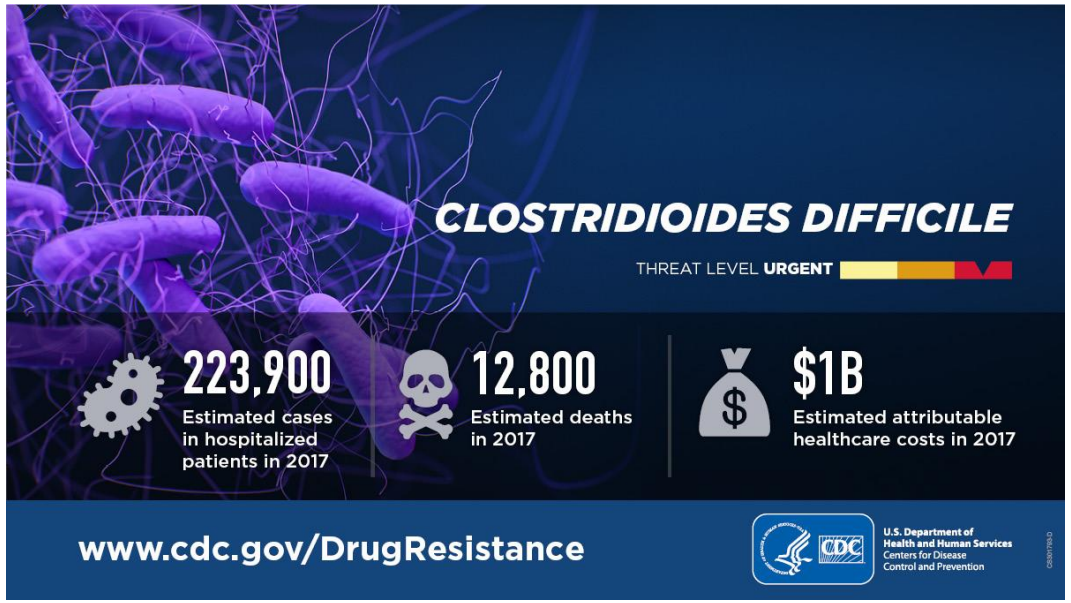
Ore 14.00-15.30	**INFEZIONI BATTERICHE E FUNGINE** Moderatore: CM. Mastroianni (Roma)
Ore 14.00-14.20	**Gestione e opzioni terapeutiche per le infezioni di cute e tessuti molli** C. Tascini (Udine)
Ore 14.20-14.40	**Infezioni da batteri gram negativi MDR: *place in context* delle nuove opzioni terapeutiche** M. Falcone (Pisa)
Ore 14.40-15.00	**Infezione da *Clostridioides difficile:* gestione terapeutica** A. Cascio (Palermo)
Ore 15.00-15.20	**Nuove opzioni terapeutiche nelle infezioni fungine invasive** F. Barchiesi (Pesaro)
Ore 15.20-15.50	**Discussione**



Infezione da Clostridioides difficile: gestione terapeutica

Antonio Cascio

Università di Palermo

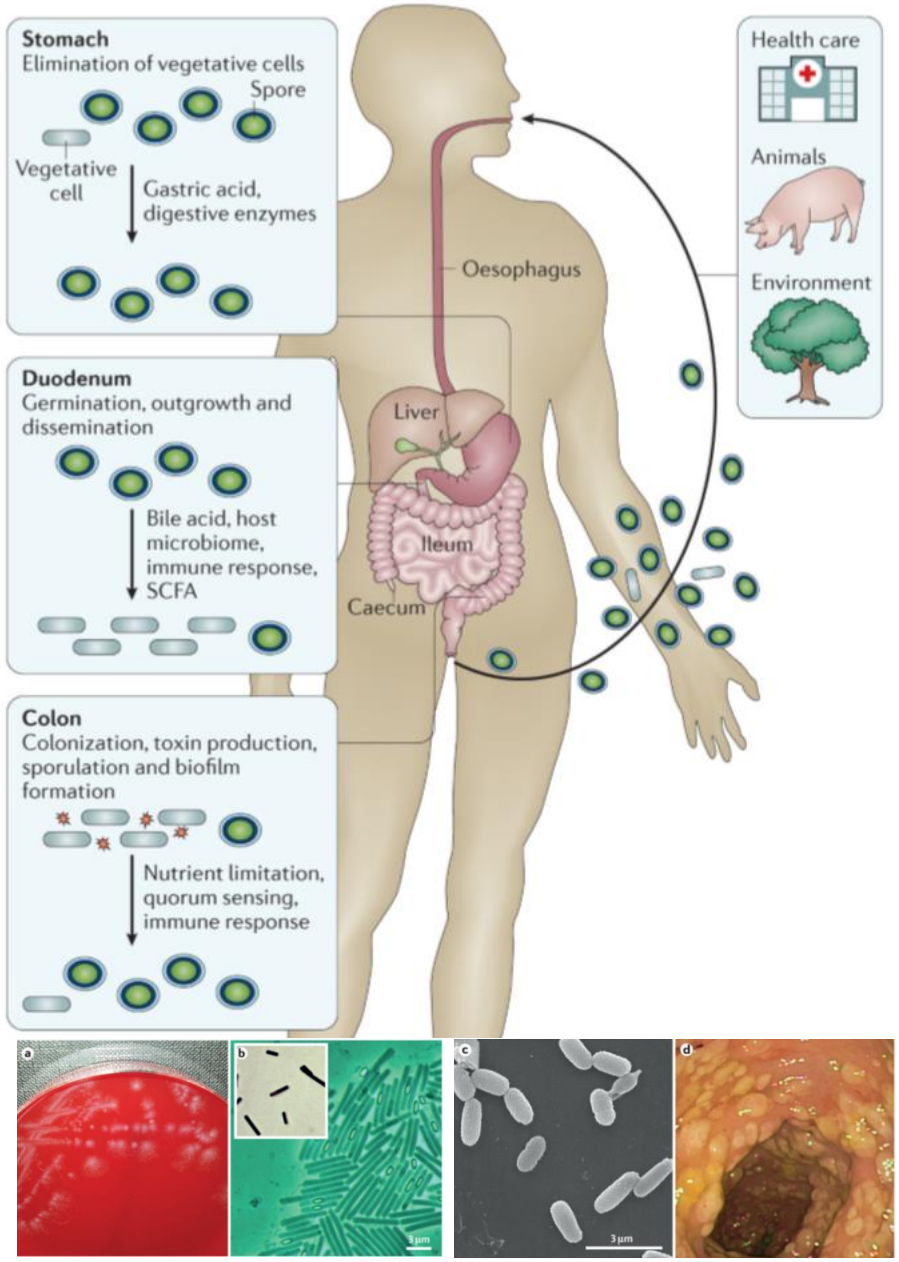
In questa slide in relatore dovrà dichiarare il conflitto d'interessi ed indicare:

Il sottoscritto **Cascio Antonio**
in qualità di (moderatore, relatore, formatore, tutor, docente)

ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
(PFIZER, GILEAD, JANSSEN, MSD, TILLOTS, ViiV)

Nat Rev Dis Primers. ; 2: 16020. doi:10.1038/nrdp.2016.20.



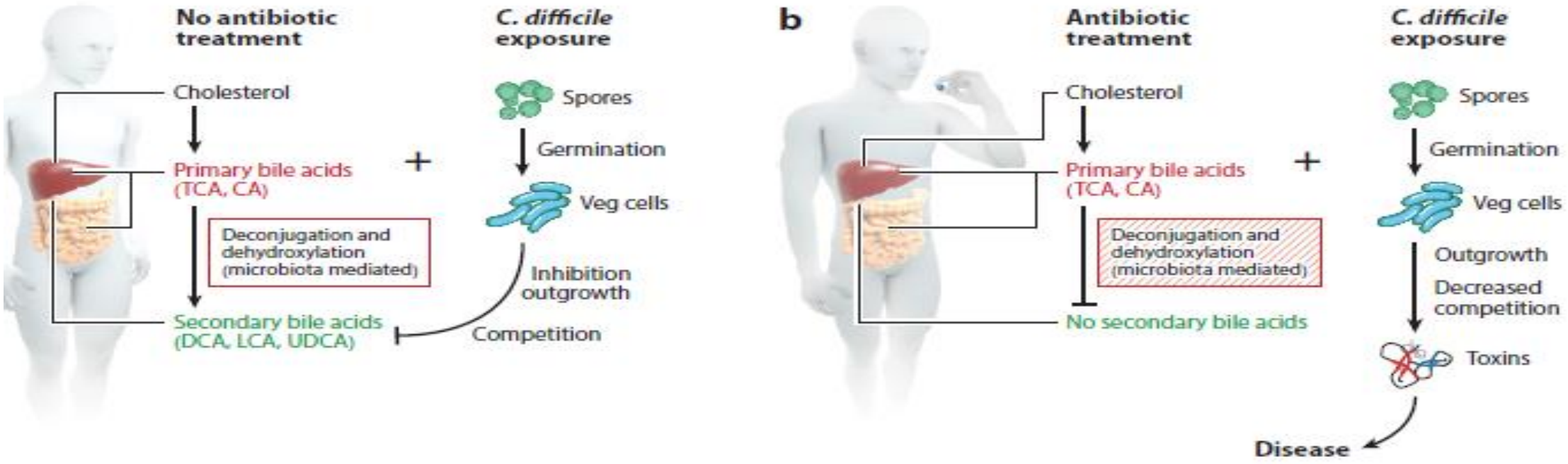
C. difficile is an **obligate anaerobic Gram positive bacterium**, transmission occurs primarily via **spores**.

Passage through the **stomach eliminates most vegetative cells** (but spores survive), and **spores germinate and grow out in the duodenum**.
In the caecum and colon, C. difficile starts producing spores again, and vegetative cells are excreted by the patient during infection.
Toxin is produced in the colon

C. difficile forms spores that are resistant to heat, oxygen and common disinfectants, such as ethanol-based hand sanitizers

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
Hand Hygiene in Healthcare Settings

Antibiotic-induced alterations in gut microbial metabolism decrease colonization resistance against *C. difficile*



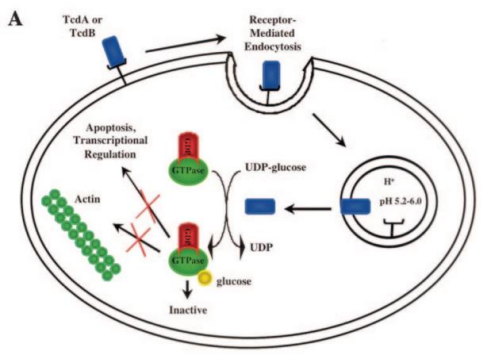
- Antibiotic treatment alters the gut microbiota structure, specifically decreasing bacteria that are able to deconjugate and dehydroxylate primary bile acids into secondary bile acids.
- **The loss of secondary bile acid** metabolism and competition from the gut microbiota allow for *C. difficile* outgrowth, toxin production, and disease.

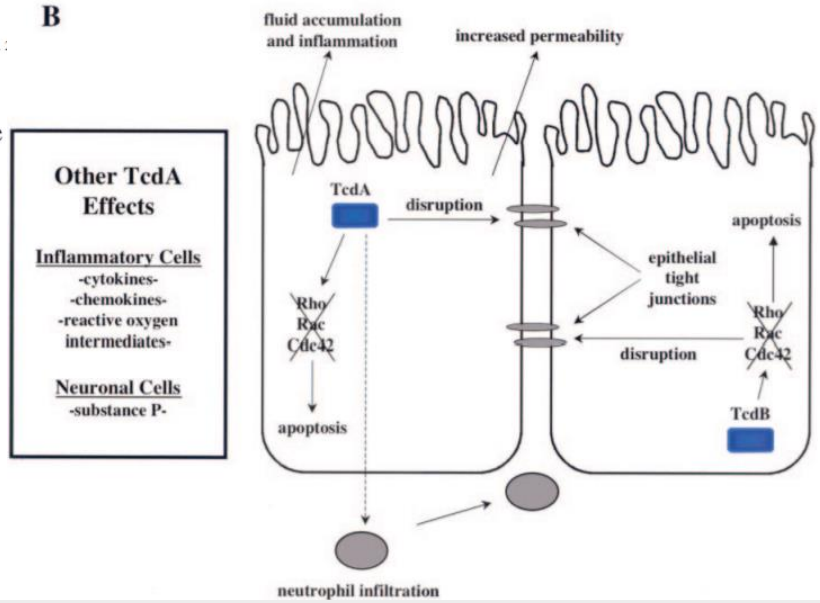
CLINICAL MICROBIOLOGY REVIEWS, Apr. 2005, p. 247–263
0893-8512/05/$08.00+0 doi:10.1128/CMR.18.2.247–263.2005

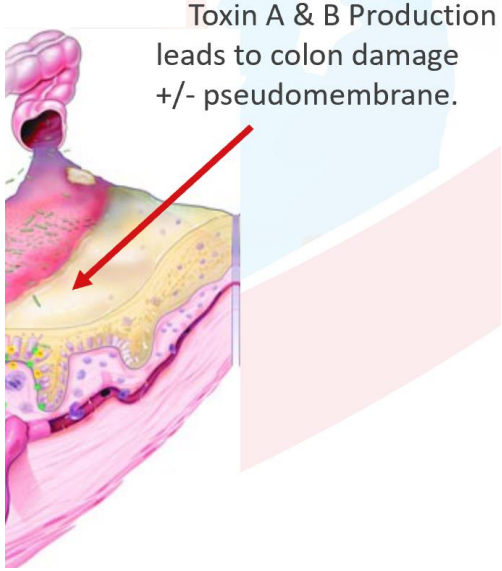
Vol. 18, No. 2

Clostridium difficile Toxins: Mechanism of Action and Role in Disease

Daniel E. Voth and Jimmy D. Ballard*







(A) Both TcdA and TcdB act intracellularly as glycosyltransferases. Each toxin modifies and inactivates Rho, Rac, and Cdc42 via transfer of a sugar moiety, with UDP-glucose as a cosubstrate. The effects of these modifications include **actin condensation, transcriptional activation, and apoptosis**.

(B) Exposure of intestinal epithelial cells to **TcdA** leads to **neutrophil infiltration, substance P production, chemokine production, reactive oxygen intermediate production, disruption of tight junctions, and apoptosis**.

(C) TcdB activity leads to disruption of tight junctions and apoptosis. A combination of one or more of these activities leads to fluid accumulation in the host and inflammatory responses.

Some strains, including the more virulent ribotypes 027 and 078, also produce a third toxin, termed **binary toxin or CD transferase CDT)**.

CDT is suggested to cause **microtubule-based protrusions on epithelial cells, thereby increasing the adherence of CD to target cells**

Infection (2021) 49:1221–1229
https://doi.org/10.1007/s15010-021-01683-w

ORIGINAL PAPER

An emergent infectious disease: *Clostridioides difficile* infection hospitalizations, 10-year trend in Sicily

Alice Annalisa Medaglia[1] · Sergio Buffa[2] · Claudia Gioè[1] · Silvia Bonura[1] · Raffaella Rubino[1] · Chiara Iaria[3] · Claudia Colomba[1,4] · Antonio Cascio[1,4]

Received: 6 June 2021 / Accepted: 9 August 2021 / Published online: 8 September 2021

- Results **1139 cases** of CDI were identifed. 97% were adults with a **median age of 73.2 years** and a male-to-female ratio of 1:1.4. Female patients were older than males and patients who died were older than patients who did not. The main comorbidities were renal disease, diabetes, pneumonia and hypertension. There were 65 reporting hospitals and 86% of cases were provided by level III and II hospitals.
- **Between 2009 and 2019, the incidence increased 40-fold**. 81.5% of cases were reported in Medicine Units, Infectious Diseases Units and long-term care facilities. The mean length of stay was 20 days. Mean case fatality rate was 8.3% over the 10-year period

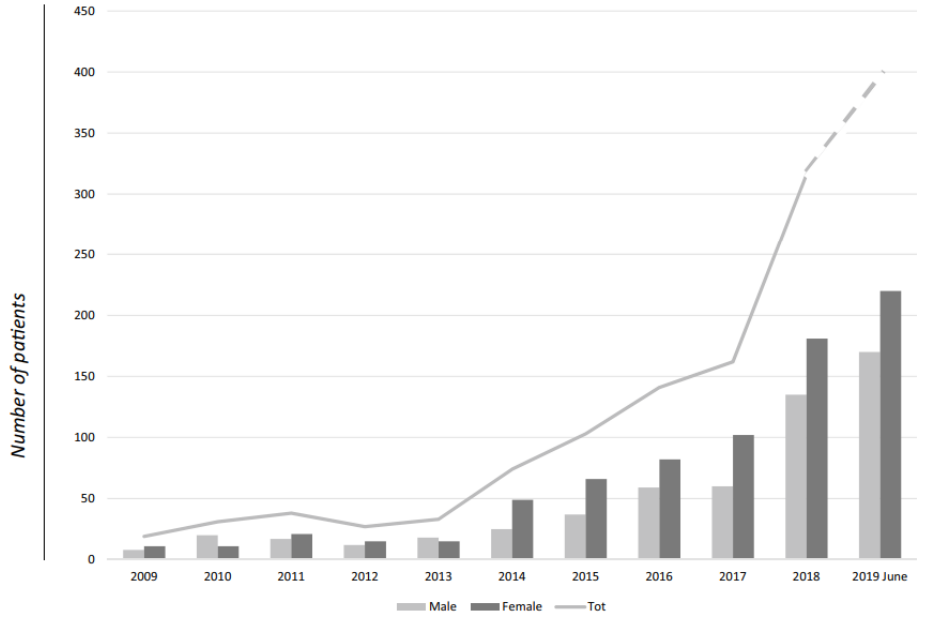


Fig. 2 Number of reported CDI cases per year (line), and number of male vs female cases per year (columns), between February 2009 and Jun 2019 in Sicily. The dotted line indicates the trend for the second half of 2019

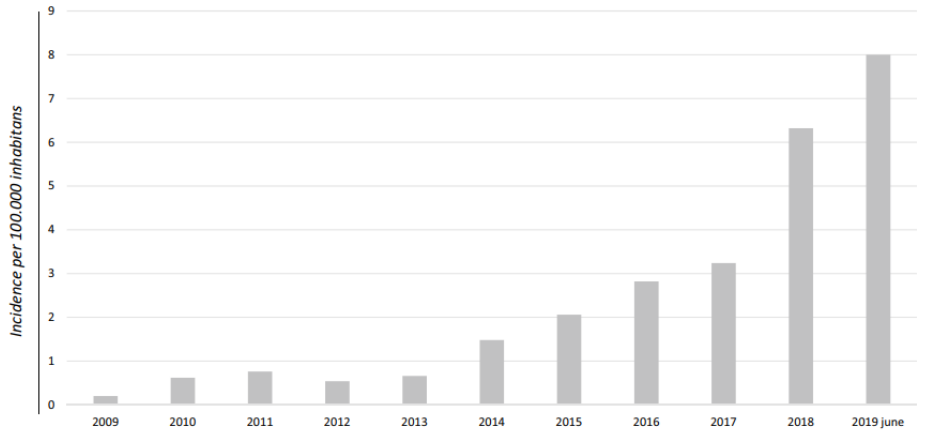


Fig. 3 CDI incidence per 100,000 inhabitants per year between February 2009 and June 2019 in Sicily

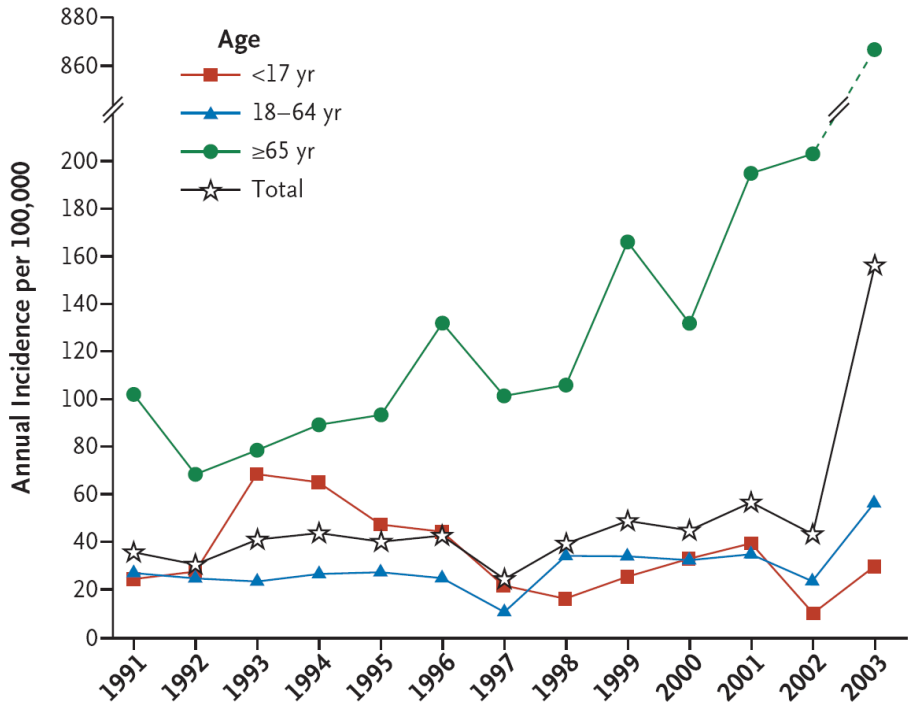
REVIEW ARTICLE

CURRENT CONCEPTS

Clostridium difficile — More Difficult Than Ever

Ciarán P. Kelly, M.D., and J. Thomas LaMont, M.D.

Figure 1. Annual Incidence (per 100,000 Population) of *C. difficile* Infection in Sherbrooke, Quebec, 1991–2003.



SURVEILLANCE

Epidemiology of *Clostridioides difficile* infections, France, 2010 to 2017

Mélanie Colomb-Cotinat[1,2], Laetitia Assouvie[1,2], Julien Durand[1], Côme Daniau[1], Lucie Leon[1], Sylvie Maugat[1], Sophan Soing-Altrach[1], Cécile Gateau[3], Jeanne Couturier[3], Isabelle Arnaud[4], Pascal Astagneau[4], Anne Berger-Carbonne[1], Frédéric Barbut[3]

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3. National reference laboratory for anaerobic bacteria and C. difficile, St Antoine Hospital, Paris, France
4. Regional center for prevention of healthcare associated infections, Paris, France

Correspondence: Mélanie Colomb-Cotinat (melanie.colomb-cotinat@santepubliquefrance.fr)

Di Bella et al. BMC Infectious Diseases 2013, 13:146
http://www.biomedcentral.com/1471-2334/13/146

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Clostridium difficile infection in Italian urban hospitals: data from 2006 through 2011

Stefano Di Bella[1], Maria Musso[1], Maria A Cataldo[1], Marcello Meledandri[2], Eugenio Bordi[1], Daniela Capozzi[3], Maria C Cava[4], Patrizia Chiaradonna[5], Grazia Prignano[6] and Nicola Petrosillo[1*]

Infezione da *Clostridium difficile* a Roma - 5 ospedali, 2.677 posti letto, media di 15.481 ricoveri/anno. Dati osservati dal 2006 al 2011

- Numero di CDI: 402 / 4.951 campioni analizzati per la ricerca di tossine CD in sei anni (166 solo nel 2011)
- aumento notevole di anno in anno (**2,3 episodi di CDI per 10.000 giorni/paziente nel 2011 con un valore massimo di 4.0/10.000 giorni/paziente in un ospedale)**

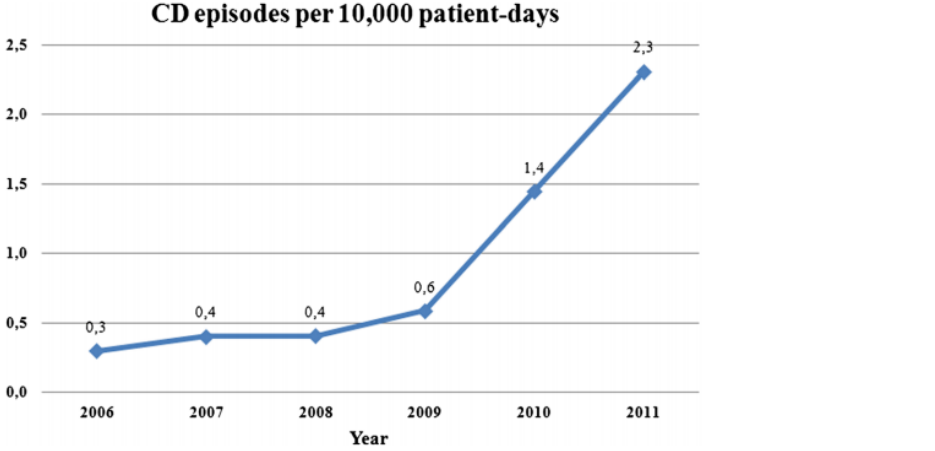


Figure 1 Distribution of Clostridium difficile infection (CDI) episode incidence per 10,000 patient-days from 2006 to 2011. Six hospitals in Rome, Italy.

- **La più alta percentuale di episodi CDI è stata riscontrata nei reparti di Chirurgia**, seguita dal reparto di **Medicina Interna** e Unità di **Terapia Intensiva**

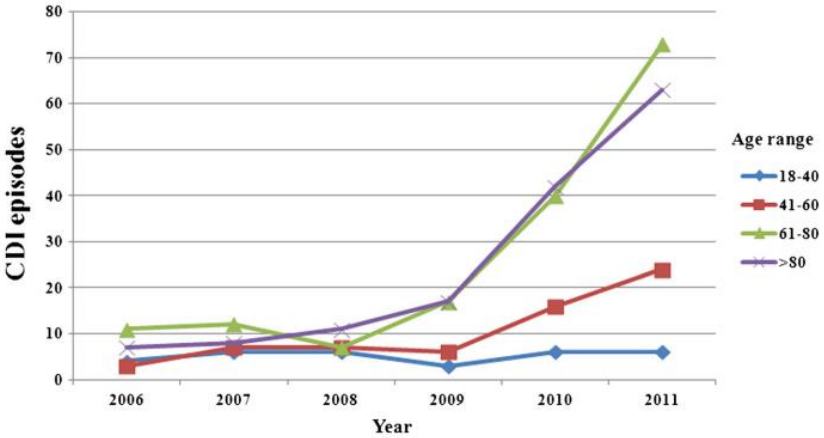


Figure 2 Clostridium difficile infection (CDI) episodes by year and age group.

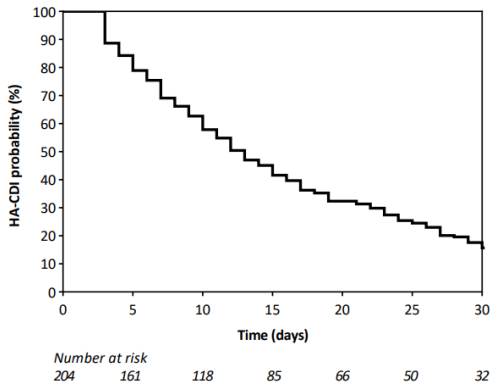
antibiotics

MDPI

Article

Clostridioides difficile Infection in an Italian Tertiary Care University Hospital: A Retrospective Analysis

Alice Annalisa Medaglia [1,2,*], Alessandro Mancuso [3], Chiara Albano [3], Giuseppe Zinna [3], Luca Pipitò [3], Cinzia Calà [3,4], Rita Immordino [4], Raffaella Rubino [1,2], Silvia Bonura [1,2], Baldassare Canino [3], Giuseppe Calamusa [2,3], Claudia Colomba [3], Pier Luigi Almasio [3] and Antonio Cascio [1,2,3]



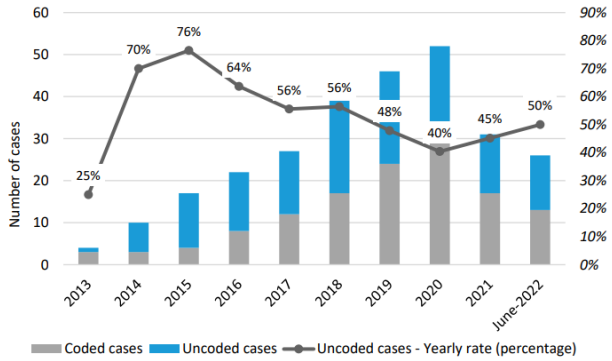
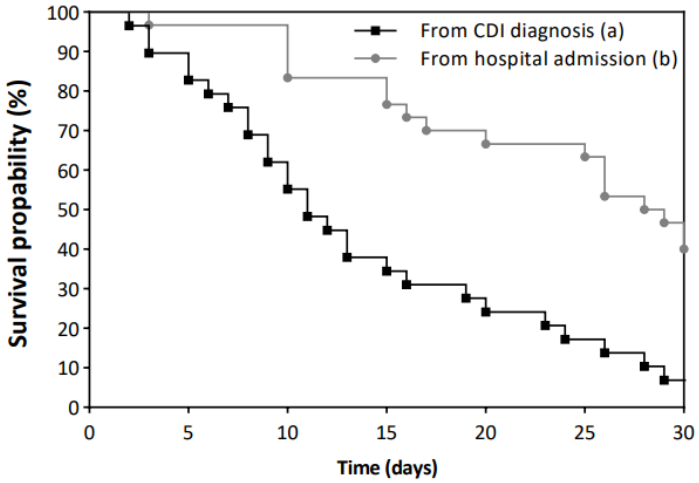


Figure 3. Time elapsed between hospital admission and CDI onset for HA-CDI cases.



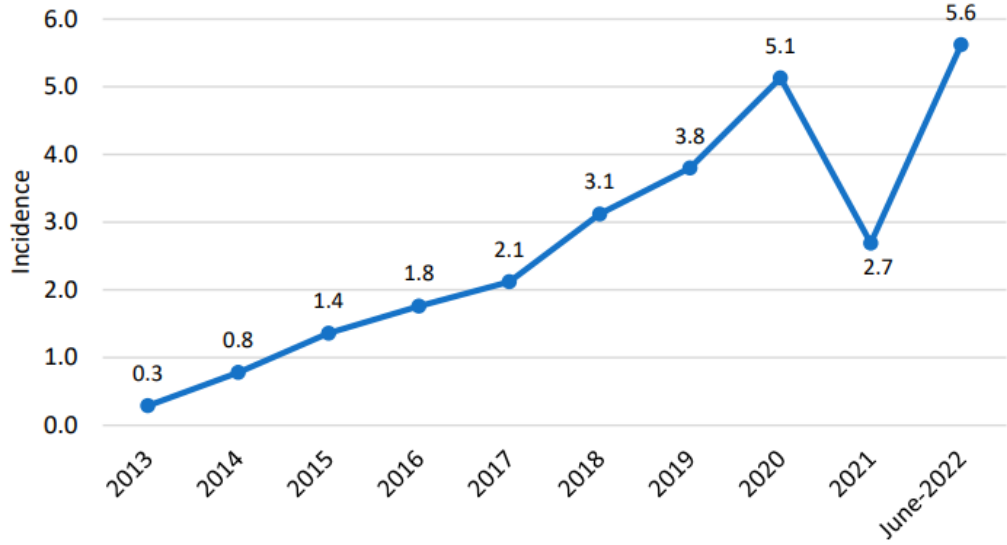


Figure 1. CDI incidence per 10,000 patient days.

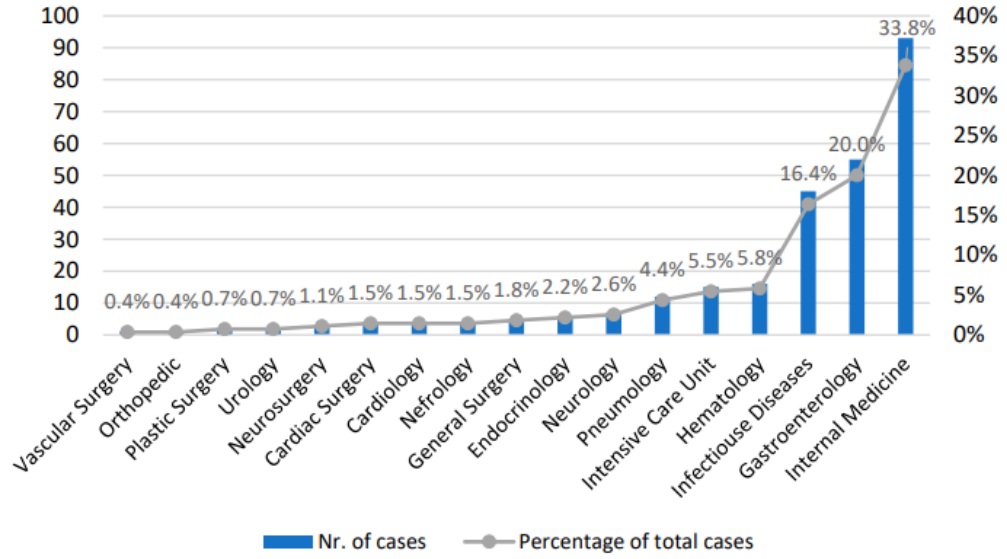


Figure 2. CDI cases by hospital wards.

Anaerobe 70 (2021) 102380

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Clostridioides difficile (including epidemiology)

Hospitalized patients with diarrhea: Rate of *Clostridioides difficile* infection underdiagnosis and drivers of clinical suspicion

Maria Adriana Cataldo [a, *], Guido Granata [a], Silvia D'Arezzo [a], Gilda Tonziello [a], Antonella Vulcano [a], Chiara De Giuli [a], Marcello Meledandri [b], Antonino Di Caro [a], Nicola Petrosillo [a]

[a] National Institute for Infectious Diseases "Lazzaro Spallanzani", Via Portuense, 292-00149, Rome, Italy
[b] San Filippo Neri Hospital, Via Giovanni Martinotti, 20-00135, Rome, Italy

Main objectives of our study were**: to assess the frequency of diarrhea of overall etiology, including CDI, as a cause of hospital admission or occurring during hospital stay;- to determine the rate of underdiagnosis of community-acquired (CA-), health care associated (HCA)- and hospital onset (HO-) CDI, and explore factors associated with its clinical suspicion by physicians**.

Methods: **A prospective cohort study included all hospitalized patients with diarrhea at two acute-care hospitals. C. difficile (CD) tests were performed on every stool samples, irrespective of the treating physician request.**

Results: We enrolled 871 (6%) patients with diarrhea. CD test performed on all diarrheic stool samples was positive in 228 cases (26%); 37, 106, 85 cases of CA- (14%), HCA- (42%) and HO- diarrhea (24%), respectively. Treating physicians did not request CD test in 207 (24%) diarrhea cases. **The rate of CDI underdiagnosis was 11% (24/228)**; it was higher **in CA-CDI (27%,** 10/37). Logistic regression analysis
identified age >65 years (RR 1.1; 95 CI 1.06e1.2) and hospitalizations in the previous 3 months (RR 1.2; 95% CI 1.1e1.3) as independent factors associated with the likelihood of requesting the CD test by the physician.

Rate of CDI underdiagnosis by epidemiological classification of CDI and participating hospital.

Hospital	CDI underdiagnoses/total CDI (%)	CA-CDI underdiagnoses/total CDI (%)	HCA-CDI underdiagnoses/total CDI (%)	HO-CDI underdiagnoses/total CDI (%)
INMI	7/117 (6)	4/16 (25)	1/66 (2)	2/35 (6)
SFN	17/111 (15)	6/21 (29)	5/40 (13)	6/50 (12)

animals

MDPI

Article

Clostridioides difficile in Calves in Central Italy: Prevalence, Molecular Typing, Antimicrobial Susceptibility and Association with Antibiotic Administration

Francesca Blasi [1], Carmela Lovito [2], Elisa Albini [1], Luca Bano [3], Gastone Dalmonte [4], Ilenia Drigo [3], Carmen Maresca [1], Francesca Romana Massacci [1], Serenella Orsini [1], Sara Primavilla [1], Eleonora Scoccia [1], Silvia Tofani [5], Claudio Forte [6,*] and Chiara Francesca Magistrali [1]

- This study aimed to assess the prevalence and risk factors of C. difficile in calves bred in dairy and beef cattle farms of the Umbria, central Italy.
- **We estimated a 19.8% prevalence of farms positive for C. difficile**.
- The C. difficile isolates from calves were potentially toxigenic and resistant to antibiotics, including lincosamides, quinolones, vancomycin and linezolid.
- Isolates belonging to ribotype RT-126, which is also commonly reported in humans, showed the highest number of resistance to the antimicrobials tested. Furthermore, we observed an almost **sixfold increased risk for C. difficile on farms where penicillins had been prescribed.**
- This, together with the detection of toxigenic and antibiotic-resistant isolates, strongly suggests the need for a reduction of antibiotic use in cattle.

frontiers in Veterinary Science

REVIEW
published: 18 September 2020
doi: 10.3389/fvets.2020.512551

Prevalence, Colonization, Epidemiology, and Public Health Significance of *Clostridioides difficile* in Companion Animals

Belen G. Hernandez[1], Akhil A. Vinithakumari[1], Brett Sponseller[2], Chandra Tangudu[2] and Shankumar Mooyottu[1]*

- The detection of genetically similar and toxigenic *C. difficile* isolates in companion animals, including **asymptomatic pets**, suggests the potential role of household pets as a source of community-associated CDI.
- The close association between companion animals and humans, in addition to the **use of similar antibiotics in both species, could provide a selective advantage for the emergence of new *C. difficile* strains** and thus increase the incidental transmission of CDI to humans. Therefore, screening household pets for *C. difficile* is becoming increasingly important from a public health standpoint and may become a part of routine testing in the future, for the benefit of susceptible or infected individuals within a household.
- The mosaic nature of *C. difficile* genomes and their susceptibility to horizontal gene transfer may facilitate the inter-mixing of genetic material, which could increase the possibility of the emergence of new community-associated CDI strains.

Open Forum Infectious Diseases
MAJOR ARTICLE

Comparison of Different Antibiotics and the Risk for Community-Associated *Clostridioides difficile* Infection: A Case–Control Study

Aaron C. Miller,[1] Alan T. Arakkal,[2] Daniel K. Sewell,[2] Alberto M. Segre,[3] Joseph Tholany,[1] and Philip M. Polgreen,[1] CDC MInD-Healthcare Group

[1]University of Iowa, Carver College of Medicine, Iowa City, Iowa, USA, [2]University of Iowa, College of Public Health, Iowa City, Iowa, USA, and [3]Department of Computer Science, University of Iowa, Iowa City, Iowa, USA

- We conducted a matched case–control study using a large database of insurance claims capturing longitudinal health care encounters and medications. Case patients with **community-associated CDI** were matched to 5 control patients by age, sex, and enrollment period. Antibiotics prescribed within 30 days before the CDI diagnosis along with other risk factors, including comorbidities, health care exposures, and gastric acid suppression were considered.

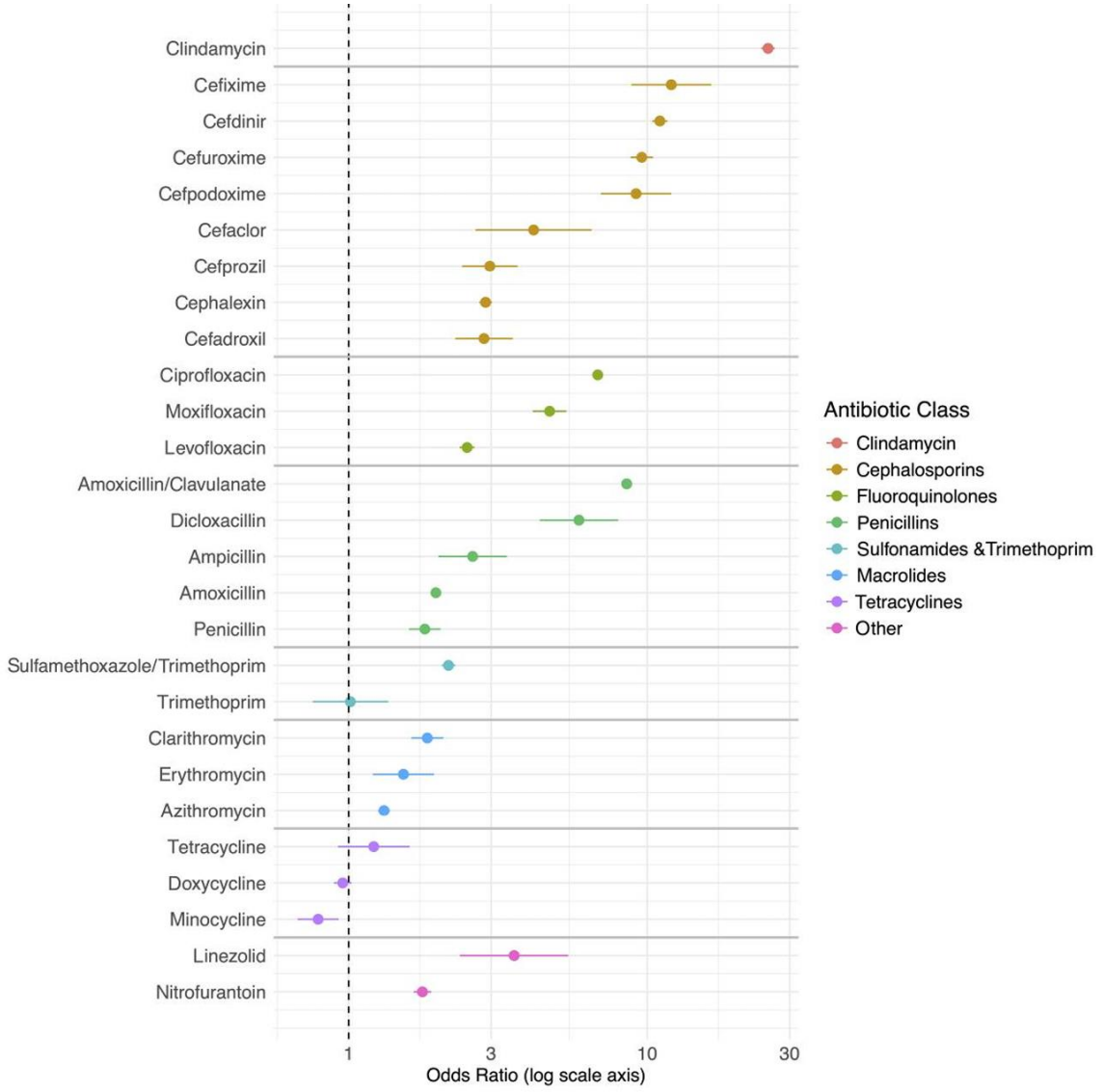


Figure 1. Visual comparison of effect estimates across antibiotic types, grouped by antibiotic class. Point estimates are depicted by the circle and 95% credible intervals by the line segments. Exact values can be found in Table 2.

Journal of *Clinical Medicine*

MDPI

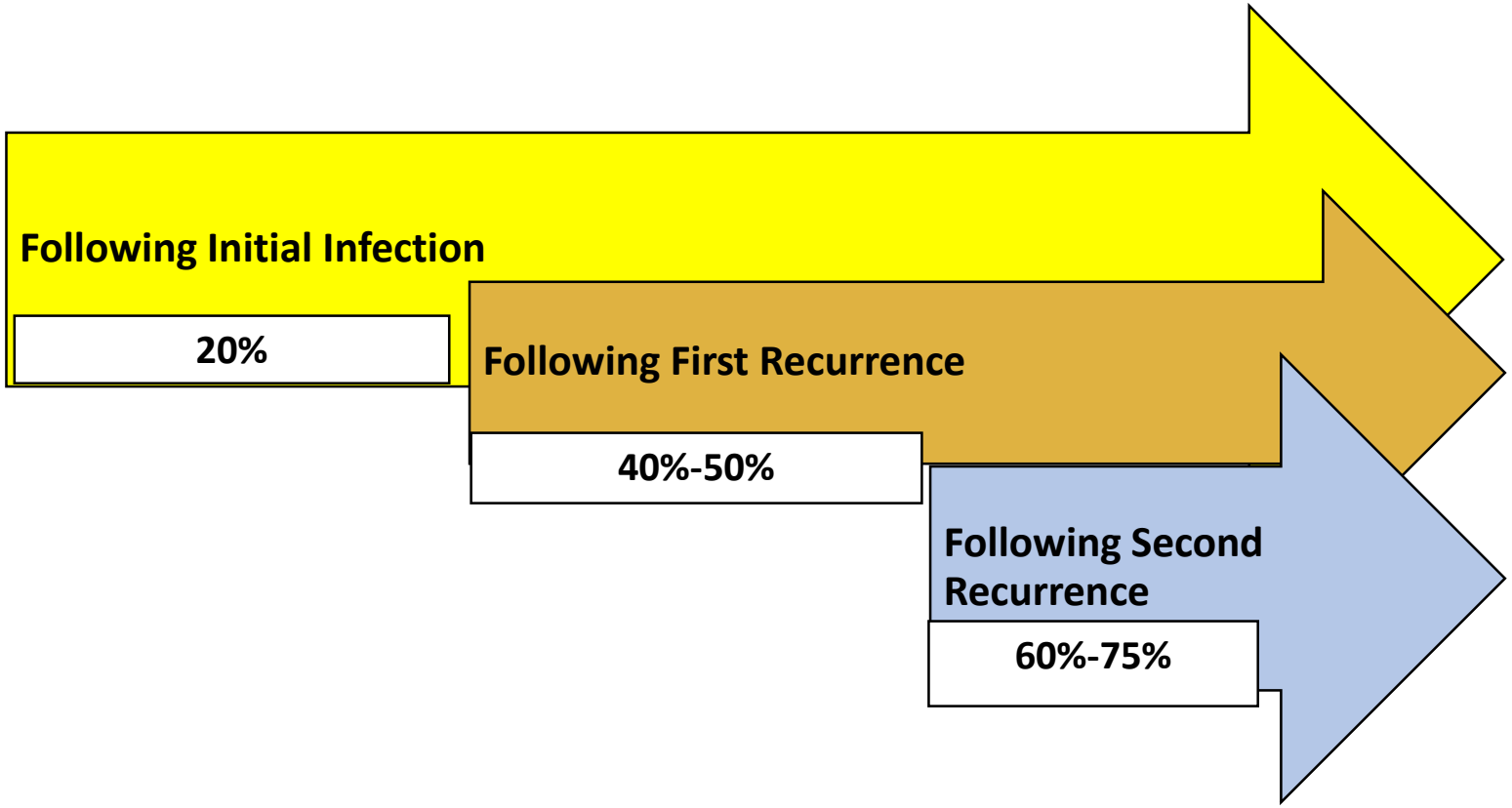
Article

Prospective Study on Incidence, Risk Factors and Outcome of Recurrent *Clostridioides difficile* Infections

Guido Granata [1], Nicola Petrosillo [1,*], Lucia Adamoli [2], Michele Bartoletti [3], Alessandro Bartoloni [4], Gregorio Basile [4], Matteo Bassetti [5,6,7], Paolo Bonfanti [8], Raffaella Borromeo [9], Giancarlo Ceccarelli [10], Anna Maria De Luca [2], Stefano Di Bella [11], Sara Fossati [11], Erica Franceschini [12], Ivan Gentile [13], Daniele Roberto Giacobbe [5,6], Enrica Giacometti [7], Fabrizio Ingrassia [9], Filippo Lagi [4], Giambattista Lobreglio [14], Andrea Lombardi [15], Laura Isabella Lupo [14], Roberto Luzzati [11], Alberto Enrico Maraolo [13], Malgorzata Mikulska [5,6], Mario Umberto Mondelli [15], Alessandra Mularoni [2], Cristina Mussini [12], Alessandra Oliva [10], Alessandro Pandolfo [16], Carlotta Rogati [12], Filippo Fabio Trapani [3], Mario Venditti [10], Pierluigi Viale [3], Emanuela Caraffa [1], Maria Adriana Cataldo [1] and on behalf of the ReCloDi (Recurrence of Clostridioides difficile Infection) Study Group [†]

- We performed a cohort study with the **aim to assess the incidence of and risk factors for rCDI**.
- Adult patients with a first CDI, hospitalized in **15 Italian hospitals**, were prospectively included and **followed-up for 30 d after the end of antimicrobial treatment for their first CDI**.
- **A case–control study was performed to identify risk factors associated with 30-day onset rCDI**.
- Results: Three hundred nine patients with a first CDI were included in the study; 32% of the CDI episodes (99/309) were severe/complicated; **complete follow-up was available for 288 patients** (19 died during the first CDI episode, and 2 were lost during follow-up). At the end of the study, **the crude all-cause mortality rate was 10.7%** (33 deaths/309 patients). Two hundred seventy-one patients completed the follow-up; **rCDI occurred in 21% of patients (56/271) with an incidence rate of 72/10,000 patient-days**.
- Logistic regression analysis identified exposure to cephalosporin as an independent risk factor associated with rCDI (RR: 1.7; 95% CI: 1.1–2.7, p = 0.03).

Risk of recurrent *Clostridium difficile* infection



Kelly et al, N Engl J Med 2008; 359:1932-40

Clinical Microbiology and Infection 27 (2021) S1–S21

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

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

Joffrey van Prehn [1], Elena Reigadas [2], Erik H. Vogelzang [3], Emilio Bouza [2], Adriana Hristea [4], Benoit Guery [5], Marcela Krutova [6], Torbjorn Norén [7], Franz Allerberger [8], John E. Coia [9], Abraham Goorhuis [10], Tessel M. van Rossen [3], Rogier E. Ooijevaar [11], Karen Burns [12], Bente R. Scharvik Olesen [13], Sarah Tschudin-Sutter [14], Mark H. Wilcox [15], Maria J.G.T. Vehreschild [16, 17], Fidelma Fitzpatrick [18, 19], Ed J. Kuijper [1, 20, *], The Guideline Committee of the European Study Group on *Clostridioides difficile*

Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Edward Hines Jr Veterans Administration Hospital, Hines, and [3]Loyola University Medical Center, Maywood, Illinois; [4]St Luke's Hospital, Duluth, Minnesota; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]Children's Hospital of Philadelphia, Pennsylvania; [7]Washington University School of Medicine, St Louis, Missouri; [8]University of Houston College of Pharmacy, Texas; [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [10]McGill University Health Centre, McGill University, Montréal, Québec, Canada; [11]Boston Children's Hospital, Massachusetts; and [12]Leeds Teaching Hospitals NHS Trust, United Kingdom

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 26, 2017 VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

Article published online: 5 October 2013

Clin Microbiol Infect 2014; **20** (Suppl. 2): 1–26 9-0691.12418

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Clinical Microbiology and Infection 24 (2018) 452–462

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Original Article

United European Gastroenterology Journal
2020, Vol. 8(10) 1236–1247

DOI: 10.1177/2050640620957765
journals.sagepub.com/home/ueg

Faecal microbiota transplantation for *Clostridioides difficile* infection: Four years' experience of the Netherlands Donor Feces Bank

Elisabeth M Terveer[1], Karuna EW Vendrik[1], Rogier E Ooijevaar[2], Emilie van Lingen[3], Eline Boeije-Koppenol[1], Els van Nood[4], Abraham Goorhuis[5], Martijn P Bauer[6], Yvette H van Beurden[2,7], Marcel GW Dijkgraaf[8], Chris JJ Mulder[2], Christina MJE Vandenbroucke-Grauls[9], Jos FML Seegers[10], Joffrey van Prehn[1], Hein W Verspaget[3,11], Ed J Kuijper[1,*] and Josbert J Keller[3,12,*]

Narrative review

Update of treatment algorithms for *Clostridium difficile* infection

R.E. Ooijevaar [1, 2, *, †], Y.H. van Beurden [1, 2, †], E.M. Terveer [4], A. Goorhuis [3], M.P. Bauer [5], J.J. Keller [6, 7], C.J.J. Mulder [2], E.J. Kuijper [4, 8]

Clinical Microbiology and Infection 27 (2021) S1–S21

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

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Guidelines

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

Joffrey van Prehn [1], Elena Reigadas [2], Erik H. Vogelzang [3], Emilio Bouza [2], Adriana Hristea [4], Benoit Guery [5], Marcela Krutova [6], Torbjorn Norén [7], Franz Allerberger [8], John E. Coia [9], Abraham Goorhuis [10], Tessel M. van Rossen [3], Rogier E. Ooijevaar [11], Karen Burns [12], Bente R. Scharvik Olesen [13], Sarah Tschudin-Sutter [14], Mark H. Wilcox [15], Maria J.G.T. Vehreschild [16, 17], Fidelma Fitzpatrick [18, 19], Ed J. Kuijper [1, 20, *], The Guideline Committee of the European Study Group on *Clostridioides difficile*

objective

- To provide clinicians with an updated overview of currently available CDI treatment options, and a systematic, transparent, evidence-based update on the optimal CDI treatment strategy based on patient and disease characteristics.
- The treatment options for CDI are subdivided into the **initial episode** of CDI, **severe CDI**, **severe-complicated CDI**, **refractory CDI, recurrent CDI**, **multiple recurrent CDI** and **CDI prophylaxis**.

Diagnostic strategies and **prevention** and control measures are described in separate ESCMID guidance documents and are outside the scope of this document

Clinical Microbiology and Infection 22 (2016) S63–S81

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Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection

M.J.T. Crobach [1], T. Planche [4], C. Eckert [5], F. Barbut [5], E.M. Terveer [1], O.M. Dekkers [2, 3], M.H. Wilcox [6], E.J. Kuijper [1, *]

[1] Department of Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands
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[5] National Reference Laboratory for Clostridium difficile, Paris, France
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Clinical Microbiology and Infection 24 (2018) 1051–1054

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Guidance document for prevention of *Clostridium difficile* infection in acute healthcare settings

S. Tschudin-Sutter [1, *], E.J. Kuijper [2], A. Durovic [1], M.J.G.T. Vehreschild [3], F. Barbut [4], C. Eckert [4], F. Fitzpatrick [5], M. Hell [6], T. Norèn [7], J. O'Driscoll [8], J. Coia [9], P. Gastmeier [10], L. von Müller [11], M.H. Wilcox [12], A.F. Widmer [1] on behalf of the Committee†

Definitions

- **An episode of CDI** is defined as clinical findings compatible with CDI and microbiological evidence of C. difficile free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhoea OR a clinical picture compatible with CDI and a positive nucleic acid amplification test (NAAT) preferably with a low cycle threshold (Ct) value, or positive toxigenic C. difficile culture OR **pseudomembranous colitis** as diagnosed during endoscopy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic C. difficile.
- **Diarrhoea** is defined as >3 loose stools, i.e. Bristol stool scale 6-7, in 24 hours. Diagnostic methods vary between studies, and many studies used PCR-only detection of toxigenic C. difficile. **Relying solely on NAAT may result in overdiagnosis of CDI**.

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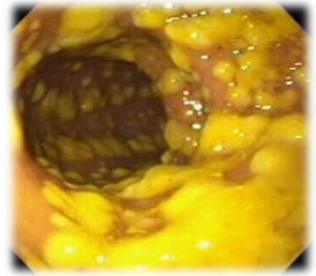
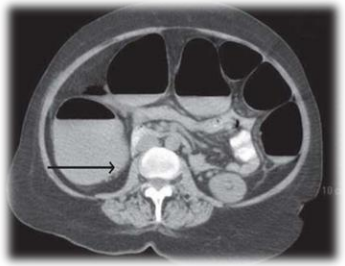




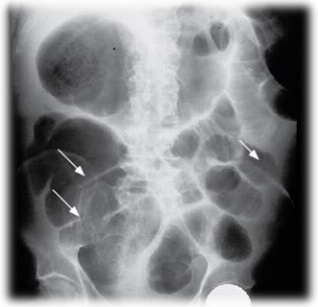
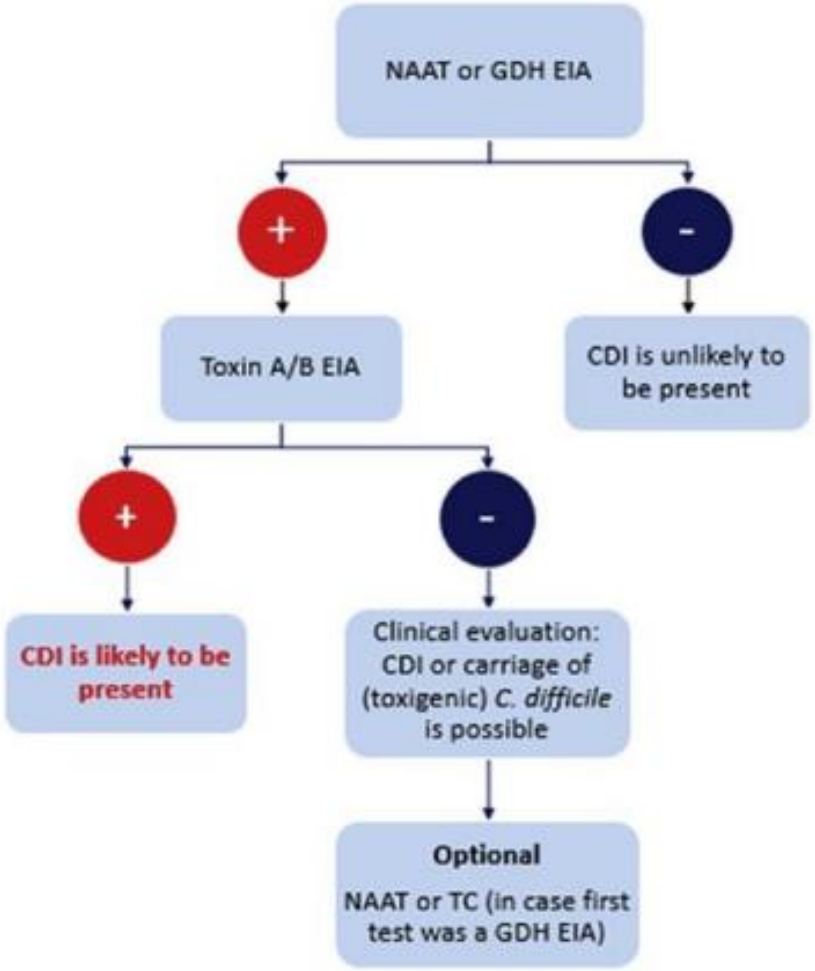
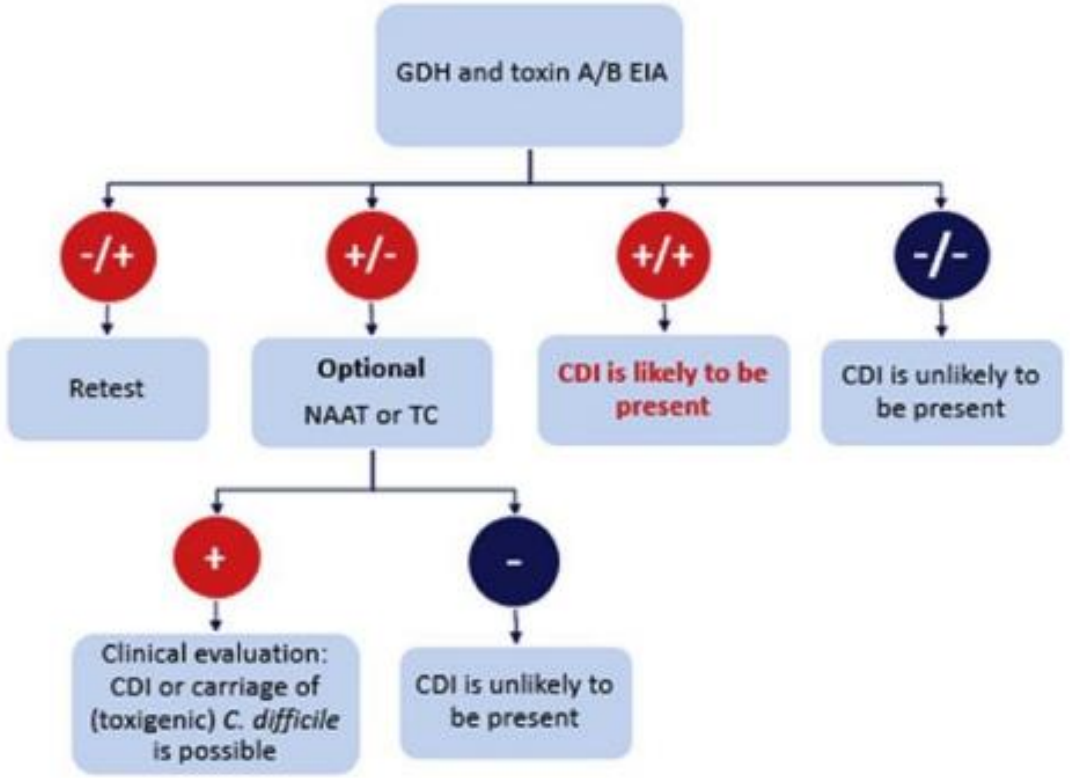


TABLE 3. **Clinical pictures compatible with *Clostridium difficile* infection. Adapted from refs [1,3,11,19,20]**

Sign/symptom	Definition
Diarrhoea	Loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7, plus a stool frequency of three stools in 24 or fewer consecutive hours or more frequently than is normal for the individual.
Ileus	Signs of severely disturbed bowel function such as vomiting and absence of stool with radiological signs of bowel distension.
Toxic megacolon	Radiological signs of distension of the colon (>6 cm in transverse width of colon) and signs of a severe systemic inflammatory response.

Diagnostic Algorithms: ESCMID Recommendations





Toxin sens 67% spec 92%; NAAT sens, 94% , spec 96 %

JOURNAL ARTICLE CORRECTED PROOF

Clinical Outcomes and Management of NAAT-Positive/Toxin-Negative *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis

Connor Prosty ✉, Ryan Hanula, Khaled Katergi, Yves Longtin, Emily G McDonald, Todd C Lee ✉

Clinical Infectious Diseases, ciad523, https://doi.org/10.1093/cid/ciad523
Published: 30 August 2023 **Article history** ▾

Do NAATs Overdiagnose *C. difficile* and Do All NAAT+/Toxin- Cases Require Treatment?

Methods

Systematic review and meta-analysis

Cohort studies or RCTs

Symptomatic patients tested for *C. difficile* infection (CDI) by NAAT and Toxin assays.

Population

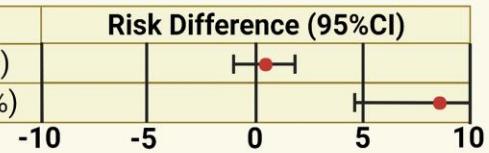
26 cohort studies

N=12737

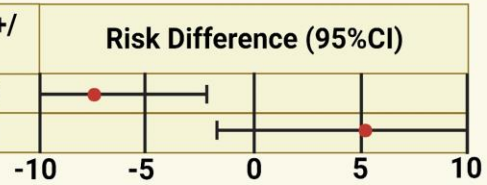
- 4530 NAAT+/Toxin+
- 5566 NAAT+/Toxin-
- 2641 NAAT-/Toxin-

Results

	NAAT+/Toxin+	NAAT+/Toxin-	Risk Difference (95%CI)
30-Day All-Cause Mortality	339/4031 (8.4%)	271/4021 (6.7%)	
60-Day CDI Recurrence	548/2768 (19.8%)	358/3254 (11.0%)	



	Treated NAAT+/Toxin-	Untreated NAAT+/Toxin-	Risk Difference (95%CI)
30-Day All-Cause Mortality	139/2776 (5.0%)	31/244 (12.7%)	
60-Day CDI Recurrence	291/2501 (11.6%)	12/172 (7.0%)	



Conclusion

Compared to NAAT+/Toxin-, NAAT+/Toxin+ cases have a significantly higher risk of CDI recurrence but not mortality. Treated NAAT+/Toxin- patients had significantly less mortality but not CDI recurrence. These results suggest that there may be benefit to the treatment of NAAT+/Toxin- cases in the correct clinical context.

Created with BioRender.com

Definitions

- **Treatment response** is present when the patient has resolution of diarrhoea, and has had a formed or normal stool for that patient, with maintenance of resolution for the duration of therapy and at least 48 hours after the end of treatment, and no further requirement for CDI therapy, AND parameters of disease severity (clinical, laboratory, radiological) have improved and no new signs of severe disease have developed. In all other cases, treatment is considered a failure. A significant decrease in bowel movement frequency may also be considered a sign of (at least partial) response. Treatment response should be observed daily and evaluated after at least 3 days, assuming that the patient is not worsening on treatment Treatment with metronidazole, in particular, may result in a clinical response only after 3-5 days. After clinical response, it may take weeks for stool consistency and frequency to normalise .
- **Refractory CDI** is CDI not responding to recommended CDI antibiotic treatment, i.e. **no response after 3-5 days of therapy**. Refractory CDI can be part of either non-complicated or complicated CDI, which are described below.
- **Sustained cure** is defined as treatment response without recurrence of CDI during follow-up.

Definitions

- **Recurrence** is present when CDI recurs **within 8 weeks** after a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment.
- However, follow-up duration for assessment of recurrence varies between studies, and many studies use 4 or 12 weeks. It is not feasible to distinguish **recurrence due to relapse** (renewed symptoms from already present CDI) from **recurrence due to reinfection** in daily practice because genotyping is not readily available.

Definitions

- **Severe CDI** is characterized by one of the following factors at presentation: **fever**, i.e. core body temperature >38.5°C, marked **leucocytosis**, i.e. leucocyte count >15 x 10^9/L, and **rise in serum creatinine**, i.e. >50% above the baseline. Additional supporting factors are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low attenuation mural thickening) at imaging.
- **Severe-complicated CDI (or fulminant CD)** is defined by the 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).

Clinical Microbiology and Infection 27 (2021) S1–S21

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

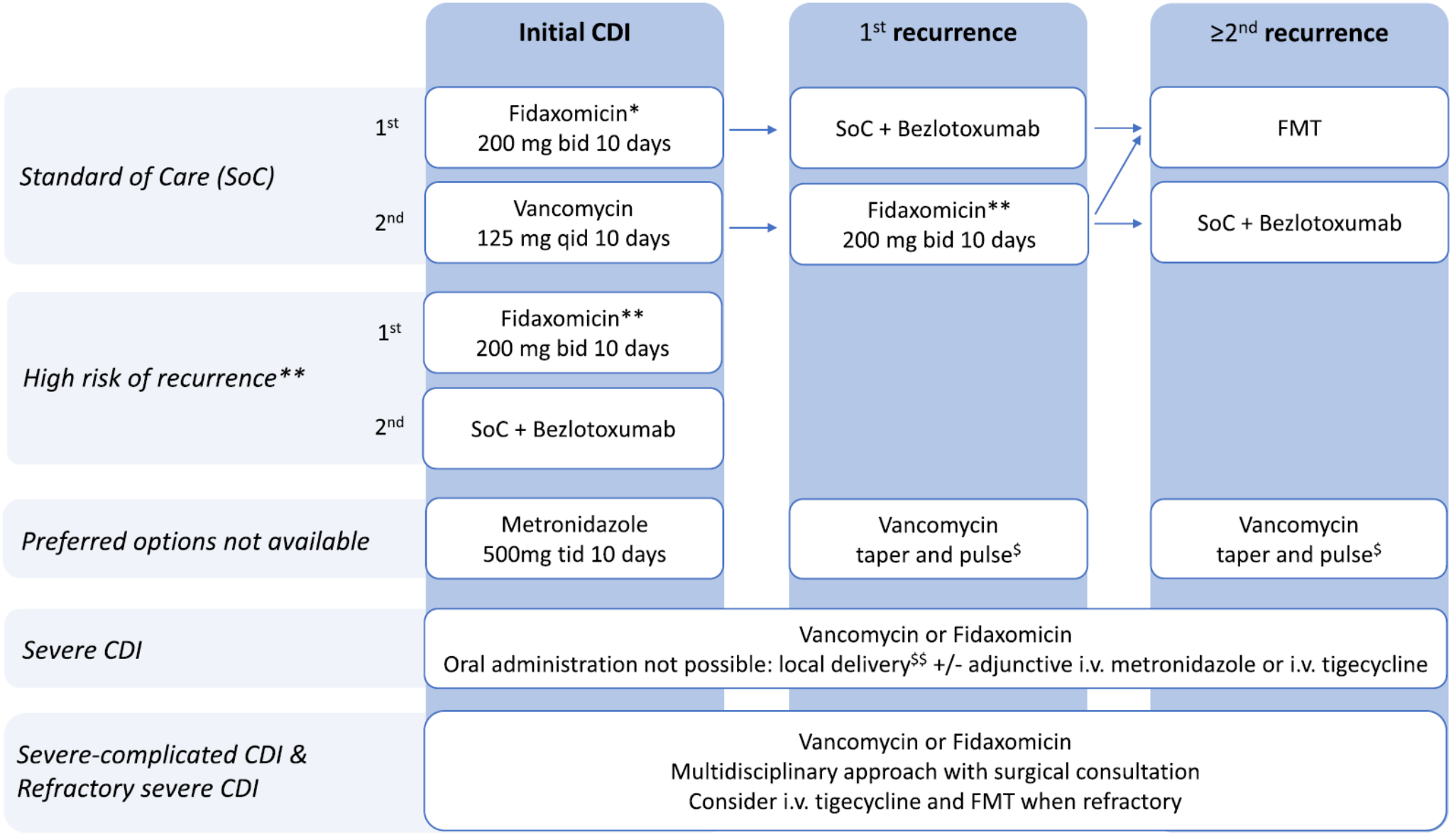
Joffrey van Prehn [1], Elena Reigadas [2], Erik H. Vogelzang [3], Emilio Bouza [2], Adriana Hristea [4], Benoit Guery [5], Marcela Krutova [6], Torbjorn Norén [7], Franz Allerberger [8], John E. Coia [9], Abraham Goorhuis [10], Tessel M. van Rossen [3], Rogier E. Ooijevaar [11], Karen Burns [12], Bente R. Scharvik Olesen [13], Sarah Tschudin-Sutter [14], Mark H. Wilcox [15], Maria J.G.T. Vehreschild [16, 17], Fidelma Fitzpatrick [18, 19], Ed J. Kuijper [1, 20, *], The Guideline Committee of the European Study Group on *Clostridioides difficile*

Questions

- What is the best treatment for initial CDI?
- What is the best treatment for severe and severe-complicated CDI?
- What is the best treatment for CDI when no oral treatment is possible?
- What is the best treatment for refractory CDI?
- What is the best treatment for recurrent CDI?
- What is the best treatment for multiple recurrences of CDI?
- Can prognostic factors identify patients at risk for severe CDI?
- Can prognostic factors identify patients at risk for recurrent CDI?
- Is there a place for prophylaxis for prevention of CDI?

The committee found it relevant to also consider the following issues:

- **How best to define severe CDI**.
- **The timing of start of empiric treatment**.
- The role of probiotics.
- **The Anti-CDI therapy during pregnancy**.
- The treatment of patients at risk for severe CDI.
- The treatment of patients at risk for recurrent CDI.



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

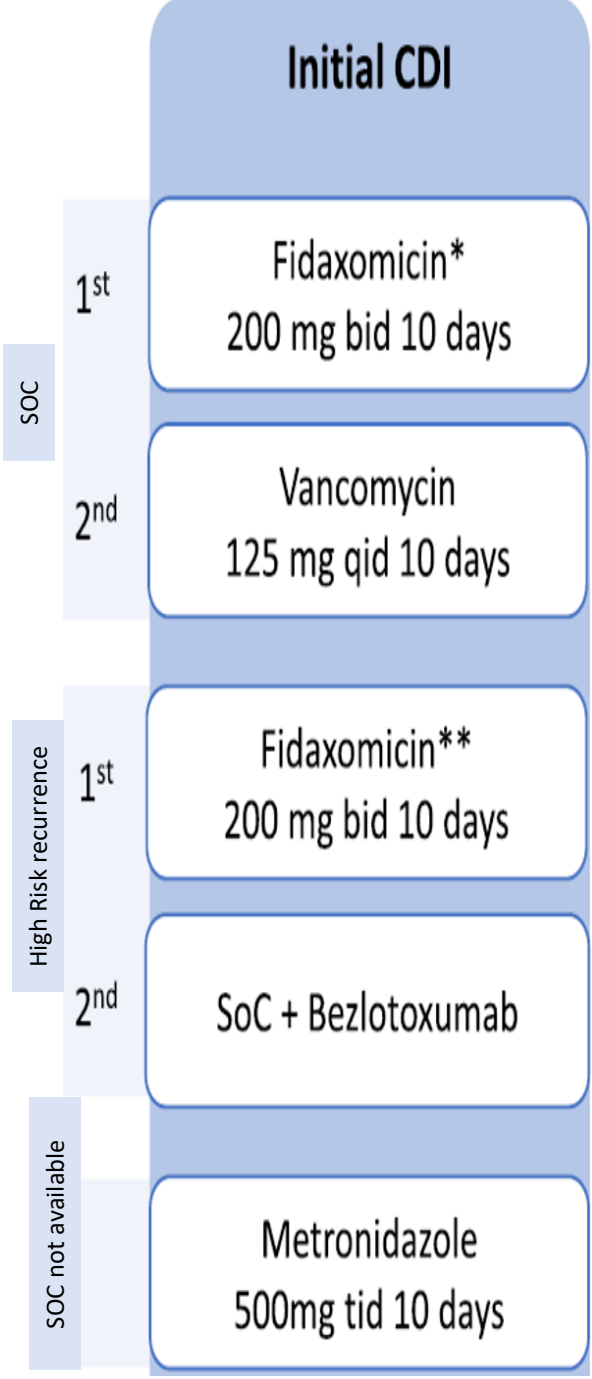
** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use,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

What is the best treatment for an initial episode of CDI?

- In case of **non-severe CDI**, we recommend to **discontinue antibiotic therapy** if possible with the inciting antibiotic and closely monitor the patient for 48 hours. Good practice statement
- For the initial episode of CDI we recommend **fidaxomicin 200 mg twice daily for 10 days**. Strong (recommendation), Moderate (level of evidence)
- **When access to fidaxomicin is limited, it is reasonable to make a risk stratification** for selected use. In this case, fidaxomicin is recommended whenever the clinicians deems the risk of recurrence high. This can be supported by an older age of the patient **(>65 years)** plus the **presence of one or more additional risk factor**(s), i.e. **healthcare-associated CDI, prior hospitalization in the last 3 months, use of concomitant antibiotics, PPIs started during/after CDI diagnosis and a prior CDI episode**. The risk of recurrence is assumed to be higher with more risk factors present. Good practice statement



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

N Engl J Med 2011;364:422-31.

ClinicalTrials.gov number, NCT00314951

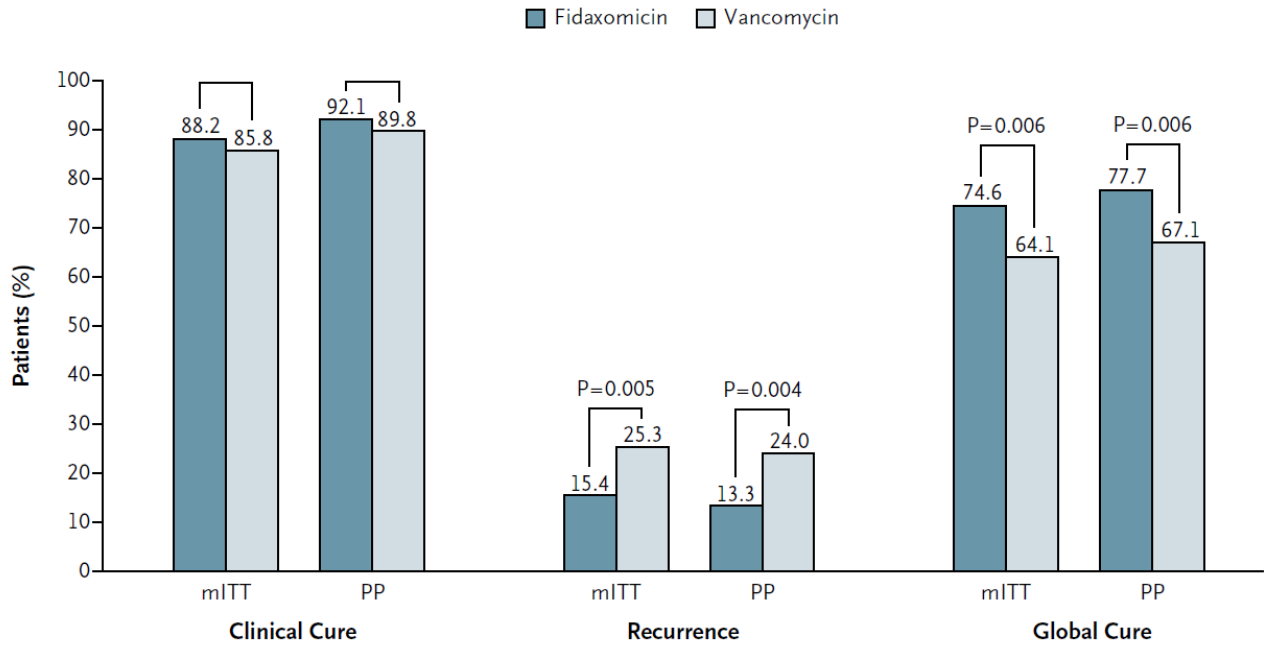


Figure 2. Rates of Primary and Secondary End Points.

For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was –3.1 percentage points in the modified intention-to-treat (mITT) analysis and –2.6 percentage points in the per-protocol (PP) analysis.

Phase 3 clinical trial -629 patients enrolled, United States, Canada
Fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days.
Primary end point was **clinical cure** (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy).
The secondary end points were **recurrence** of *C. difficile* infection **within 4 weeks** after treatment) and global cure

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group

Summary

Background Infection with *Clostridium difficile* is the primary infective cause of antibiotic-associated diarrhoea. We aimed to compare efficacy and safety of fidaxomicin and vancomycin to treat patients with *C difficile* infection in Europe, Canada, and the USA.

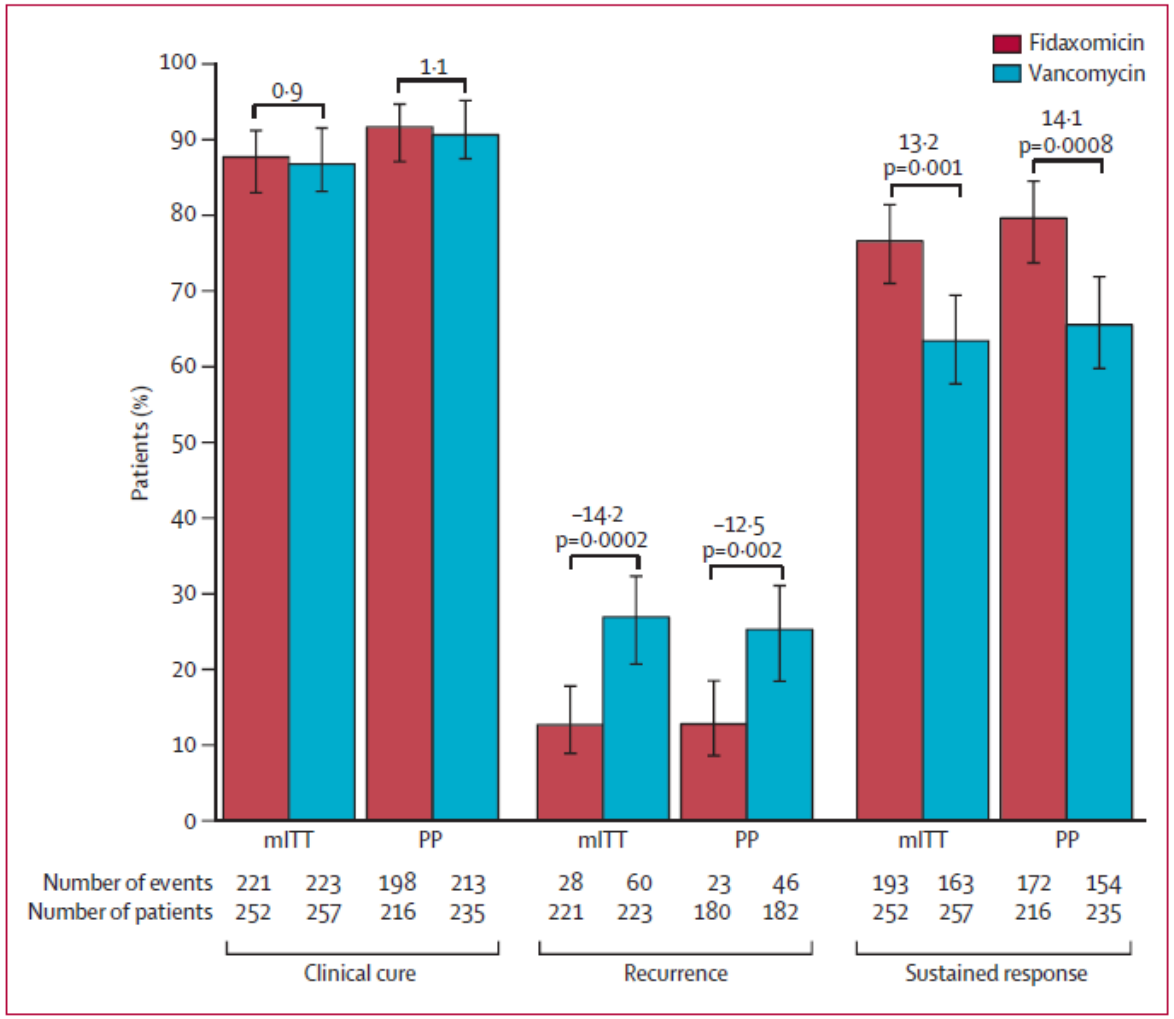
Lancet Infect Dis 2012; 12: 281–89

Published Online

ClinicalTrials.gov, number NCT00468728

- Multicentre, double-blind, randomised, non-inferiority trial, we enrolled patients from 45 sites in Europe and 41 sites in the USA and Canada between April 19, 2007, and Dec 11, 2009
- Fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days.

Patients receiving concomitant antibiotics for other infections had a higher cure rate with fidaxomicin (46 [90·2%] of 51) than with vancomycin (33 [73·3%] of 45; p=0·031).



MAJOR ARTICLE

Clinical Infectious Diseases 2011;53(5):440–447

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Kathleen M. Mullane,[1] Mark A. Miller,[2] Karl Weiss,[3] Arnold Lentnek,[4] Yoav Golan,[5] Pamela S. Sears,[6] Youe-Kong Shue,[6] Thomas J. Louie,[7] and Sherwood L. Gorbach[5,6]

[1]Department of Medicine, University of Chicago, Chicago, Illinois; [2]Division of Infectious Disease, Jewish General Hospital, McGill University, Toronto, Ontario, Canada; [3]Department of Infectious Diseases and Microbiology, Maisonneuve-Rosemont Hospital, Université de Montréal, Montreal, Quebec, Canada; [4]Wellstar Infectious Disease, Marrietta, Georgia; [5]Department of Medicine, Tufts Medical Center, Boston, Massachusetts; [6]Optimer Pharmaceuticals Inc, San Diego, California; and [7]Department of Medicine, University of Calgary, Calgary, Canada

- Subjects from **2 prospective double-blinded, randomized**, parallel-group, noninferiority studies were pooled for these analyses (www.clinicaltrials.gov:
- study **NCT00314951**, May 2006 through August 2008, United States, Canada;
- study **NCT00468728**, April 2007 through December 2009, United States, Belgium, Canada, France, Germany, Italy, Spain, Sweden, United Kingdom).

When subjects received **concomitant antibiotics (CAs).** concurrent with CDI treatment, **the cure rate was 90.0% for fidaxomicin and 79.4% for vancomycin (P =0.04).**

In subjects receiving CAs during treatment and/or follow-up, treatment with **fidaxomicin** compared with vancomycin was associated with **12.3% fewer recurrences (16.9% vs 29.2%; P =0.048).**

Conclusions

Fidaxomicin was significantly more effective than vancomycin in achieving clinical cure in the presence of CA therapy and in preventing recurrence regardless of CA use.

VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Resolution of *Clostridium difficile*–Associated Diarrhea in Patients With Cancer Treated With Fidaxomicin or Vancomycin

Oliver A. Cornely, Mark A. Miller, Bruno Fantin, Kathleen Mullane, Yin Kean, and Sherwood Gorbach

Oliver A. Cornely, University Hospital of Cologne and Zentrum für Klinische Studien Köln–BMBF 01KN1106, Cologne, Germany; Mark A. Miller, Jewish General Hospital, Montreal, Quebec, Canada; Bruno Fantin, University Paris Diderot, Paris, France; Kathleen Mullane, University of Chicago, Chicago, IL; Yin Kean and Sherwood Gorbach, Optimer Pharmaceuticals, San Diego, CA; and Sherwood Gorbach, Tufts University, Boston, MA.

Published online ahead of print at www.jco.org on May 28, 2013.

Supported by Optimer Pharmaceuticals, San Diego, CA.

Presented in part at the European Congress of Clinical Microbiology and Infectious Diseases, March 31-April 3, 2012, London, United Kingdom; and 48th Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2012, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00314951, NCT00468728

ABSTRACT

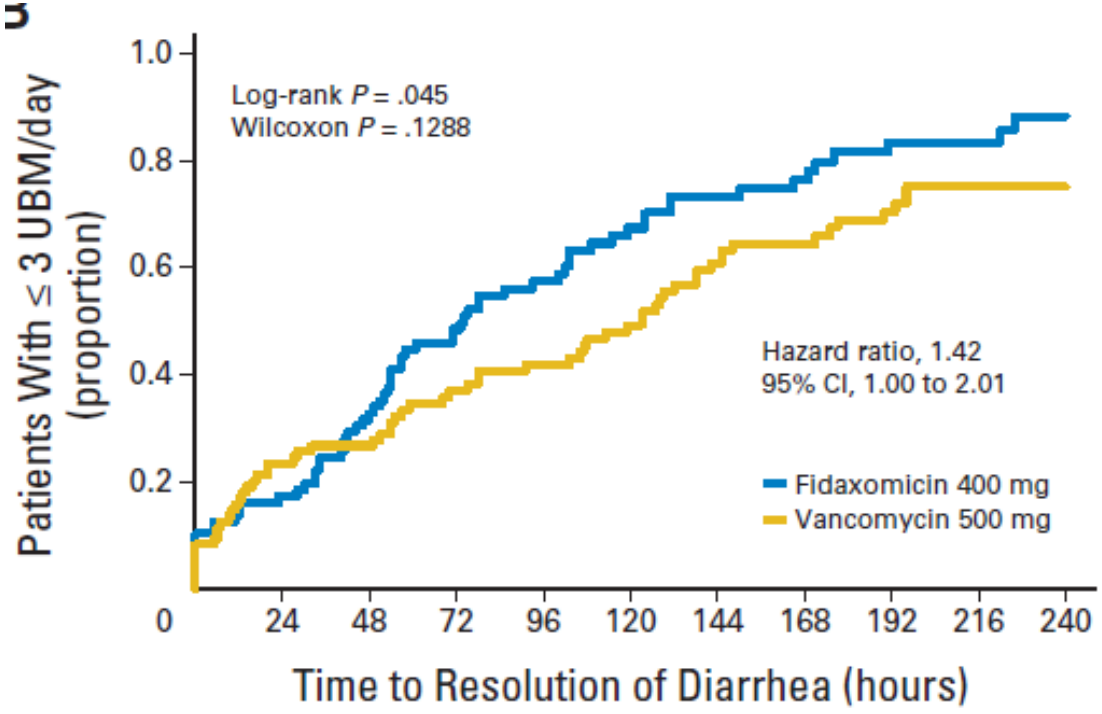
Purpose
Patients with cancer are at increased risk for *Clostridium difficile*–associated diarrhea (CDAD). Little is known about treatment response.

Patients and Methods
Two double-blind trials randomly allocated 1,105 patients with CDAD to fidaxomicin or vancomycin treatment (modified intent-to-treat [mITT]), and 183 of these had cancer. Univariate and multivariate post hoc analyses compared effects of treatment and patient characteristics on cure, recurrence, and sustained response after 4 weeks. Time to resolution of diarrhea (TTROD) was also evaluated.

Results
Patients with cancer had a lower cure rate and longer TTROD than patients without cancer. Recurrence rates were similar. Cure was more likely with fidaxomicin than vancomycin (odds ratio [OR] 2.0; $P = .065$), recurrence was less likely (OR = 0.37; $P = .018$), and sustained response more frequent (OR = 2.56; $P = .003$). Under vancomycin, median TTROD was longer in patients with cancer than in those without (123 *v* 58 hours; log-rank $P < .001$). With fidaxomicin, median TTROD was not significantly affected by presence of cancer (74 *v* 54 hours; log-rank $P = .145$). In the full mITT population, age, hypoalbuminemia, and cancer were inversely associated with clinical cure by multivariate analysis. Study treatment with vancomycin was a significant predictor of recurrence ($P < .001$). Within the cancer population, low albumin was negatively and fidaxomicin was positively associated with improved cure.

Conclusion
For patients with cancer, fidaxomicin treatment was superior to vancomycin, resulting in higher cure and sustained response rates, shorter TTROD, and fewer recurrences.

J Clin Oncol 31:2493-2499. © 2013 by American Society of Clinical Oncology

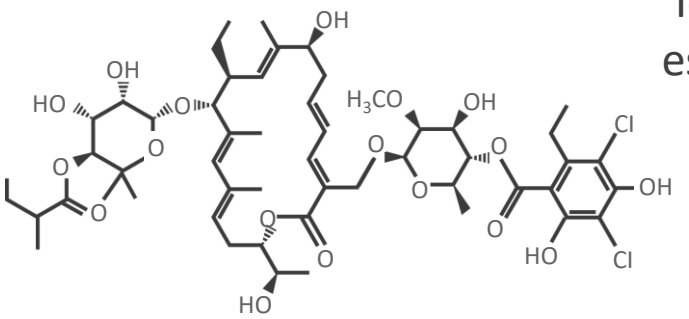


For patients with cancer, fidaxomicin treatment was superior to vancomycin, resulting **in:**

- **higher cure**
- **higher sustained response rates,**
- **shorter Time to resolution of diarrhea,**
- **fewer recurrences.**

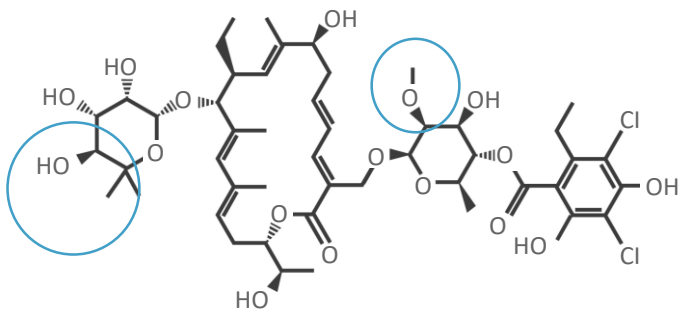
Modalità d'azione di fidaxomicina e metabolismo

Fidaxomicina



Idrolisi da parte di esterasi nel colon[1,2]

OP-1118



MIC_{50}[3]	**0,125 µg/mL**	**4 µg/mL**
MIC_{90}[3]	**0,25 µg/mL**	**8 µg/mL**

Meccanismo d'azione di fidaxomicina[1]

- Inibizione della RNA polimerasi batterica
- Agisce nella fase di iniziazione della sintesi dell'RNA
- L'attività è altamente specifica per *C. difficile*

OP-1118 è un **metabolita attivo**; presenta un'attività antibatterica vs *C. difficile di per sé*[1]

1. Zhanel GG, et al. Can J Infect Dis Med Microbiol 2015;26:305-312; 2. Drug Bank. Structure of OP-1118. Available at: https://www.drugbank.ca/metabolites/DBMET00972. (Accessed February 2022);
3. Goldstein EJC, et al. Clin Infect Dis 2012;55(Suppl. 2):S143-148.

Antimicrobial Activities of Fidaxomicin

Clinical Infectious Diseases 2012;55(S2):S143–8

Ellie J. C. Goldstein,[1,2] Farah Babakhani,[3] and Diane M. Citron[1]

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Table 2. In Vitro Activity of Fidaxomicin, Compared With Vancomycin and Metronidazole, Against *Clostridium difficile* Isolates From 8 Published Studies

Drug	No. of isolates	MIC (μg/mL) Range	MIC_{50}	MIC_{90}	[Ref] Year/sites
Fidaxomicin	16	0.12–0.25	0.25	0.25	[1] 1991/US
Vancomycin		0.5–1	0.5	1	
Metronidazole		0.12–0.5	0.25	0.5	
Fidaxomicin	207	≤0.001–0.625	0.002	0.008	[4] 2004/Europe
Vancomycin		0.016–0.5	0.5	0.5	
Metronidazole		0.004–0.5	0.06	0.06	
Fidaxomicin	23	0.06–2	0.12	0.25	[5] 2004/US
Vancomycin		0.5–4	1	2	
Metronidazole		0.25–1	0.12	0.25	
Fidaxomicin	208	0.06–1	0.25	0.5	[8] 2008/Canada
Vancomycin		0.5–4	0.5	1	
Metronidazole		0.25–4	0.5	1	
Fidaxomicin	110	0.015–0.25	0.125	0.125	[6] 1983–2004/US
Vancomycin		0.06–4	1	1	
Metronidazole		0.025–0.5	0.125	0.25	
Fidaxomicin	21	≤0.016–0.25	0.016	0.12	[7] 2004/US
Vancomycin		0.5–2	1	2	
Metronidazole		≤0.125–0.5	0.25	0.5	
Fidaxomicin	38	≤0.008–0.25	…	0.125	[9] 2004–2005/US
Vancomycin		0.25–2	…	1	
Metronidazole		0.25–2	…	1	
Fidaxomicin	716	≤0.008–1	0.125	0.5	[10] 2005–2010/US & Europe
Vancomycin		0.5–8	1	2	
Metronidazole		0.02–4	0.5	1	

Table 1. Antimicrobial Profile of Fidaxomicin for Various Aerobic and Anaerobic Bacteria and Yeast

Gram-Negative Bacteria			Gram-Positive Bacteria			Yeast		
Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC	Strain	ATCC No.	FDX MIC
Acinetobacter baumannii	19606	>32	*Bacillus cereus*	11778	1	Yeast		
Acinetobacter calcoaceticus	23055	1	*B. cereus*	14579	1	*Candida albicans*	24433	>64
Bacteroides distasonis	8503	>32	*Clostridium difficile*	43255	0.125	*C. albicans*	90028	>64
Bacteroides fragilis	23745	>32	*C. difficile*	9689	0.06	*C. albicans*	14053	>64
B. fragilis	25285	>32	*C. difficile*	17857	0.031	*Candida krusei*	6258	>64
Bacteroides ovatus	8483	>32	*Clostridium perfringens*	13124	≤0.015	*Candida glabrata*	2001	>64
Bacteroides uniformis	8492	>32	*Enterococcus faecalis*	19433	4	*Candida lusitaniae*	66035	>64
Campylobacter jejuni	29428	64	*Enterococcus faecium*	19434	4	*Candida parapsilosis*	22019	>64
C. jejuni	33291	>64	*E. faecium*	49032	4	*Candida tropicalis*	750	>64
C. jejuni	49943	64	*E. faecium*	700221	4			
Citrobacter braakii	43162	>64	*Lactobacillus acidophilus*	4356	>32			
Citrobacter freundii	43864	>64	*Lactobacillus casei*	393	1			
Enterobacter aerogenes	35028	>64	*Lactobacillus rhamnosus*	7469	16			
E. aerogenes	13048	>64	*Micrococcus luteus*	381	≤0.125			
Enterobacter cloacae	49141	>64	*M. luteus*	49732	≤0.125			
E. cloacae	23355	>32	*M. luteus*	533	≤0.125			
Escherichia coli	25922	>32	*M. luteus*	4698	≤0.06			
Fusobacterium nucleatum	25586	>32	*Peptostreptococcus anaerobius*	27337	≤0.06			
Haemophilus influenzae	49247	>32	*Peptostreptococcus (Peptoniphilus) asaccharolyticus*	29743	1			
Helicobacter pylori	43504	>32	*Peptococcus (Finegoldia) magna*	29328	0.5			
Klebsiella oxytoca	43165	>64	*Peptococcus (Micromonas) micros*	33270	0.125			
K. oxytoca	49131	>64	*Propionibacterium acnes*	11827	8			
Klebsiella pneumoniae	33495	>64	*P. acnes*	6919	8			
K. pneumoniae	27736	>64	*Staphylococcus aureus*	33591	8			
K. pneumoniae	13883	>32	*S. aureus*	25923	16			
Moraxella catarrhalis	25238	2	*S. aureus*	29213	8			
M. catarrhalis	49143	1	*Staphylococcus epidermidis*	12228	1			
Neisseria meningitidis	13077	64	*S. epidermidis*	14990	1			
Neisseria gonorrhoeae	19424	8	*Staphylococcus intermedius*	29663	4			
N. gonorrhoeae	49226	32	*Streptococcus agalactiae*	12386	16			
Neisseria lactamica	23970	32	*S. agalactiae*	13813	32			
Porphyromonas asaccharolytica	25260	32	*Streptococcus pyogenes*	19615	16			
Prevotella loescheii	15930	>32	*Streptococcus pneumoniae*	49619	>32			
Proteus mirabilis	25933	>64	*Streptococcus sanguinis*	10556	32			

1.

Basis of narrow-spectrum activity of fidaxomicin on *Clostridioides difficile*

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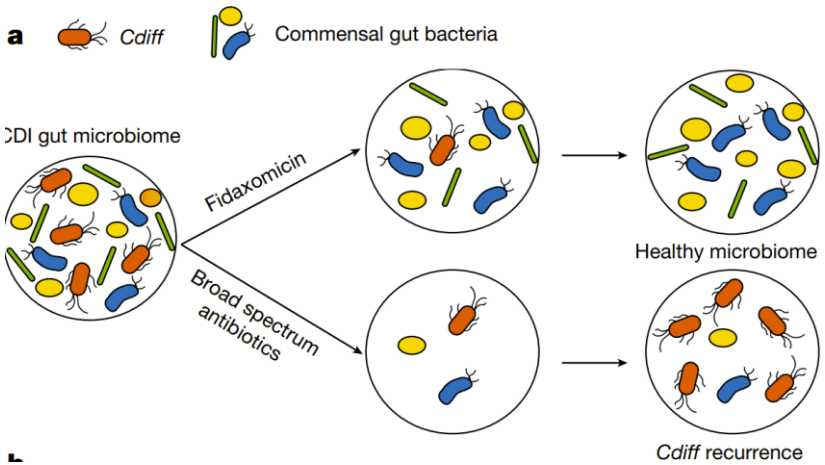
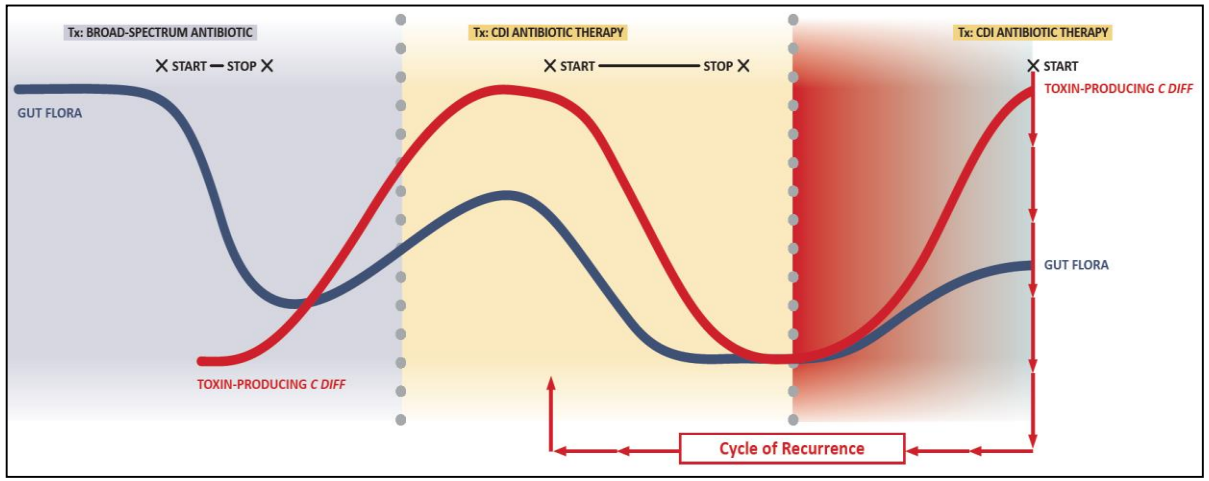
Xinyun Cao[1,4], Hande Boyaci[2,4], James Chen[2], Yu Bao[1], Robert Landick[1,3]✉ & Elizabeth A. Campbell[2]✉





Fidaxomicin Inhibits Spore Production in *Clostridium difficile*

2012:55 (Suppl 2)

Farah Babakhani,[1] Laurent Bouillaut,[2] Abraham Gomez,[1] Pamela Sears,[1] Ly Nguyen,[1] and Abraham L. Sonenshein[2]

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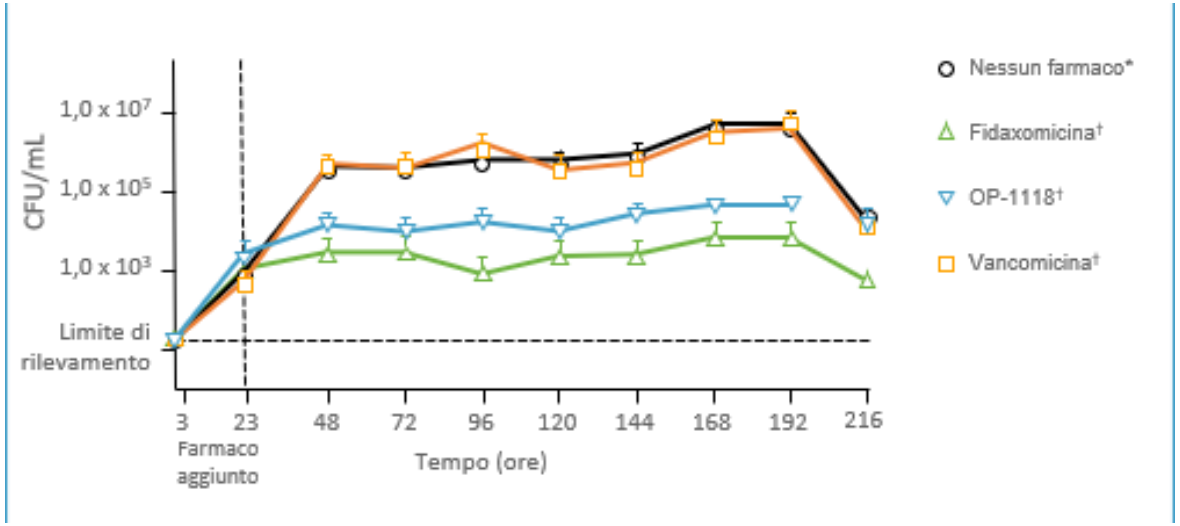
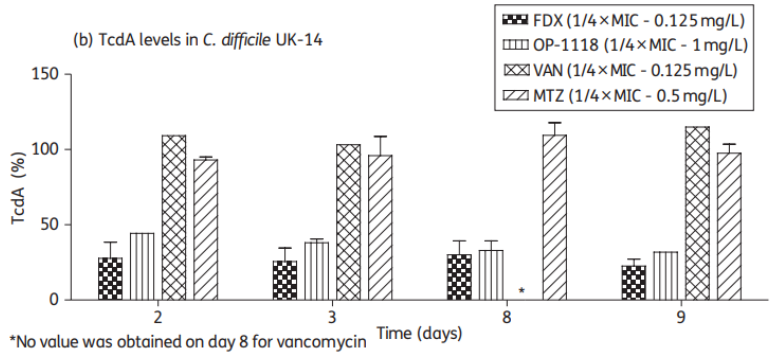


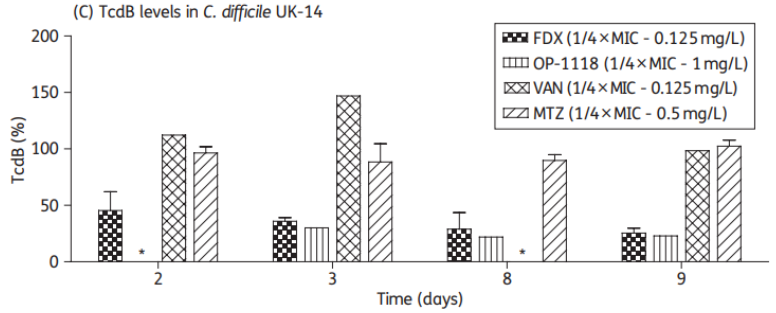
J Antimicrob Chemother 2013; **68**: 515–522
doi:10.1093/jac/dks450 Advance Access publication 2 December 2012

Journal of Antimicrobial Chemotherapy

Fidaxomicin inhibits toxin production in *Clostridium difficile*

Farah Babakhani[1]*, Laurent Bouillaut[2], Pamela Sears[1], Carlee Sims[1], Abraham Gomez[1] and Abraham L. Sonenshein[2]





Clinical Infectious Diseases

MAJOR ARTICLE

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

Clinical Infectious Diseases® 2022;74(4):648–56

Impact of Oral Metronidazole, Vancomycin, and Fidaxomicin on Host Shedding and Environmental Contamination With *Clostridioides difficile*

Nicholas A. Turner,[1,2] Bobby G. Warren,[1,2] Maria F. Gergen-Teague,[3] Rachel M. Addison,[1,2] Bechtler Addison,[1,2] William A. Rutala,[3] David J. Weber,[3] Daniel J. Sexton,[1,2] and Deverick J. Anderson[1,2]

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- Methods. In this prospective, unblinded, randomized controlled trial of hospitalized adults with C. difficile infection, patients were randomized 1:1:1 to receive fidaxomicin, oral vancomycin, or metronidazole. The primary outcome was change in environmental contamination rate during treatment. Secondary outcomes included stool shedding, total burden of contamination, and molecular relatedness of stool versus environmental C. difficile isolates.
- Results. Of 33 patients enrolled, 31 (94%) completed the study. Fidaxomicin (−0.36 log10 colony-forming units [CFUs]/d [95% confidence interval (CI), −.52 to −.19]; P < .01) and vancomycin (−0.17 log10 CFUs/d [−.34 to −.01]; P = .05) were associated with more rapid decline in C. difficile shedding than metronidazole (−0.01 log10 CFUs/d [95% CI, −.10 to .08). Both vancomycin (6.3% [95% CI, 4.7–8.3) and fidaxomicin (13.1% [10.7–15.9]) were associated with lower rates of environmental contamination than metronidazole (21.4% [18.0– 25.2]). With specific modeling of within-subject change over time, fidaxomicin (adjusted odds ratio, 0.83 [95% CI, .70–.99]; P = .04) was associated with more rapid decline in environmental contamination than vancomycin or metronidazole. Overall, 207 of 233 environmental C. difficile isolates (88.8%) matched patient stool isolates by ribotyping, without significant difference by treatment.
- Conclusions. **Fidaxomicin, and to a lesser extent vancomycin, reduces C. difficile shedding and contamination of the hospital environment relative to metronidazole**. Treatment choice may play a role in reducing healthcare-associated C. difficile transmission. Clinical Trials Registration. NCT02057198.

Fidaxomicina: farmacocinetica

Fidaxomicina è associata a un basso assorbimento sistemico e a limitate interazioni con altri farmaci[1]

- Farmaco topico con **basso assorbimento sistemico**
- La concentrazione plasmatica media di picco dopo una singola dose (C_{max}) è di circa 9,88 ng/ml negli adulti sani
- C_{max} per fidaxomicina e OP-1118 nel plasma è del 22% e 33%, più bassa dopo un pasto ricco di grassi rispetto al digiuno
- Non influisce sul metabolismo dei farmaci metabolizzati dagli enzimi CYP450
- Può interagire con potenti inibitori della P-glicoproteina

Alte concentrazioni nel colon[2]

Le concentrazioni fecali superano la MIC_{90} di *C. difficile*

Assorbimento sistemico minimo[1,3,4]

Escrezione fecale quasi completa (fidaxomicina e OP-1118)
Assorbimento minimo nei pazienti e nei volontari sani

Viene metabolizzata nel suo **metabolita attivo,** OP-1118[1,5,6]

L'esposizione al farmaco non è influenzata dal cibo[1]

L'esposizione è mantenuta in misura superiore dopo un pasto ricco di grassi rispetto al digiuno

C. difficile, *Clostridioides difficile*; MIC, concentrazione inibitoria minima; VRE, Enterococchi vancomicina-resistenti.

1. European Medicines Agency. Fidaxomicin Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/dificlir-epar-product-information_en.pdf (Accessed February 2022);
2. Louie TJ, et al. Antimicrob Agents Chemother 2009;53:223-8; 3. FDA Meeting Briefing Document for Anti-Infective Drugs Advisory Committee. 5 April 2011; 4. Shue YK, et al. Antimicrob Agents Chemother 2008;52:1391-5; 5. Mullane KM & Gorbach S. Expert Rev Anti Infect 2011;9:767–77; 6. Babakhani F, et al. J Med Microbiol 2011;60:1213–7.

Clinical Microbiology and Infection 29 (2023) 616–622

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Original article

Fecal pharmacokinetics/pharmacodynamics characteristics of fidaxomicin and vancomycin against *Clostridioides difficile* infection elucidated by *in vivo* feces-based infectious evaluation models

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Vancomycin
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ABSTRACT

Objectives: The pharmacokinetics (PK)/pharmacodynamics (PD; PK/PD) characteristics of fidaxomicin (FDX) and vancomycin (VCM) against *Clostridioides difficile* infection (CDI) are yet to be elucidated because of the lack of an established PK/PD analysis method for intestinal infections and unabsorbed oral drugs. Here, we developed a feces-based PK/PD analysis method and determined the fecal PK/PD index, with target values of FDX and VCM against CDI.

Methods: The antimicrobial susceptibility, time-kill curves, and post-antibiotic effects (PAEs) of FDX and VCM against *C. difficile* were determined *in vitro*. The optimal fecal PK/PD indices, with target values, were determined from the results of PK and PD studies involving 5-week-old female C57BL/6J mice infected with *C. difficile* ATCC® 43255. The minimum inhibitory concentration (MIC) breakpoints for *C. difficile* were estimated based on clinical data concerning fecal antibiotic concentrations in patients with CDI.

Results: FDX and VCM inhibited *C. difficile* growth via time-dependent antibacterial activity and exerted PAEs. In the CDI mouse model experiments, the changes in *C. difficile* load and clinical cures (72-hour survival rates and clinical sickness score grading) were most highly correlated with the ratio of area under the fecal drug concentration-time curve to MIC ($AUC_{0\rightarrow\infty}$/MIC). The target $AUC_{0\rightarrow\infty}$/MIC values of FDX and VCM for 3 $\log_{10}$ reduction in *C. difficile* load was 13,173 and 8,308, respectively. The MIC breakpoints of FDX and VCM for *C. difficile* was estimated to be 1.0 and 2.0 μg/mL, respectively.

Conclusions: The developed *in vivo* feces-based PK/PD analysis method elucidated the optimal fecal PK/PD index, with target values of FDX and VCM against CDI. **Sho Tashiro, Clin Microbiol Infect 2023;29:616**

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]

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ALLEGATO

Agenzia Italiana del Farmaco AIFA

SCHEDA DI MONITORAGGIO AIFA PER LA PRESCRIZIONE DI DIFICLIR (fidaxomicina)
(valido per una unica prescrizione)

Paziente (nome, cognome) _____ Età _____

Sesso M ☐ F ☐ Codice fiscale (CF)_____

Indirizzo _____ Tel._____

ASL di residenza _____ Medico curante (MMG)_____

DIFICLIR è indicato per il trattamento negli adulti delle infezioni da *Clostridium difficile* (CDI - *Clostridium difficile infections*) note anche come diarrea associata a C. difficile (*CDAD - C. Difficile - associated diarrhoea*). Può essere prescritto da centri ospedalieri e territoriali del SSN in pazienti con diagnosi microbiologica di CDI/CDAD (GDH positivo *oppure* con tossina A e/o B positiva) per il trattamento:

☐ **Del primo episodio** in:

- Pazienti intolleranti o che non rispondono alla terapia di prima scelta (vancomicina e metronidazolo) *oppure*
- Pazienti ad alto rischio di recidiva come:
  - Paziente immunocompromesso (trapiantato, sotto chemioterapia antritumorale, HIV positivo/AIDS, altre immunodeficienze), *oppure*
  - Paziente con altre gravi patologie concomitanti. In questo caso, specificare _____

☐ **Degli episodi successivi al primo**:

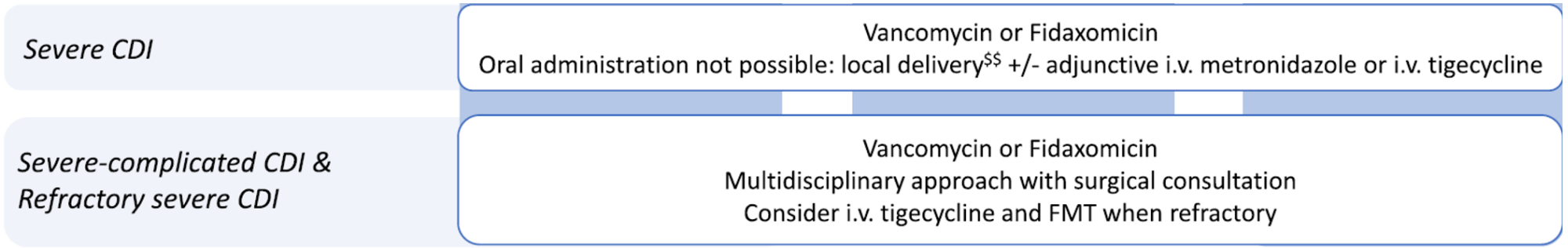
- Trattamenti delle infezioni ricorrenti da CD.

Dose e durata del trattamento

☐ Dose/die: **200 mg x 2/die** Durata prevista del trattamento: **10 giorni**

patient **(>65 years)** plus the **presence of one or more additional risk factor**(s), i.e. **healthcare-associated CDI, prior hospitalization in the last 3 months, use of concomitant antibiotics, PPIs started during/after CDI diagnosis and a prior CDI episode**

What is the best treatment for severe and severe-complicated CDI?

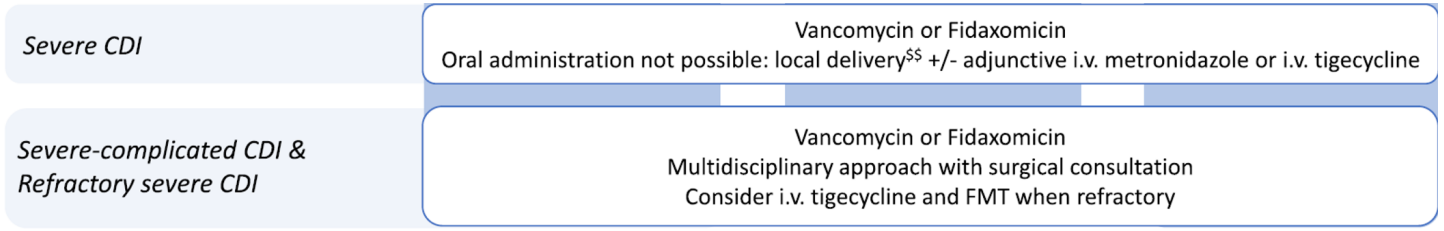


- **vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg twice daily for 10 days**. **There is no data supporting the superiority of one over the other**. Good practice statement _ For severe CDI, routine addition of iv metronidazole to oral SoC therapy is not recommended. Weak, Very Low _ When a patient is deteriorating or progressing to severecomplicated CDI **while on anti-CDI antibiotic therapy**, **addition of iv tigecycline 50 mg twice daily (100 mg loading dose) may be considered on a case-by-case basis**. Weak, Very Low _ **Consult a surgeon** for any severe-complicated case. Good practice statement _ Total abdominal colectomy might be prevented by partial colectomy or loop ileostomy. Weak, Very Low Antibiotic treatment

- **The use of vancomycin in these groups is based on historical grounds**. In the subgroup of patients with severe CDI in two pivotal RCTs (n = 235 and n = 124), oral vancomycin and fidaxomicin had similar outcomes in terms of cure rate and

The optimal antibiotic therapy for critically ill patients, i.e. severe complicated CDI is unknown, as these patients are typically excluded from prospective (randomized) clinical trials that investigate CDI agents.

What is the best treatment for severe and severe-complicated CDI?



- **Intravenous metronidazole** There is no new evidence that supports the routine addition of iv metronidazole in severe CDI.
- **Intravenous tigecycline** Tigecycline shows in vitro activity against C. difficile and intravenous tigecycline has been studied in observational cohorts. No (randomized) clinical trial has investigated tigecycline for treatment of CDI. Nevertheless, the committee concludes that tigecycline merits consideration when a patient is deteriorating or progressing to severe-complicated disease.
- **Surgery for severe-complicated CDI** Analysis of a nationwide US database (2007e2015) confirms that 30-day mortality in patients that underwent total or partial colectomy for CDI is high, 37% and 35% respectively. It is difficult to provide an evidence-based recommendation on the optimal timing of surgery for severe complicated CDI. **A review from 2010 suggests that colectomy is associated with a lower mortality than continued medical treatment when the patient is no longer improving** . **Total abdominal colectomy (TAC)** is the standard when surgery is needed, but might be prevented by partial colectomy or loop ileostomy. **Loop ileostomy** (LI) for CDI includes intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, with postoperative antegrade instillation of vancomycin flushes via the ileostomy.

Clinical Microbiology and Infection 29 (2023) 656–657

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Letter to the Editor

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]

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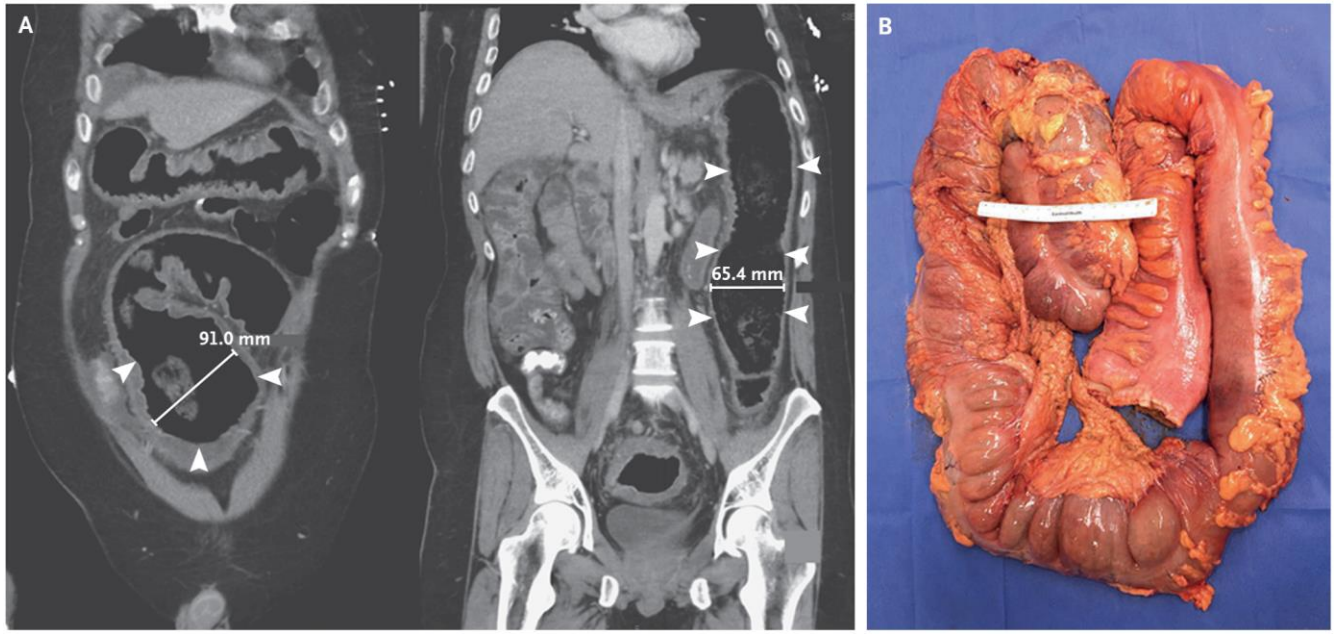
[2)] *Clinical and Research Department for Infectious Diseases, Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani Istituto di Ricerca e Cura a Carattere Scientifico, Rome, Italy*
[3)] *Department of Surgery, Macerata Hospital, Macerata, Italy*
[4)] *Infectious Disease Unit, University Hospital Paolo Giaccone, Palermo, Italy*

Toxic Megacolon Due to Fulminant *Clostridioides difficile* Infection



A 40-year-old man presented to the emergency department with vomiting and diarrhea. He had no known medical history and had not received antimicrobial therapy recently. His heart rate was 132 beats per minute, and other vital signs were normal. Examination was notable for confusion and for diffuse tenderness to palpation of the abdomen with tympany. Laboratory testing showed a **white-cell count of 29,000** per cubic millimeter and a positive nucleic acid amplification test for Clostridioides difficile.

- Computed tomography of the abdomen revealed pancolitis with distention of the sigmoid and descending colon (Panel A; arrowheads indicate the areas of distention, and two-dimensional measurements of colon width are shown). Despite 2 days of treatment with oral and rectal vancomycin and intravenous metronidazole, shock developed in the patient on hospital day 3. An urgently obtained radiograph of the abdomen showed worsening distention of the transverse colon near the hepatic flexure to 120 mm (abnormal width, >60 mm). Owing to concern for toxic megacolon due to fulminant C. difficile colitis, an emergency total colectomy with end ileostomy was performed. Gross pathological examination showed colonic dilatation with pseudomembranes (Panel B). Histopathological assessment showed pseudomembranous colitis, a finding consistent with C. difficile infection. The patient did well after surgery and was discharged 6 days after the procedure.

What is the best treatment for CDI when no oral treatment is possible?

- When oral therapy is not possible, attempt intraluminal (**gastroduodenal or coloscopic**) delivery of vancomycin or fidaxomicin. Good practice statement _ and **consider adjunctive treatment with iv metronidazole 500 mg three times daily or iv tigecycline 50 mg two times daily (100 mg loading dose)**. Weak, Very Low
- The evidence for intraluminal vancomycin is limited to case series and dosages range from 250 mg once daily to 1 g four times a day.
- There are no data on intraluminal fidaxomicin delivery. It seems reasonable use standard oral dosages for intraluminal delivery. Addition of an intravenous antibiotic might be beneficial on a theoretical basis when low intraluminal concentrations of oral CDI agents are expected.

Akamine *et al. BMC Infectious Diseases* (2016) 16:316
DOI 10.1186/s12879-016-1657-1

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

The efficacy of intracolonic vancomycin for severe *Clostridium difficile* colitis: a case series

Christine M. Akamine[1], Michael B. Ing[1,2], Christian S. Jackson[1,3] and Lawrence K. Loo[1*]

Case Reports › J Crit Care Med (Targu Mures). 2017 Feb 18;3(1):39-44.
doi: 10.1515/jccm-2017-0008. eCollection 2017 Feb.

Toxic Megacolon - A Three Case Presentation

Irina Magdalena Dumitru [1], Eugen Dumitru [2], Sorin Rugina [1 3], Liliana Ana Tuta [2]

Affiliations + expand

PMID: 29967870 PMCID: PMC5769890 DOI: 10.1515/jccm-2017-0008

Cureus

Open Access Original Article

DOI: 10.7759/cureus.11573

Intracolonic Administration of Vancomycin in Intensive Care Unit Patients with Severe Clostridium Difficile Colitis

Alex Teixeira [1], Kartikeya Tripathi [2], Yesenia Greeff [3], Omar Sorour [4], Paul Mccallion [5], Garrison Davis [6], Khaled Sorour [7]

International Journal of Infectious Diseases 55 (2017) 27–28

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Case Report

Successful treatment of severe Clostridium difficile infection by administration of crushed fidaxomicin via a nasogastric tube in a critically ill patient

Sven Arends[a,*], Jerome Defosse[a], Cori Diaz[b], Frank Wappler[a], Samir G. Sakka[a]

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[b] MVZ synlab Leverkusen GmbH, Leverkusen, Germany

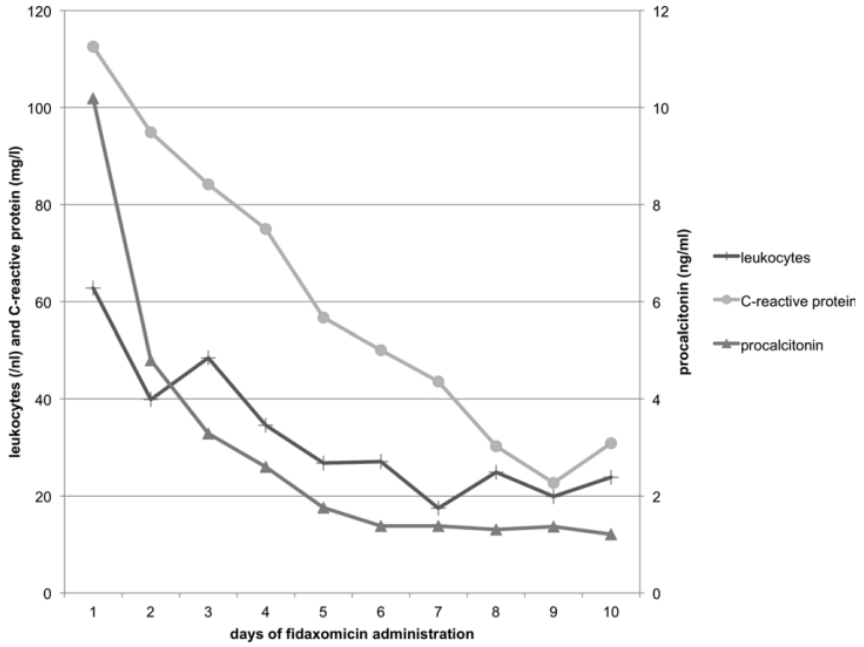
Drugs R D (2014) 14:309–314
DOI 10.1007/s40268-014-0067-3

ORIGINAL RESEARCH ARTICLE

Stability and Recovery of DIFICID® (Fidaxomicin) 200-mg Crushed Tablet Preparations from Three Delivery Vehicles, and Administration of an Aqueous Dispersion via Nasogastric Tube

Anna Tousseeva · J. Derek Jackson · Mark Redell · Teresa Henry · Michael Hui · Shelley Capurso · C. Andrew DeRyke

- We report a case of a 79-year old patient who developed septic shock with an increasing need for norepinephrine and acute renal failure due to a severe Clostridium difficile infection. Antimicrobial therapy with vancomycin via a nasogastric tube and metronidazole i.v. did not lead to improvement, infection parameters further increased, and the clinical condition became increasingly impaired. After 10 days, antimicrobial therapy was changed to fidaxomicin, crushed and administered via nasogastric tube. Within 24 hours, infection parameters decreased. Further diarrhoea ceased and stool samples were negative for Clostridium difficile antigen

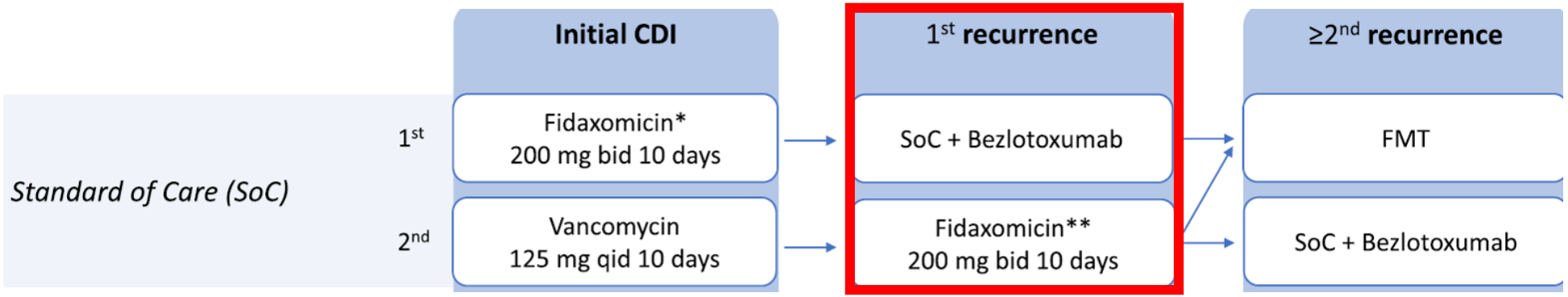


What is the best treatment for refractory CDI?

Carefully re-evaluate the diagnosis of CDI and **consider an alternative diagnosis**. Good practice statement

- **Consult a surgeon as soon as a patient's condition is deteriorating and the patient is not responding to CDI treatment**. Good practice statement _
- **FMT** may be a rescue therapy for patients with severe complicated CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible. The risk-benefit analysis of FMT and/or surgical management should be taken on a case-by-case basis and discussed by the multidisciplinary team. Weak, Very Low Non-complicated refractory CDI
- Vancomycin and fidaxomicin resistance is very rare in Europe. The susceptibility percentages for vancomycin and fidaxomicin were 96.8% and 100%, respectively, in a pan-European study that included 918 C. difficile isolates.

What is the best treatment for recurrent CDI?



- **Consider a vancomycin tapering and pulse scheme for recurrent CDI when fidaxomicin or bezlotoxumab are not available or feasible**. Weak, Very low

First CDI recurrence	Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[b]

Therapeutic Advances in Infectious Disease Systematic Review

Extended duration vancomycin in recurrent *Clostridium difficile* infection: a systematic review

Madison M. Murphy, Edna Patatanian and Mark A. Gales

Ther Adv Infectious Dis
2018, Vol. 5(6) 111–119
DOI: 10.1177/2049936118798276

Case series reported success rates for EDV in rCDI from 61% to 100%, while randomized trials found lower success rates from 26% to 58%. Taper and pulse regimens reported superior outcomes compared to pulse-only regimens, 58–100% versus 26–81%, respectively.

J Antimicrob Chemother 2018; **73**: 2529–2539
doi:10.1093/jac/dky184 Advance Access publication 24 May 2018

Journal of Antimicrobial Chemotherapy

Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients aged ≥60 years (EXTEND): analysis of cost-effectiveness

Oliver A. Cornely[1]*, Maureen Watt[2]†, Charles McCrea[3], Simon D. Goldenberg[4] and Enrico De Nigris[2]

Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial

Lancet Infect Dis 2018; 18: 296–307

*Benoit Guery, Francesco Menichetti, Veli-Jukka Anttila, Nicholas Adomakoh, Jose Maria Aguado, Karen Bisnauthsing, Areti Georgopali, Simon D Goldenberg, Andreas Karas, Gbenga Kazeem, Chris Longshaw, Jose Alejandro Palacios-Fabrega, Oliver A Cornely, Maria J G T Vehreschild, for the EXTEND Clinical Study Group**

Patients were randomly assigned (1:1) using an interactive web response system to receive extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1–5,
then once daily on alternate days on days 7–25) or vancomycin (125 mg oral capsules, four times daily on days 1–10),
Extended-pulsed fidaxomicin was superior to standard-dose vancomycin for sustained cure of C difficile infection, and, to our knowledge, extended-pulsed fidaxomicin recurrence rates in this study are the lowest observed in a randomised clinical trial of antibiotic treatment for C difficile infection.

In conclusion, this analysis suggests that a treatment strategy
with EPFX as first-line therapy for CDI in older patients improves outcomes and saves costs compared with vancomycin

Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial

*Benoit Guery, Francesco Menichetti, Veli-Jukka Anttila, Nicholas Adomakoh, Jose Maria Aguado, Karen Bisnauthsing, Areti Georgopali, Simon D Goldenberg, Andreas Karas, Gbenga Kazeem, Chris Longshaw, Jose Alejandro Palacios-Fabrega, Oliver A Cornely, Maria J G T Vehreschild, for the EXTEND Clinical Study Group**

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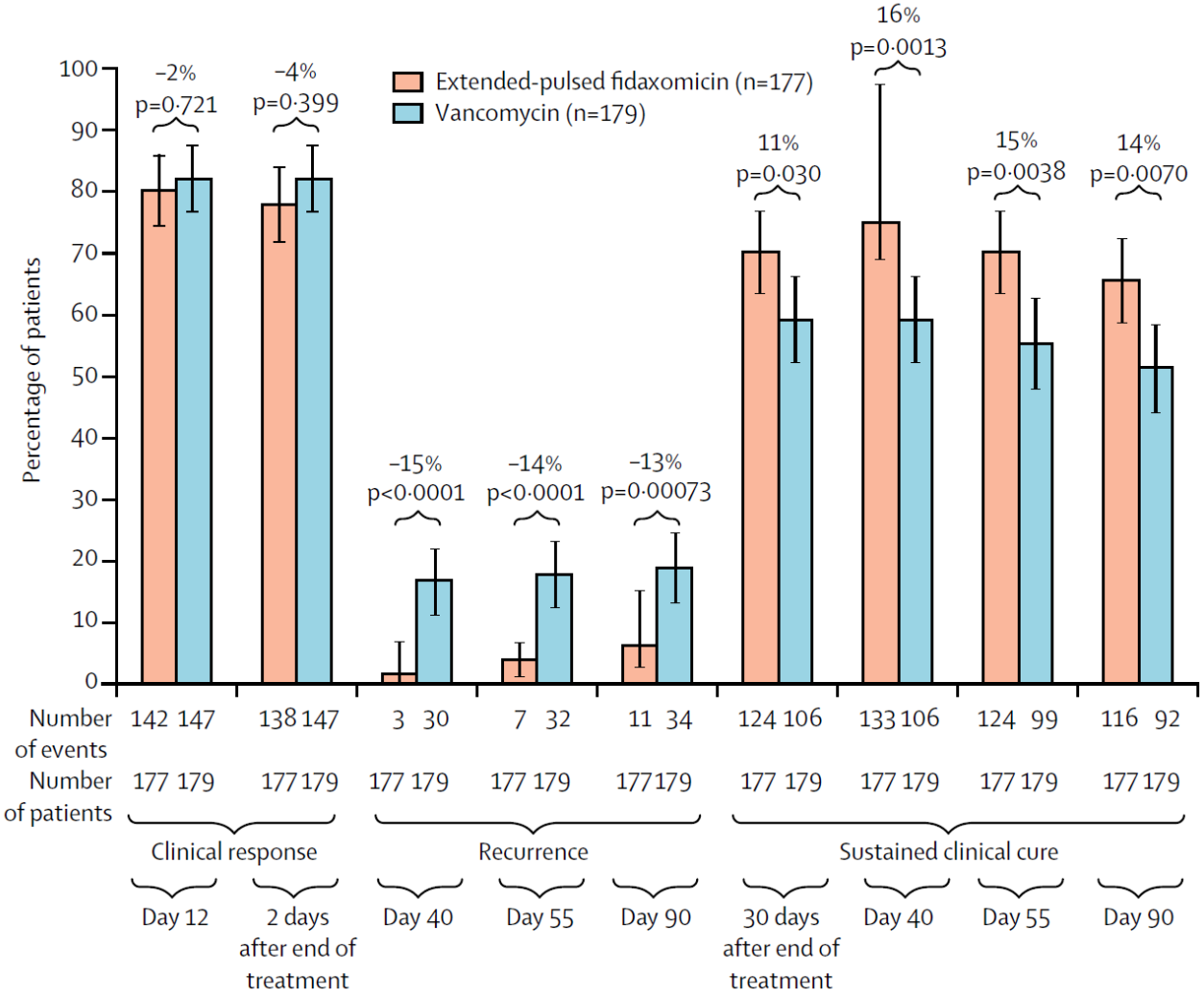
  - vancomycin (125 mg oral capsules, four times daily on days 1–10), Extended-pulsed
- **fidaxomicin was superior to standard-dose vancomycin for sustained cure of C difficile infection**, and, to our knowledge, extended-pulsed fidaxomicin recurrence rates in this study are the lowest observed in a randomised clinical trial of antibiotic treatment for C difficile infection.

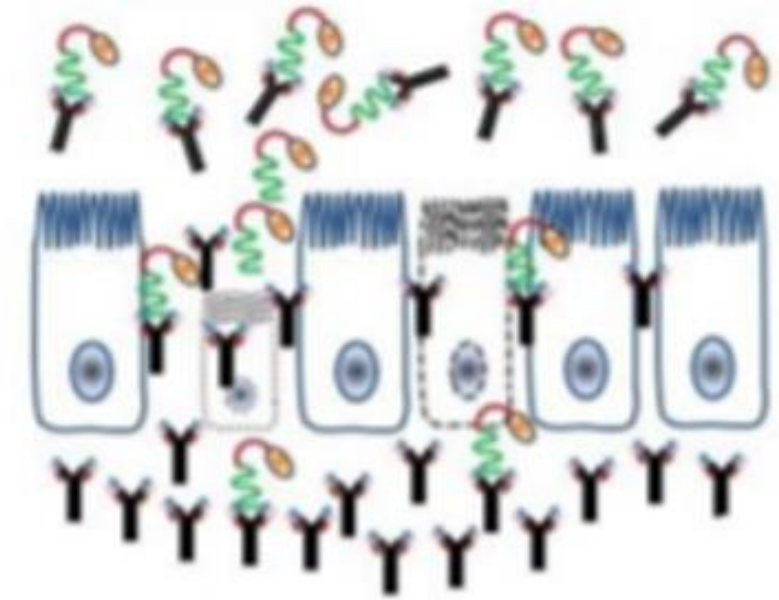


Clin Infect Dis. 2018 Jul 18. doi: 10.1093/cid/ciy577. [Epub ahead of print]

Bezlotoxumab.

Johnson S[1,2], Gerding DN[1].

- 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

The NEW ENGLAND JOURNAL of MEDICINE

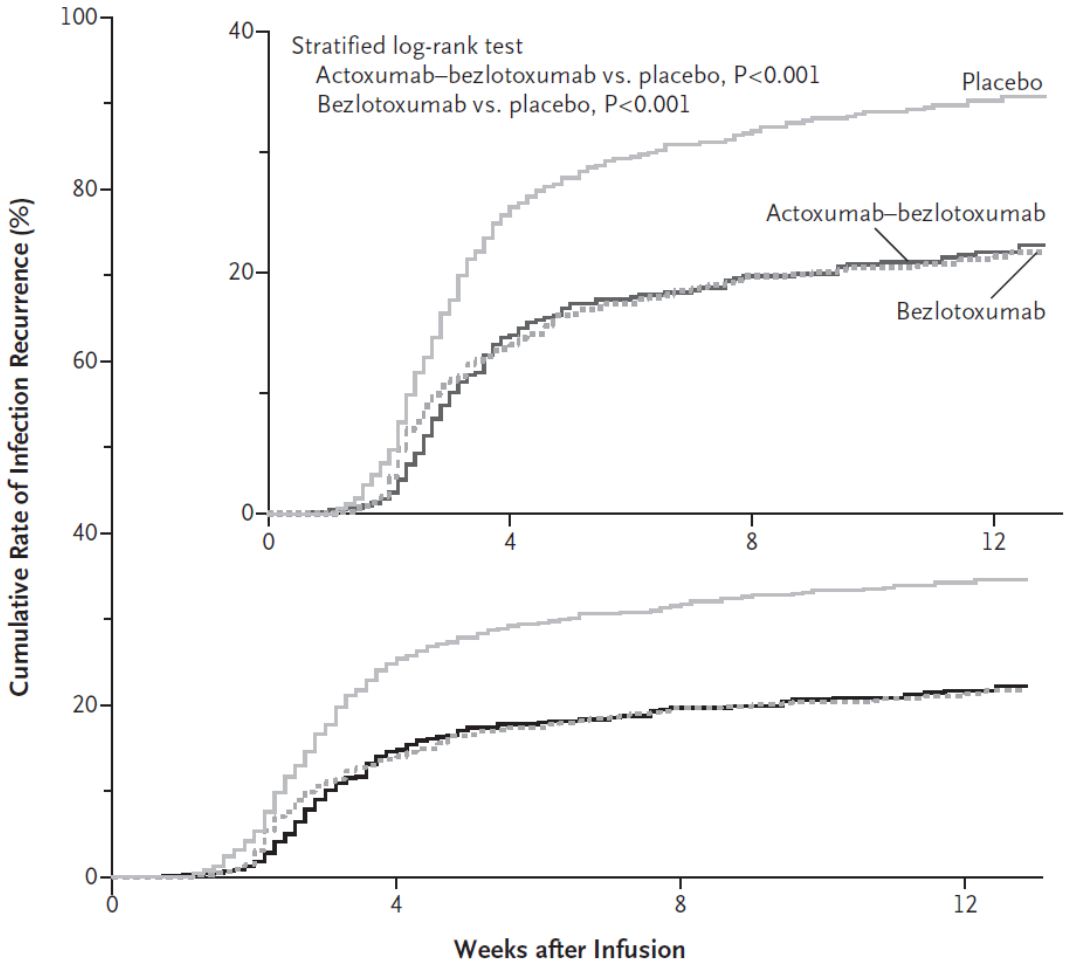
ESTABLISHED IN 1812 JANUARY 26, 2017 VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

Two double-blind, randomized, placebo-controlled, phase 3 trials**, MODIFY I** and **MODIFY II**, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection.

Participants received an infusion of **bezlotoxumab** (10 mg per kilogram of body weight), **actoxumab plus bezlotoxumab** (10 mg per kilogram each), **or placebo**; The primary end point was recurrent infection (new episode after initial clinical cure) **within 12 weeks** after infusion in the modified intention-to-treat population.



No. at Risk				
Actoxumab–bezlotoxumab	773	465	416	301
Bezlotoxumab	781	518	463	343
Placebo	773	443	386	272
Kaplan–Meier Rate Estimates (95% CI) — %				
Actoxumab–bezlotoxumab		15 (12–18)	20 (16–23)	22 (18–25)
Bezlotoxumab		14 (11–17)	20 (16–23)	21 (18–25)
Placebo		26 (22–29)	32 (28–36)	34 (30–38)

Clinical Infectious Diseases

MAJOR ARTICLE

Clinical Infectious Diseases® 2018;

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection in Patients at Increased Risk for Recurrence

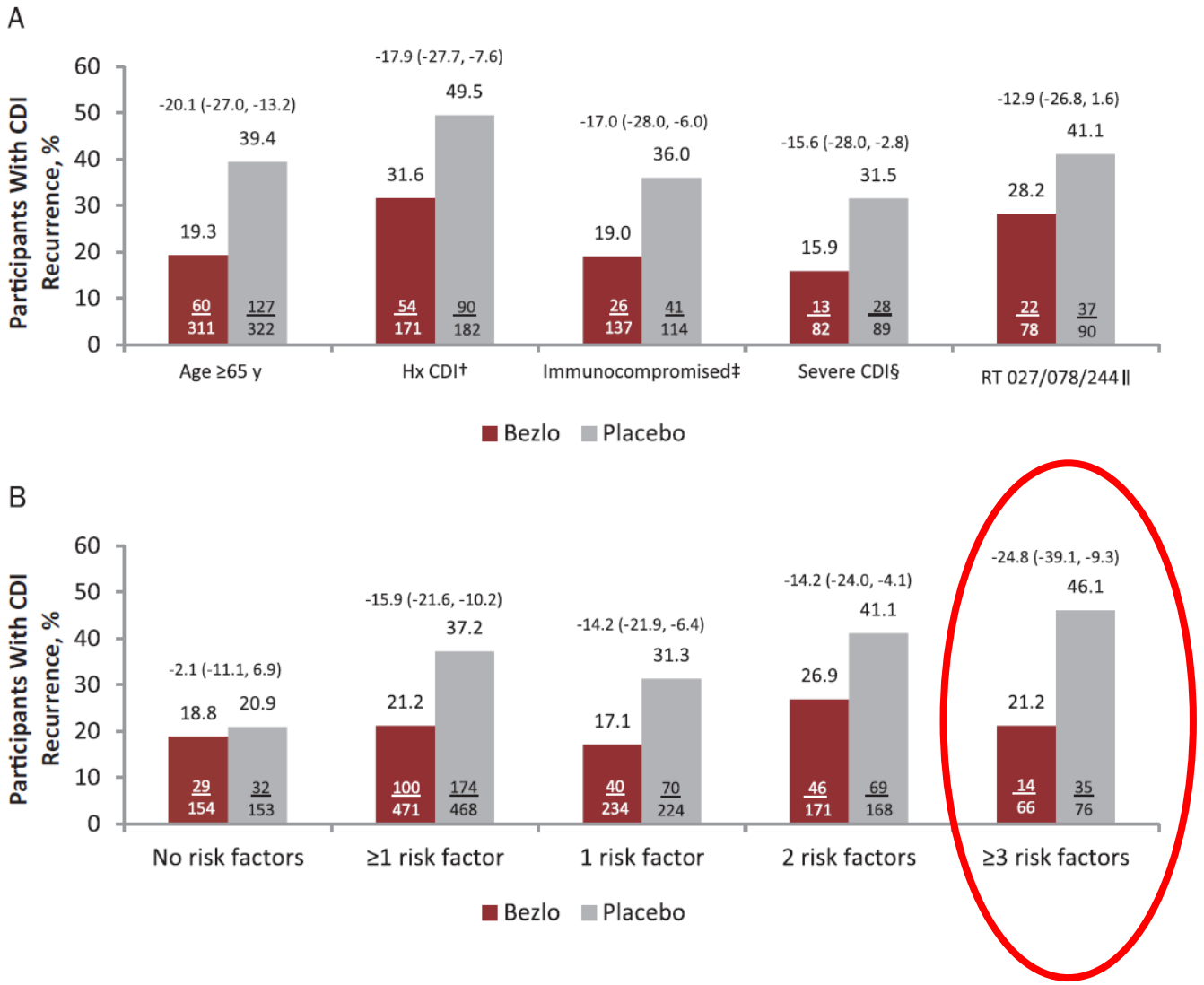
Dale N. Gerding,[1] Ciaran P. Kelly,[2] Galia Rahav,[3] Christine Lee,[4,5] Erik R. Dubberke,[6] Princy N. Kumar,[7] Bruce Yacyshyn,[8] Dina Kao,[9] Karen Eves,[10] Misoo C. Ellison,[11] Mary E. Hanson,[12] Dalya Guris,[10] and Mary Beth Dorr[10]

[1]Department of Veterans Affairs, Edward Hines Jr Veterans Affairs Hospital, Illinois; [2]Gastroenterology Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; [3]Infectious Diseases, Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel-Aviv University, Israel; [4]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, and [5]McMaster University, Hamilton, Ontario, Canada; [6]Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri;

post hoc analysis of pooled monocolonal antibodies for *C. difficile* therapy (MODIFY) I/II data

The proportion of placebo participants who experienced rCDI exceeded 30% for each risk factor compared with 20.9% among those without a risk factor, and the rCDI rate increased with the number of risk factors (1 risk factor: 31.3%; ≥3 risk factors: 46.1%)

While participants with ≥3 risk factors had the greatest reduction of rCDI with bezlotoxumab, those with 1 or 2 risk factors may also benefit.



The NEW ENGLAND JOURNAL of MEDICINE

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Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

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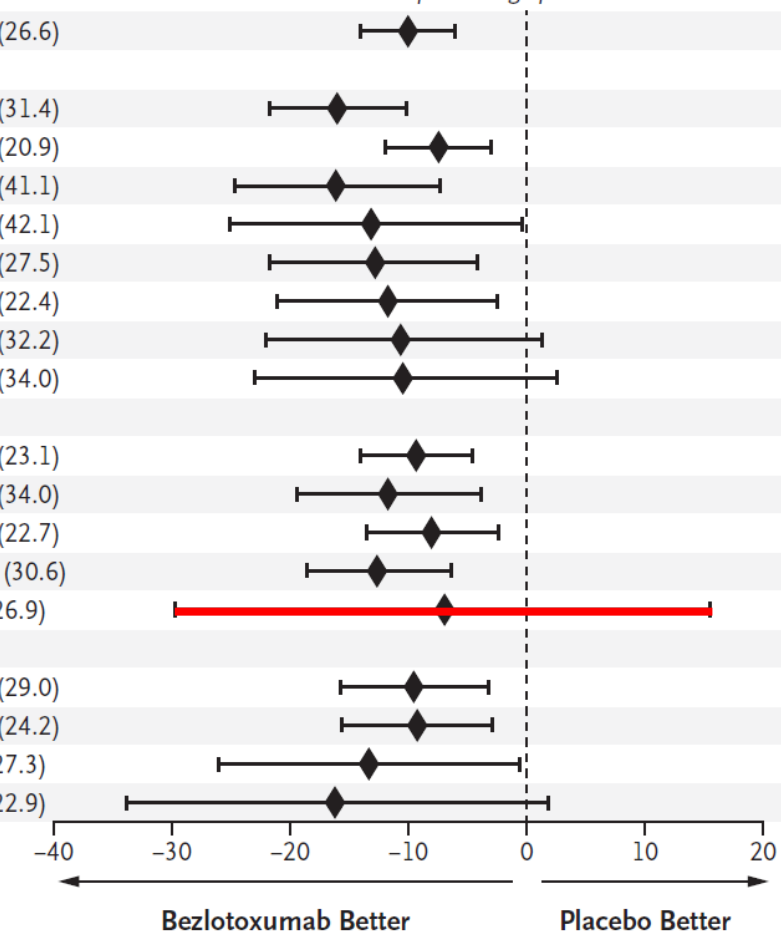
A

Subgroup	Bezlotoxumab	Placebo	Absolute Rate Difference (95% CI)	Rate Difference	
				Absolute	Relative
	no./total no. (%)		*percentage points*		
All participants	129/781 (16.5)	206/773 (26.6)		−10.0	−37.5
Risk factors for recurrence					
≥65 yr of age	60/390 (15.4)	127/405 (31.4)		−16.0	−50.9
No CDI in past 6 mo	75/556 (13.5)	114/545 (20.9)		−7.4	−35.5
≥1 CDI episodes in past 6 mo	54/216 (25.0)	90/219 (41.1)		−16.1	−39.2
≥2 previous CDI episodes ever	29/100 (29.0)	53/126 (42.1)		−13.1	−31.1
Immunocompromised	26/178 (14.6)	42/153 (27.5)		−12.8	−46.8
Severe CDI: Zar score ≥2	13/122 (10.7)	28/125 (22.4)		−11.7	−52.4
027, 078, or 244 strain	22/102 (21.6)	37/115 (32.2)		−10.6	−33.0
027 strain	21/89 (23.6)	34/100 (34.0)		−10.4	−30.6
Stratification variables					
Inpatient	73/530 (13.8)	120/520 (23.1)		−9.3	−40.3
Outpatient	56/251 (22.3)	86/253 (34.0)		−11.7	−34.4
Metronidazole	56/379 (14.8)	85/374 (22.7)		−8.0	−35.0
Vancomycin	67/372 (18.0)	114/373 (30.6)		−12.6	−41.1
Fidaxomicin	6/30 (20.0)	7/26 (26.9)		−6.9	−25.7
Geographic region					
North America	69/354 (19.5)	106/366 (29.0)		−9.5	−32.7
Europe	47/313 (15.0)	71/293 (24.2)		−9.2	−38.0
Asia–Pacific	11/79 (13.9)	21/77 (27.3)		−13.3	−48.9
Latin America	2/30 (6.7)	8/35 (22.9)		−16.2	−70.8



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

Contents lists available at ScienceDirect

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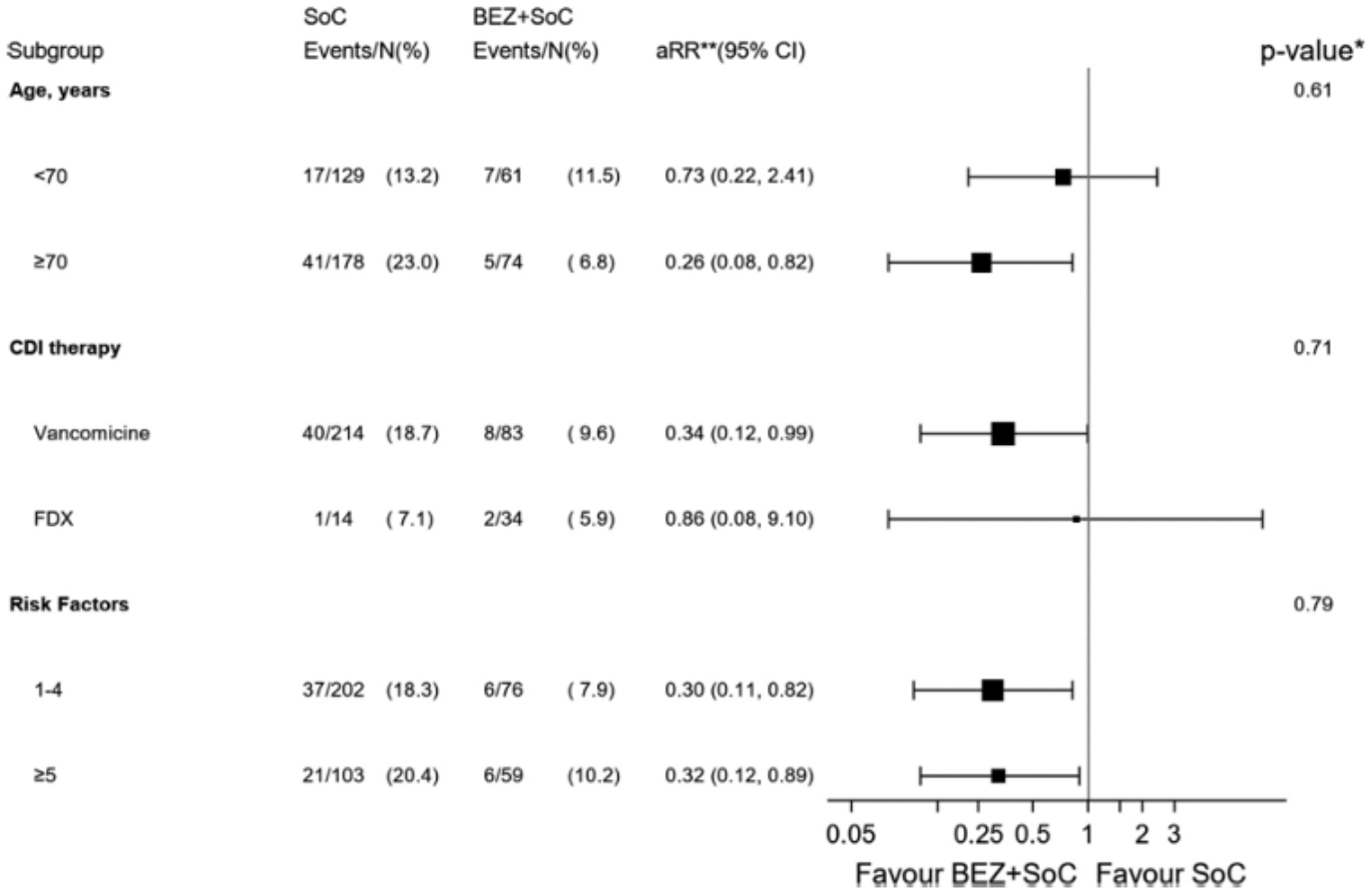
journal homepage: www.elsevier.com/locate/ijid

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

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

- Methods: A multicenter cohort study was conducted including **442 patients** with Clostridioides difficile infection from 2018 to 2022, collected from **18 Italian centers**. The main outcome was the 30-day occurrence of rCDI. The secondary outcomes were (i) all-cause mortality at 30 days (ii) and the composite outcome (30-day recurrence and/or all-cause death).
- Results: rCDI at day 30 occurred in 54 (12%): 11 in the BEZ + SoC group and 43 treated with SoC alone (8% vs 14%, odds ratio [OR] = 0.58, 95% confidence interval [CI]: 0.31-1.09, P = 0.09). The difference between BEZ + SoC versus SoC was statistically significant after controlling for confounding factors (ad- justed OR = 0.40, 95% CI: 018-0.88, P = 0.02) and even more using the composite outcome (adjusted OR = 0.35, 95% CI: 0.17-0.73, P = 0.005).
- Conclusion: Our study confirms the efficacy of BEZ + SoC for the prevention of rCDI and death in a real-world setting. BEZ should be routinely considered among participants at high risk of rCDI regardless of age, type of Clostridioides difficile infection therapy (vancomycin vs fidaxomicin), and number of risk factors



antibiotics

MDPI

Perspective

Bezlotoxumab in Patients with a Primary *Clostridioides difficile* Infection: A Literature Review

Guido Granata [1,*], Francesco Schiavone [2] and Giuseppe Pipitone [3]

[1] Clinical and Research Department for Infectious Diseases, National Institute for Infectious Diseases L. Spallanzani, IRCCS, 00149 Rome, Italy
[2] Divers and Raiders Group Command "Teseo Tesei" COMSUBIN, Medical Service, Italian Navy, 19025 Portovenere, Italy
[3] Infectious Disease Unit, ARNAS Civico-Di Cristina, Piazza Leotta, 5, 90100 Palermo, Italy
* Correspondence: guido.granata@inmi.it; Tel.: +39-06-55170264

ALLEGA

Agenzia Italiana del Farmaco
AIFA

Scheda cartacea per la prescrizione della specialità medicinale ZINPLAVA

Indicazioni terapeutiche: ZINPLAVA è 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
☐	Zinplava	25 mg/mL concentrato per soluzione per infusione	10 mg/kg

ZINPLAVA 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.

Nome e cognome del Medico*: _____

Recapiti del Medico*: _____

** La prescrivibilità è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica ad hoc identificato dal Comitato Infezioni Ospedaliere (CIO) istituito per legge presso tutti i presidi ospedalieri (Circolare Ministero della Sanità n. 52/1985).*

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

ZAR–score

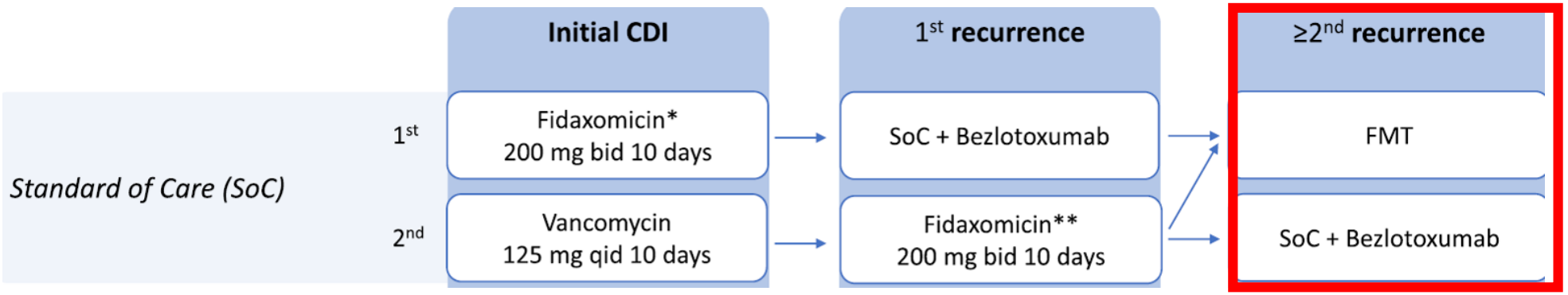
- **One point** is given for each of the following:
  - age >60 years
  - temperature >38.3°C
  - albumin level <2.5 mg/dL
  - WBC count >15,000 cells/mm^3.
- **Two points** are given for
  - endoscopic evidence of pseudomembranous colitis
  - treatment in the ICU.

A Comparison of Vancomycin and Metronidazole for the Treatment of *Clostridium difficile*–Associated Diarrhea, Stratified by Disease Severity FREE

Fred A. Zar ✉, Srinivasa R. Bakkanagari, K. M. L. S. T. Moorthi, Melinda B. Davis

Clinical Infectious Diseases, Volume 45, Issue 3, 1 August 2007, Pages 302–307, https://doi.org/10.1086/519265
Published: 01 August 2007 **Article history** ▾

What is the best treatment for multiple recurrent CDI?



- Treatment options for a second or further CDI recurrence include FMT after SoC antibiotic pre-treatment or bezlotoxumab in addition to SoC antibiotic treatment. The choice between either depends on patients' characteristics, previous treatment, local regulations, availability and feasibility.

- For **FMT** an adequate multidisciplinary risk assessment is mandatory and **FMT products should be available with standardized preparation and screening**. Weak, Moderate (FMT) / Low (bezlotoxumab)

Ann Ist Super Sanità 2021 | Vol. 57, No. 3: 239-243
DOI: 10.4415/ANN_21_03_07

The Italian National Faecal Microbiota Transplantation Program: a coordinated effort against *Clostridioides difficile* infection

Maria Chiara de Stefano[1], Benedetta Mazzanti[1], Francesca Vespasiano[1], Giovanni Cammarota[2], Gianluca Ianiro[2], Luca Masucci[3], Maurizio Sanguinetti[3], Antonio Gasbarrini[2], Letizia Lombardini[1] and Massimo Cardillo[1]

- In **2018**, the Italian National FMT Program was launched, with the aim to provide high quality standards in FMT application to adults with rCDI not responding to antibiotic therapy.
- **Currently, the FMT center within Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome is the only one to carry out microbiota transplants**, as the service has been able to adapt its operational workflow during COVID-19 pandemic, in order to continue offering FMT treatment to patients with rCDI.
- With regard to the surveillance of FMT safety and efficacy, the CNT has developed a client-server application (MySQL database) to register the procedures carried out within the Italian National FMT Program and the users can easily enter data relating to donor, patient, stool sample processing, route of delivery, and transplant outcomes including any serious adverse events and/or reactions occurring during the followup period (8 weeks). This system ensures transplants traceability and represents the nationwide collection of faecal microbiota transplants.

Table 1
Characteristics of treated patients, donors, transplants and outcomes

	N
Patients	31
Male/female	17/14
Median age (min-max)	70 (20-94)
Vancomycin/fidaxomicin treatment pre-FMT	31/0
Donors	6
Male/female	2/4
Median age (min-max)	50 (37-60)
Unrelated/related	5/1
Transplants	
Frozen/fresh material	31/0
Colonoscopy/enema/nasogastric tube	31/0/0
Single/sequential infusions in patients with completed follow-up	18/6
Outcomes	
Follow-up at 8 weeks completed/ongoing	24/7
Successful/failed outcome	24/0
Serious adverse events/serious adverse reactions	0/0

Hindawi
BioMed Research International
Volume 2022, Article ID 5787373, 9 pages
https://doi.org/10.1155/2022/5787373

Research Article

"Bacterial Consortium": A Potential Evolution of Fecal Microbiota Transplantation for the Treatment of *Clostridioides difficile* Infection

Gianluca Quaranta,[1] **Gianluca Ianiro**,[2] **Flavio De Maio**,[1] **Alessandra Guarnaccia**,[1] **Giovanni Fancello**,[1] **Chiara Agrillo**,[1] **Federica Iannarelli**,[1] **Stefano Bibbo**,[2] **Amedeo Amedei**,[3] **Maurizio Sanguinetti**,[1,4] **Giovanni Cammarota**,[2] **and Luca Masucci**[1,4]

Gastroenterol Hepatol (N Y). 2023 Jun;19(6):319-328.

Clostridioides *difficile* Infection: Landscape and Microbiome Therapeutics

Brent J Gawey [1], Sahil Khanna [1]

Table 2. Microbiota Restoration Therapies for Prevention of Recurrent *Clostridioides difficile* Infection

Composition and route of administration	Product	Recurrence	Current status
Stool-derived enema	Fecal microbiota, live-jslm; formerly RBX2660	Second/third	Received FDA approval for prevention of recurrence
Stool-derived oral capsule	CP101	Second/third	Clinical development has been discontinued
	MET-2	Second/third	Phase 2 is being planned
	RBX7455	Second/third	Phase 3 is being planned
	Fecal microbiota spores, live-brpk; formerly SER-109	Third	Received FDA approval for prevention of recurrence
Synthetic oral capsule	SER-262	First	No active trials
	VE303	First/second/third	Phase 3 is underway

Can prognostic factors identify patients at risk for severe CDI?

- The use of PPIs, H2 receptor antagonists and antibiotics did not appear to influence the risk of severe CDI, nor did the presence of C. difficile strains capable to produce binary toxin
- We observed a high level of inconsistency in the results of studies assessing infection with the C difficle 027 strain as a risk factor.

Due to the heterogeneity of studies reporting on comorbidities as a risk factor, we cannot define an exact number of comorbidities required to predict a severe course of CDI.

Can prognostic factors identify patients at risk for recurrent CDI?

- **Older age (>65 years old)** is the most important risk factor for recurrent CDI. Strong, Moderate _ Patients with prior CDI episode(s) are at an increased risk for recurrent CDI. Strong, Moderate _
- **Patients with healthcare-associated CDI** and **prior hospitalization** in the last three months are considered at increased risk for recurrent CDI. Weak, Low _
- **Patients with concomitant non-CDI antibiotic use after the diagnosis of CDI** are considered at increased risk for recurrence of CDI. Weak, Very low _
- **Patients using PPIs started during/after CDI diagnosis** are considered at increased risk for recurrent CDI. Weak, Very low As mentioned in the previous paragraph, an important characteristic (albeit limitation or strength) of our analysis is the selection of articles complying to predefined criteria and a strict GRADE approach.

- **Overall quality of evidence for the prognosis of recurrent CDI was low to moderate.**
- **Most of the studies were retrospective, with a high to moderate risk of bias**

Is there a place for prophylaxis for prevention of CDI?

- Routine administration of **probiotics** to prevent CDI when on antibiotic treatment **is not recommended**. Strong, low

- Routine prophylaxis with **anti-CDI antibiotics** when on systemic antibiotic treatment **is not recommended**. Good practice statement

Prophylaxis with CDI antibiotics

Clinical Infectious Diseases
MAJOR ARTICLE
CID 2020:71 (1 September) • 1133

Effectiveness of Oral Vancomycin for Prevention of Healthcare Facility–Onset *Clostridioides difficile* Infection in Targeted Patients During Systemic Antibiotic Exposure

Steven W. Johnson,[1,2] Shannon V. Brown,[1] and David H. Priest[3,4]

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An open label RCT (n = 100) with a follow-up of 3 months **found a benefit of oral vancomycin prophylaxis vs. no prophylaxis** (CDI occurrence 0% vs. 16%) in patients aged 60 years or older who received systemic antibiotics and who had prior hospitalization with systemic antibiotic therapy in the previous month.

Clinical Infectious Diseases
MAJOR ARTICLE
CID 2019:68 (15 January)

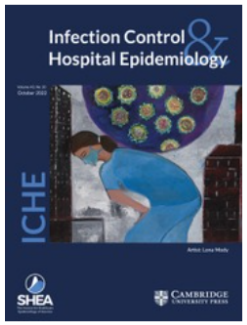
A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of *Clostridium difficile*–associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation

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

A placebo-controlled RCT in patients undergoing stem cell transplantation with planned fluoroquinolone prophylaxis found **no difference between fidaxomicin prophylaxis and placebo in the composite end-point of prophylaxis failure** (confirmed CDI, receiving CDI active medication, missing CDI assessment). However, follow-up was limited to 30 days and a sensitivity analysis found a 6.4% reduction (95% CI 2.2e10.6) in CDI occurrence with fidaxomicin prophylaxis.

Prophylaxis with CDI antibiotics

- potential side-effects, microbiome distortion,
- acquisition of antimicrobial resistance and an associated increased risk for recurrent
- VRE colonization



Oral vancomycin prophylaxis against recurrent *Clostridioides difficile* infection: Efficacy and side effects in two hospitals

Published online by Cambridge University Press: **16 June 2020**

Ioannis M. Zacharioudakis, Fainareti N. Zervou, Yanina Dubrovskaya and Michael S. Phillips

Prophylactic vancomycin is an effective strategy to prevent CDI recurrence, but it increases the risk of VRE colonization. Thus, a careful selection of patients with high benefit-to-risk ratio is needed for the implementation of this preventive policy.

CID 2012:55 (Suppl 2) • S121

Reduced Acquisition and Overgrowth of Vancomycin-Resistant Enterococci and *Candida* Species in Patients Treated With Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection

Michelle M. Nerandzic,[1] Kathleen Mullane,[2] Mark A. Miller,[3] Farah Babakhani,[4] and Curtis J. Donskey[1,5]

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The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

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

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

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

- Oral vancomycin is highly disruptive to the gut microbiome, more so than cephalosporins alone, which theoretically makes the risk of *C. difficile* infection once vancomycin is stopped higher than if it had never been administered.
- Even tapering vancomycin may not provide benefit to prevent *C. difficile* infection after secondary prophylaxis with oral vancomycin.
- Given these factors, while we wait for results from randomized, well-controlled trials (e.g., ClinicalTrials.gov number, NCT03462459), we **would recommend against the use of oral vancomycin as secondary prophylaxis for this patient.**

Optimal CDI therapy during pregnancy

- **Pregnant or breast-feeding woman are typically excluded from pivotal trials**.
- Fidaxomicin, oral vancomycin and metronidazole were originally classified as pregnancy **category B by the FDA** (no evidence in risk studies), whereas **iv vancomycin hydrochloride** was designated **category C** (risk cannot be ruled out) Importantly, some pre-constituted **iv formulation of vancomycin contain the excipients PEG 400 and NADA** and therefore cannot be used for oral administration in pregnant woman, as these have caused foetal malformations in animal reproductive studies

The timing of the start of empirical treatment

- The 2017 IDSA guideline advised to start empiric treatment only **when a significant delay in laboratory confirmation is expected or when dealing with fulminant CDI** (weak recommendation).
- We concur with the suggested approach and **strongly discourage the start of empirical therapy without diagnostic testing in other cases**.
- In the absence of evidence and based on clinical experience, we also discourage treatment beyond the recommended standard duration of 10-14 days with SoC antibiotics because of lack of response or co-administered antibiotic treatment

Research gaps/ **future research**

- Assessing the optimal treatment in **severe-complicated and refractory CDI**.
- **Comparing the effectiveness of bezlotoxumab and FMT** for the treatment of multiple recurrent CDI.
- Assessing the **benefit of adding bezlotoxumab to fidaxomicin** treatment.
- Discontinue therapy with the inciting antimicrobial agent in non-severe CDI as a single intervention.
- Investigation into optimal CDI treatment and treatment algorithms in large scale trials independent from pharmaceutical industry (i.e. not as sponsor or subsidising party).
- Optimal identification of patients at risk for recurrent CDI. These patients might be offered adjuvant bezlotoxumab or FMT earlier in the course of disease.
- Insight into the exact mechanism of FMT for CDI treatment. This might enable a more regulated and standardized preparation process of FMT products.

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Omadacycline and *Clostridioides difficile*: A Systematic Review of Preclinical and Clinical Evidence

Kevin W. Garey, PharmD, MS[1*], Warren Rose, PharmD, MPH[2*], Kyle Gunter, PharmD, MBA[3], Alisa W. Serio, PhD[3], and Mark H. Wilcox, MD[4]

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https://doi.org/10.1093/jac/dkad170 Advance Access publication 5 June 2023

Journal of Antimicrobial Chemotherapy

Antimicrobial susceptibility of *Clostridioides difficile* to omadacycline and comparator antimicrobials

Andrew M. Skinner [1,2]*, Laurica A. Petrella[2], Adam Cheknis[2] and Stuart Johnson [1,2]

- Omadacycline is an aminomethylcycline within the tetracycline class of antimicrobials that has demonstrated in vitro activity towards Gram-positive and Gram-negative bacteria.
- Similar to other tetracyclines, omadacycline binds to the 30S ribosomal subunit and inhibits protein synthesis.
- Notably, omadacycline has been modified to overcome efflux mechanisms of resistance (tetA/tetB) as well as the ribosomal resistance mechanisms (tetM) resulting in broader antibacterial coverage.
- In 2018, omadacycline was approved for use by the US FDA for the treatment of community-associated bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI).
- Omadacycline has also been shown to be a potent inhibitor of CD because recent data reveal a low MIC towards CD compared with the standard-of-care antimicrobials for CD treatment. These data have led to the postulation that omadacycline provides protection against the development of a CDI in part due to the potent inhibitory effects towards CD..

- Although omadacycline activity towards CD might predict a lower risk of CDI compared with comparator antimicrobials, other factors, such as effects on the gut microbiome, may also impact on this risk. Because this was an in vitro study, we are unable to determine the impact on the gut microbiome that omadacycline would have compared with these comparator antimicrobials. However, previously published data show that although omadacycline impacts the gut microbiome in a well-established human gut model, neither CD germination nor toxin production was detected.32Further research is required to determine the clinical implication of these data.

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Phage therapy for *Clostridioides difficile* infection

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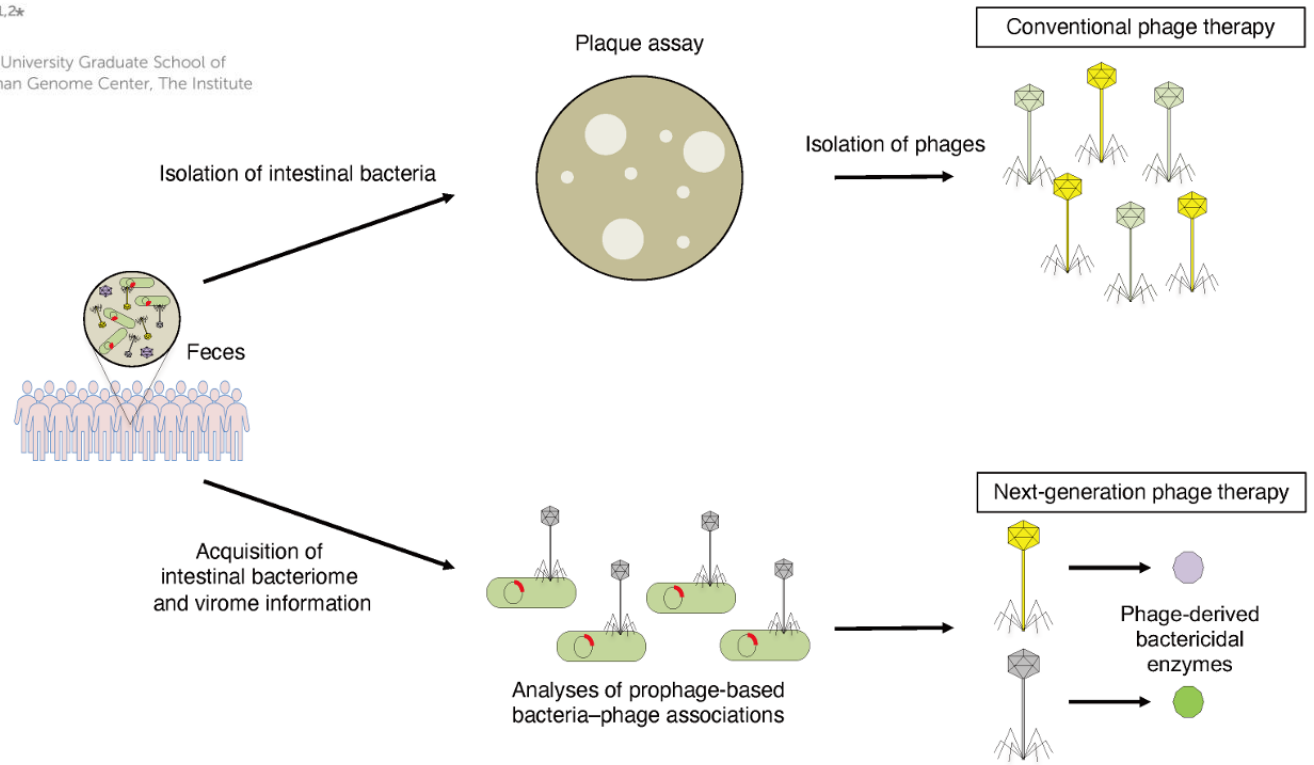

FIGURE 2
Conventional phage therapy and next-generation phage therapy based on metagenomic information. To isolate phages that can specifically control pathobionts, host bacteria is isolated from human fecal samples and plaque assay is performed. Isolated phages are used for phage therapy (conventional phage therapy). To detect phage-derived antibacterial enzymes that can specifically regulate pathobionts, intestinal bacterial and viral metagenomic information is acquired from human fecal samples. Phage-derived bactericidal enzymes can kill host bacteria specifically (next-generation phage therapy).

Journal of Medicinal Chemistry

Editors' Choice

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Featured Article

A Potent and Narrow-Spectrum Antibacterial against *Clostridioides difficile* Infection

Yuanyuan Qian, Biruk T. Birhanu, Jingdong Yang, Derong Ding, Jeshina Janardhanan, Shahriar Mobashery, and Mayland Chang*

Cite This: https://doi.org/10.1021/acs.jmedchem.3c01249

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- We screened a library of 75 oxadiazoles against C. difficile ATCC 43255. The findings from this collection served as the basis for the syntheses of an additional 58 analogs, which were tested against the same strain.
- We report a potent (MIC50 = 0.5 μg/mL and MIC90 = 1 μg/mL values for 101 C. difficile strains) and narrow-spectrum oxadiazole (3-(4-(cyclopentyloxy)phenyl)-5-(4-nitro-1H-imidazol-2-yl)-1,2,4-oxadiazole; compound 57), which is not active against common gut bacteria or other tested organisms. Compound 57 is selectively bactericidal against C. difficile and targets cell-wall synthesis.

antibiotics

MDPI

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Article

Identification of an Antimicrobial Peptide from the Venom of the Trinidad Thick-Tailed Scorpion *Tityus trinitatis* with Potent Activity against ESKAPE Pathogens and *Clostridioides difficile*

Milena Mechkarska [1,*], Taylor S. Cunning [2], Megan G. Taggart [2], Nigel G. Ternan [2], Jérôme Leprince [3], Laurent Coquet [4], Thierry Jouenne [4], Jordi Tena-Garcés [5], Juan J. Calvete [5] and J. Michael Conlon [6]

Journal of Infection (2014) xx, 1–6

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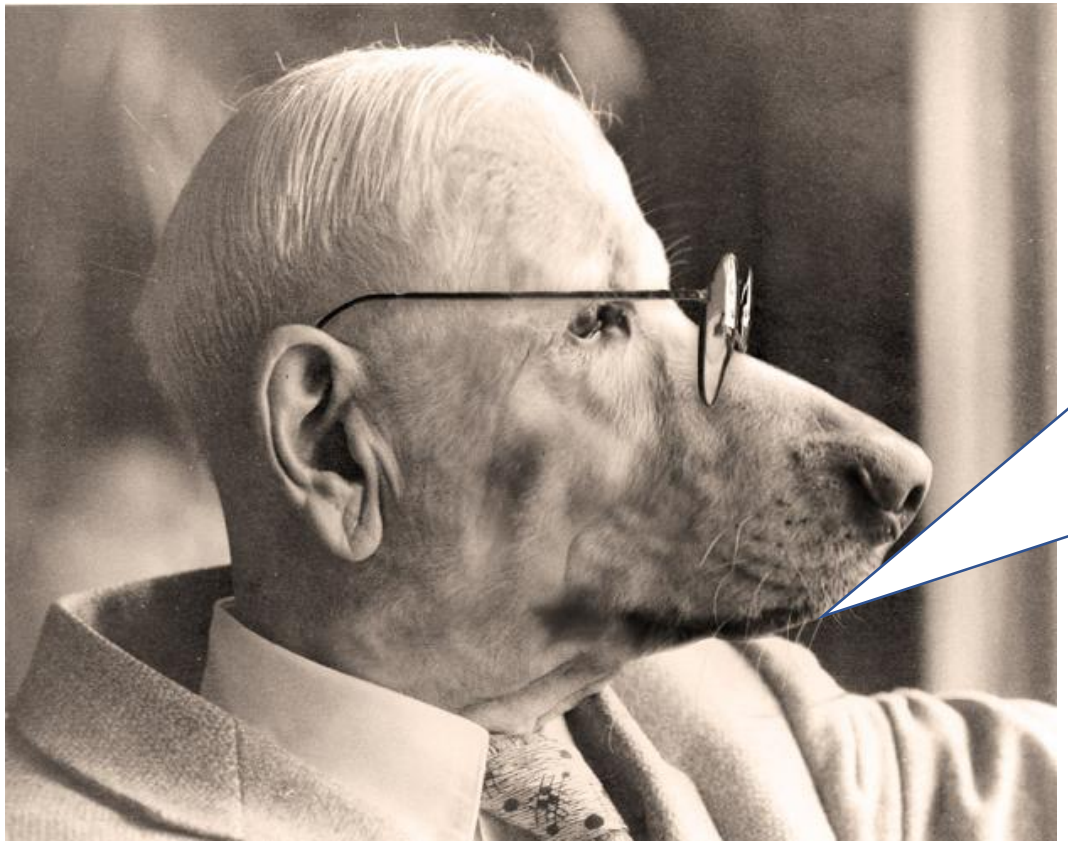
BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

A detection dog to identify patients with *Clostridium difficile* infection during a hospital outbreak

Marije K. Bomers [a,*], Michiel A. van Agtmael [a], Hotsche Luik [b], Christina MJE. Vandenbroucke-Grauls [c], Yvo M. Smulders [a]

Figure 1 Cliff in detection dog outfit on one of the hospital wards.



Thank you