hybrid	iv	Denove	?	-	-	-
Ibezapolstat (ACX-362E)	2	DNA polymerase IIIC inhibitor	oral, not absorbed	Acurx Pharmaceuticals	?	✓	✓	✓
MGB-BP-3	2	Distamycin (DNA minor groove binder)	oral, not absorbed	MGB Biopharma	?	✓	✓	✓

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data; - criterion not fulfilled.

CC: chemical class; CDIs: *C. difficile* infections; Iv: intravenous; MoA: new mode of action; NCR: no cross-resistance; NIAID: National Institute of Allergy and Infectious Diseases; T: new target.

World Health Organization

THANKS FOR YOUR ATTENTION