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ARS TOSCANA agenzia regionale di sanità
Regione Toscana
SST Servizio Sanitario della Toscana
antibiotico-resistenza: sconfiggiamola insieme!

Convegno

Antimicrobico-resistenza: cure e ambiente

Firenze, 6 -7 giugno 2019

Istituto Stensen, viale Don Minzoni n. 25/C, Firenze

15:30 Nuove e vecchie terapie e novità di laboratorio

C. Tascini

Carlo Tascini
pursuant to art. 3.3 concerning Conflict of Interest, pg. 17 of the Reg. Application of State-Region Agreement of the 5th November 2009

hereby declares

direct relationships of financial involvement in the past two years with the following subjects with commercial interests in the health field:

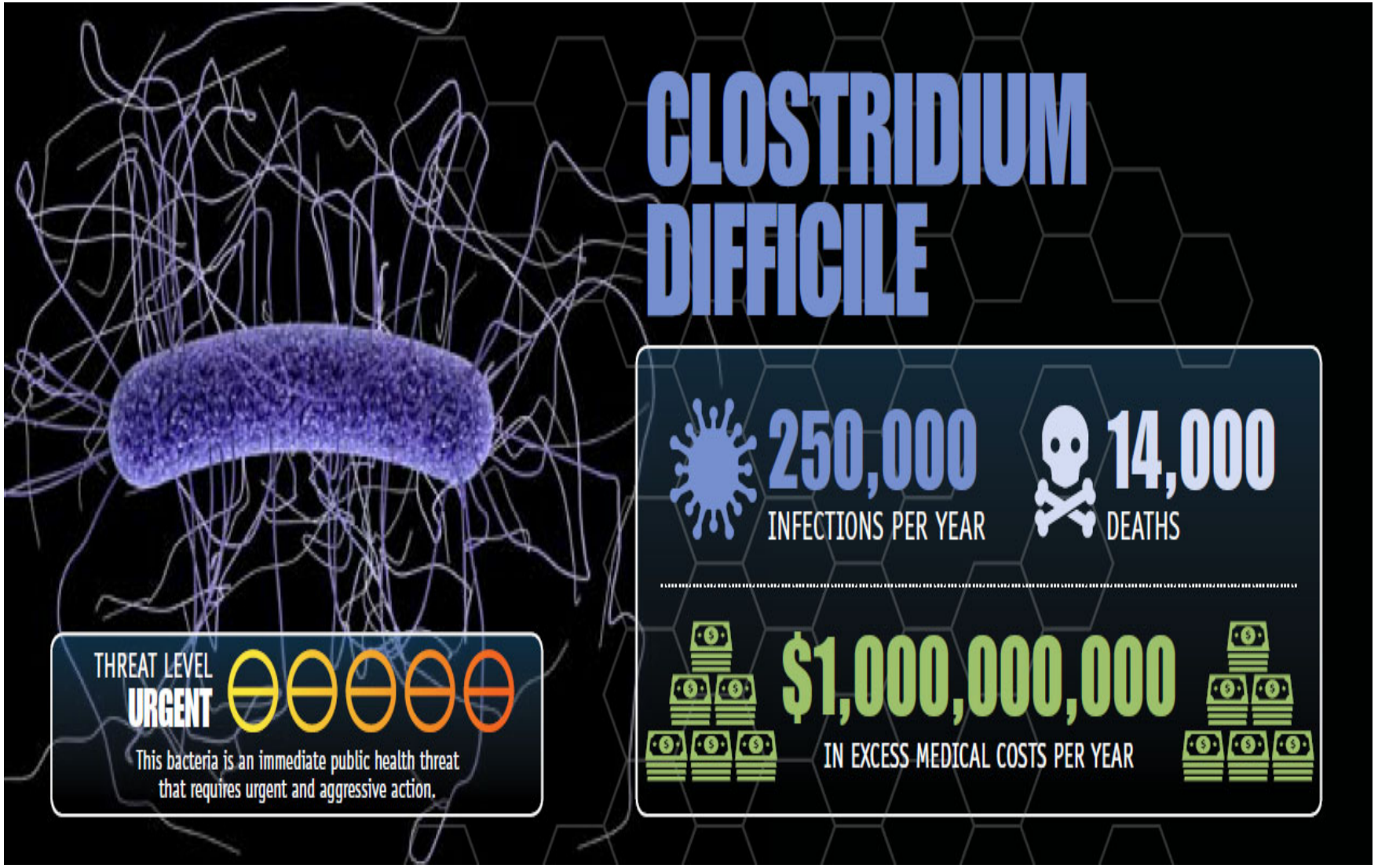
-*Merck*
-*Pfizer*
-*Astellas*
-*Angelini*
-*Gilead*
-*Novartis*
-*Thermofischer*
-*Biotest*
-*Correvio*

CDI History

Mandell, Douglas & Bennett's 2015

- 1979
  - Hospital environment contaminated with spores
- 1981
  - Persistence up to 24 weeks in the environment
  - Vancomycin treatment effective
- 1986
  - First prospective case-control study
  - 87% cases health-care associated
    - Gerding DN et al Arch Intern Med 1986
- 1989
  - Hospital acquisition by rectal swab: 21% of patients → 63% asymptomatic
    - Mc Farland MV et al NEJM 1989
- 2001
  - Association between humoral response to toxin and recurrence rate
    - Kyne L et al Lancet 2001
- Fidaxomicin & Bezlotoxumab

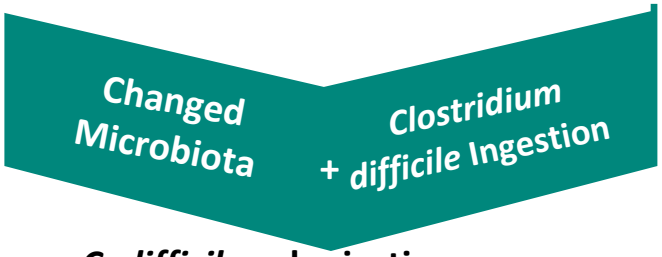
Clostridium difficile



ANTIBIOTIC RESISTANCE THREATS in the United States, 2013; US Dep. of Health and Human Services, CDC

C. difficile Infection

Alterations of Gastrointestinal Microbiota[1–3]:
Age, antibiotics, comorbidities, PPIs



***C. difficile* colonization, spore production, toxin expression[1,4]**

Toxin B more important than A[5,6,7]

- ***Clostridium difficile*: anaerobe, sporigen, Gram-positive bacteria**
- **Toxin A-B associated[1]**
- **Leading cause of diarrhea in hospitalized patients**
- **Marked neutrophilic inflammatory response in the colon, resulting in diarrhea, erosion of the mucosa**
- **Asymptomatic colonization to mild-moderate-severe disease and up to pseudomembranous colitis[4]**
- **Necrotic cells and proteinaceous material over the mucosa**
- **Diagnosis of CDI: GDH EIA test and toxin A-B detection[4]**

1.Britton RA, Young VB. *Gastroenterology*. 2014;146(6):1547–1553. **2.** Seekatz AM, Young VB. *J Clin Invest*. 2014;124(10):4182–4189. **3.** Biedermann L, Rogler G. *Eur J Pediatr*. 2015;174(2):151–167. **4.** Bagdasarian N et al. *JAMA*. 2015;313(4):398–408. **5.** Carter GP et al. *MBio*. 2015;6(3):e00551. doi:10.1128/mBio.00551-15. **6.** Lyras D et al. *Nature*. 2009;458(7242):1176–1179. **7.** Steele J et al. *J Infect Dis*. 2013;207(2):323–330

C. difficile Toxins

- **Most *C. difficile* strains → two toxins: TcdA and TcdB**
  - **A: permeability and fluid secretion**
  - **B: cytotoxicity → colonic inflammation**
- **Some *C. difficile* strains produce a binary toxin:**
  - ***C. difficile* transferase (CDT)**
  - **Closely related to the *C. perfringens* binary toxin**
  - **50-60% higher fatality rates than CDT-deficient strains**
  - **CDT enhanced *C. difficile* virulence**
  - **By suppressing protective colonic eosinophilia**

Eckert C et al *New microbes and new infections 2015;*3**:** 12-17.
Chowdhury PR et al. *BMC microbiology 2016;* 16:41.
Cowardin CA et al. *Nature Microbiology 2016;*1**:** 16108.
Bacci S. *Emerging Infectious Diseases 2011;* 17**:** 976-982.

C.difficile Epidemiology in Italy

Rome, 5 Hospitals, 2677 inbeds

15481 admissions per year

2006-2011

- CDI: 402/4.951 stool samples analyzed
- 2,3 CDI per 10.000 patient/days; up to 4.0/10.000 patient/days
- Higher rates: Surgical wards> Internal Medicine > ICUs

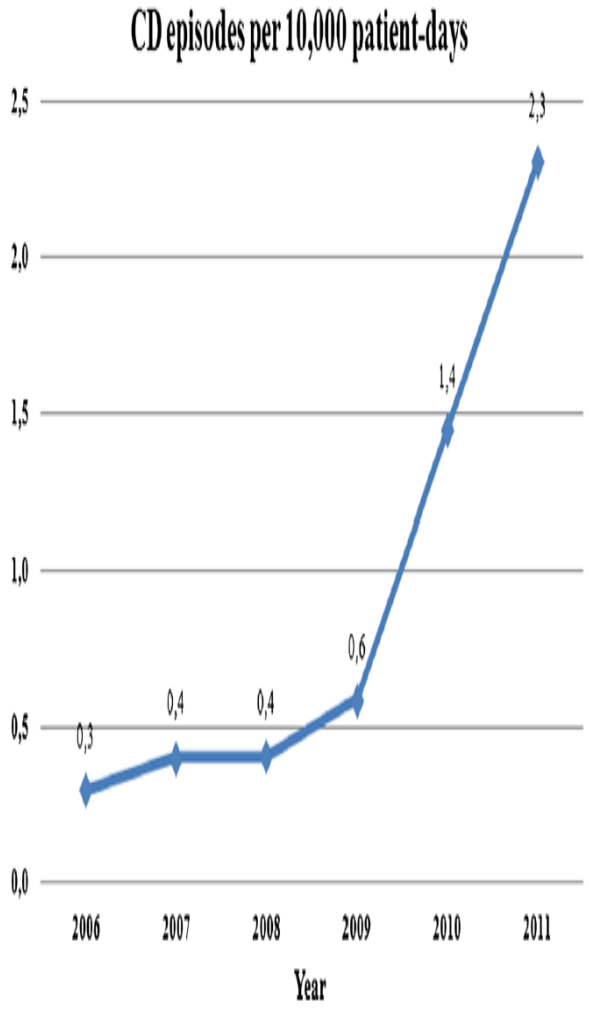


Figure 1 Distribution of Clostridium difficile infection (CDI) episode incidence per 10,000 patient-days from 2006 to 2011. Six hospitals in Rome, Italy.

Di Bella et al. BMC Infectious Diseases 2013, 13:146

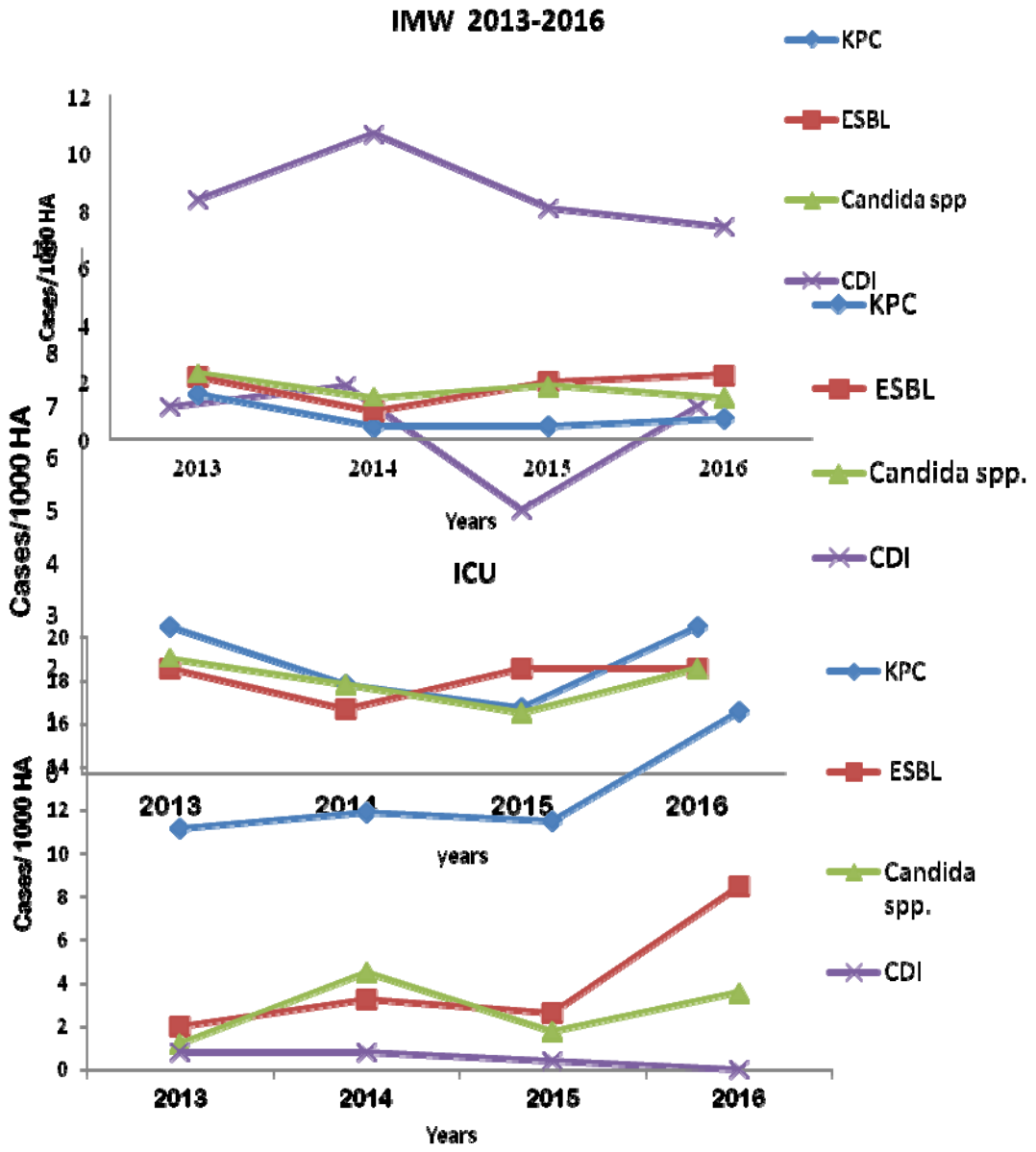
Epidemiology and Risk factors for Mortality in Bloodstream Infection by CP-Kp, ESBL-E, Candida and CDI: A Single Center Retrospective Study

Corcione et al. Eur J Intern Med 2018;48:44-49

- **Single centre retrospective study**
  - Patients admitted to Molinette Hospital, Turin, Italy
  - January 2013 to April 2015
  - CDI or BSI caused by Candida, ESBL-E or CP-Kp
- **786 cases:**
  - 398 CDI, 137 candidemia, 125 ESBL-E BSI and 126 CP-Kp BSI
  - 66% rate of previous hospitalization
  - In-hospital death rate = 23.4%
- **Internal Medicine Wards (IMW)**
  - CDI, candidemia and ESBL-E BSI more frequent
- **ICU:**
  - CP-Kp more frequent

Epidemiology and Risk factors for Mortality in Bloodstream Infection by CP-Kp, ESBL-E, Candida and CDI: A Single Center Retrospective Study

Corcione et al. Eur J Intern Med 2018;48:44-49



CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Candidemia in Patients with Body Temperature Below 37°C and Admitted to Internal Medicine Wards: Assessment of Risk Factors

Carlo Tascini, MD,[a] Marco Falcone, MD,[b] Matteo Bassetti, MD,[c] Francesco G. De Rosa, MD,[d,e] Emanuela Sozio, MD,[f] Alessandro Russo, MD,[b] Francesco Sbrana, MD,[g] Andrea Ripoli, PhD,[g] Maria Merelli, MD,[c] Claudio Scarparo, MD,[c] Franco Carmassi, MD,[f] Mario Venditti, MD,[b] Francesco Menichetti, MD[a]

CLINICAL SIGNIFICANCE

- An increase in episodes of candidemia has been reported in patients cared for in internal medicine wards.
- An increasing number of invasive candidiasis cases may lack fever at onset.
- Diabetes and *C. difficile* infection are associated with afebrile candidemia in IMWs.
- A delayed diagnosis of candidemia may complicate management of this infection.

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)

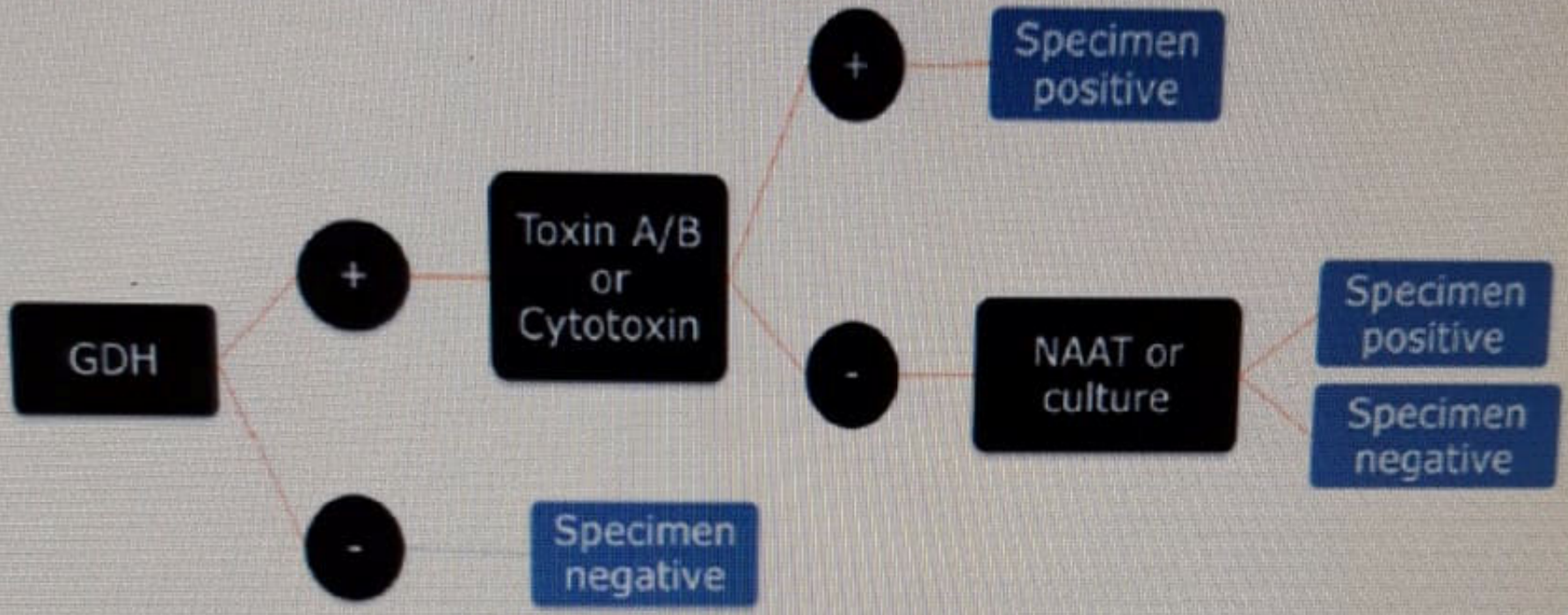
L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

Table 3. Summary of Available Tests for *Clostridium difficile* Infection, in Decreasing Order of Sensitivity

Test	Sensitivity	Specificity	Substance Detected
Toxigenic culture	High	Low[a]	*Clostridium difficile* vegetative cells or spores
Nucleic acid amplification tests	High	Low/moderate	*C. difficile* nucleic acid (toxin genes)
Glutamate dehydrogenase	High	Low[a]	*C. difficile* common antigen
Cell culture cytotoxicity neutralization assay	High	High	Free toxins
Toxin A and B enzyme immunoassays	Low	Moderate	Free toxins

[a]Must be combined with a toxin test.

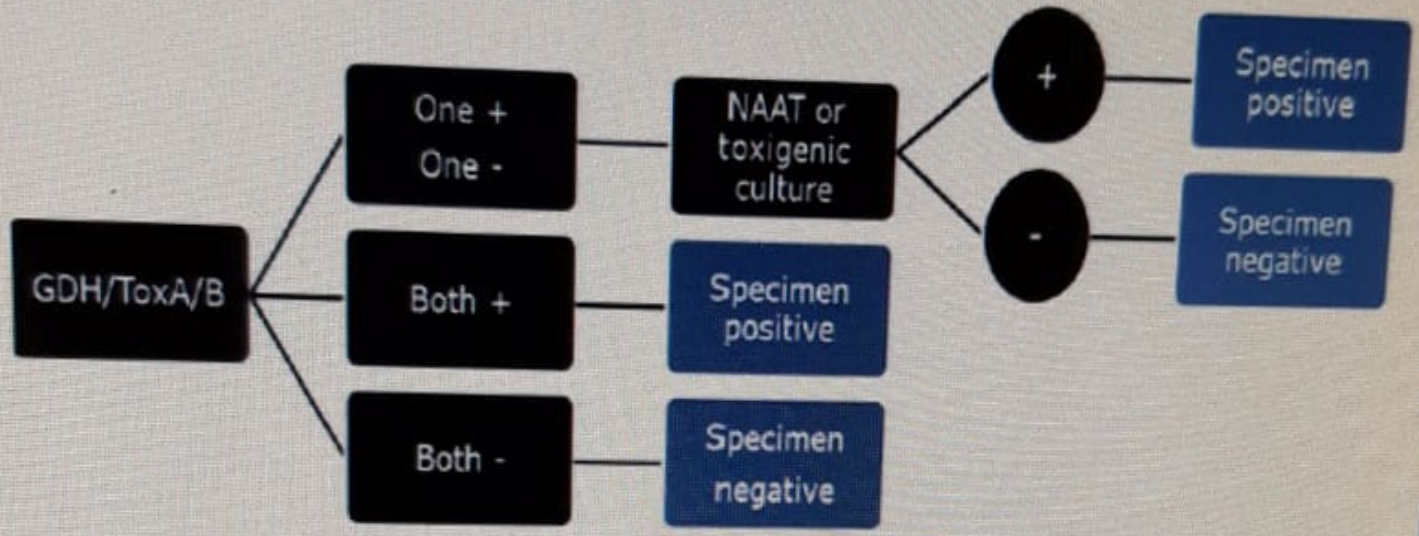
ASM GDH Screen Algorithm (A)



AMERICAN SOCIETY FOR MICROBIOLOGY

A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*
September 21, 2010*

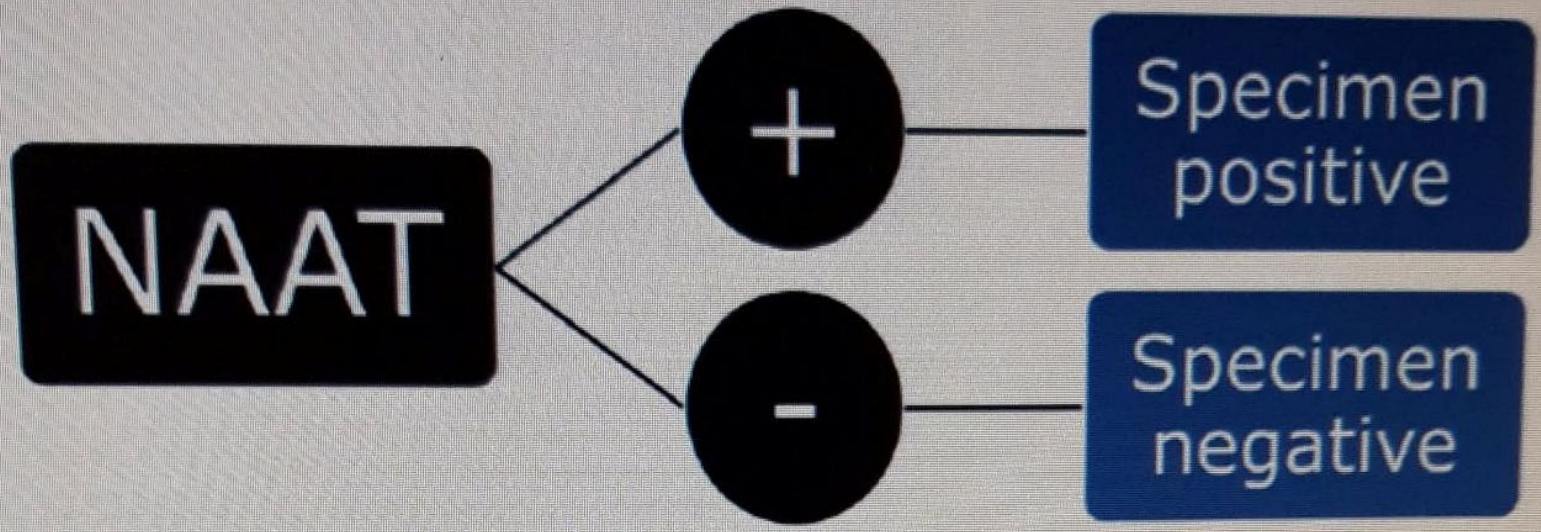
ASM GDH-Toxin A/B combo algorithm (B)



AMERICAN SOCIETY FOR MICROBIOLOGY

A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*
September 21, 2010*

ASM NAAT Stand alone test (Algorithm C)



AMERICAN SOCIETY FOR MICROBIOLOGY

A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*
September 21, 2010*


GeneXpert.
Cepheid

Differences in outcome according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C difficile* infection

Timothy D Planche, Kerrie A Davies, Pietro G Coen, John M Finney, Irene M Monahan, Kirsti A Morris, Lily O'Connor, Sarah J Oakley, Cassie F Pope, Mike W Wren, Nandini P Shetty, Derrick W Crook, Mark H Wilcox

Lancet Infect Dis 2013; 13: 936-45

Summary

Background Diagnosis of *Clostridium difficile* infection is controversial because of many laboratory methods, compounded by two reference methods. Cytotoxigenic culture detects toxigenic *C difficile* and gives a positive result more frequently

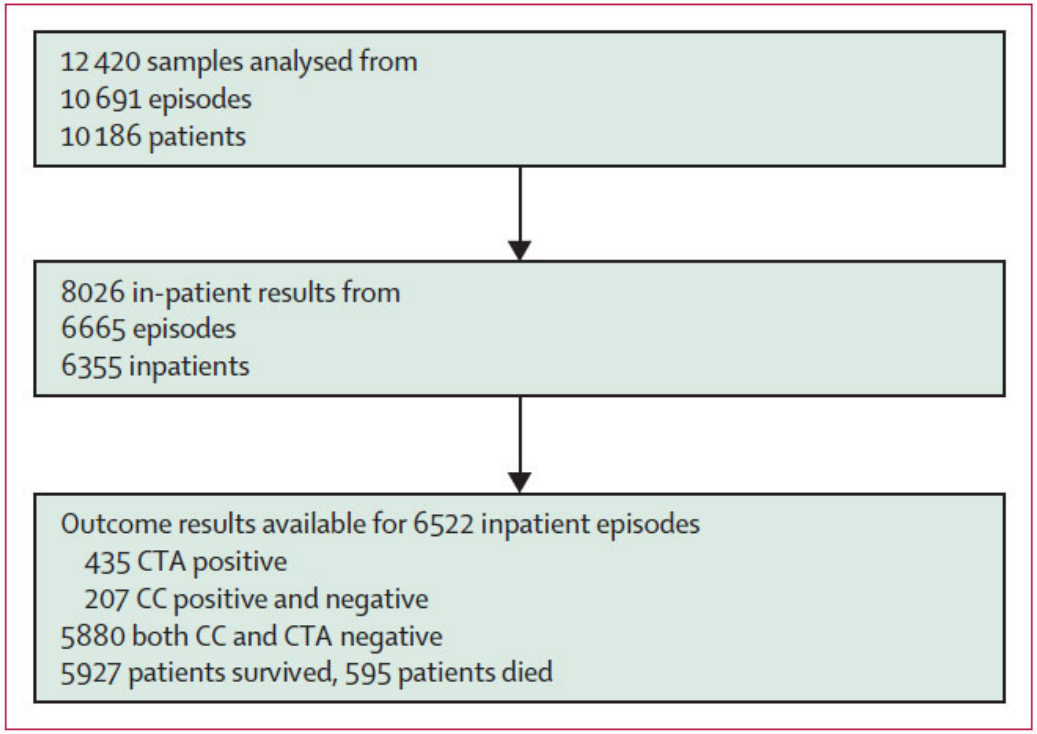


Figure 1: **Patient and sample selection**

CC=cytotoxigenic culture. CTA=cytotoxin assay.

	CTA positive	NAAT positive/ CTA negative	CTA and NAAT negative	CTA positive *vs* NAAT positive/CTA negative p value	CTA positive *vs* CTA and NAAT negative p value
Number	435	311	3943	..	..
Female (%)	243/435 (56%)	174/311 (56%)	2117/3941* (54%)	..	..
Mean age (years; SD)	69 (20)	64 (22)	64 (21)	..	..
Mean white cell count (×10^9/L; SD)	12·4 (8·9)	9·9 (6·6)	10·0 (12·0)	<0·0001	<0·0001
Mean rise in creatinine (%; SD)	37% (63)	49% (132)	34% (81)	0·0222	0·3018
>100% rise in creatinine (%)	40/316 (13%)	30/245 (12%)	321/3163 (9%)	..	..
Mean albumin (g/L; SD)	31 (7)	33 (8)	33 (8)	0·0328	<0·0001
Albumin <20 g/L (%)	13/344 (4%)	15/258 (6%)	166/3223 (5%)	..	..
Died (%)	72/435 (16·6%)	30/311 (9·7%)	349/3943 (8·9%)	0·004	<0·0001
Mean length of stay before sample (days; SD)	17·9 (29)	13·6 (23)	11·2 (22)	0·0311	<0·0001
Mean length of stay after sample (days; SD)	19·4 (25)	16·5 (24)	15·1 (24)	0·1869	0·0010
Death rate per 1000 inpatient days	9·03	6·04	6·05	0·0317	0·0018

CTA=cytotoxin assay. CC=cytotoxigenic culture. NAAT=nucleic acid amplification test. *Sex was not recorded for two patients in this group.

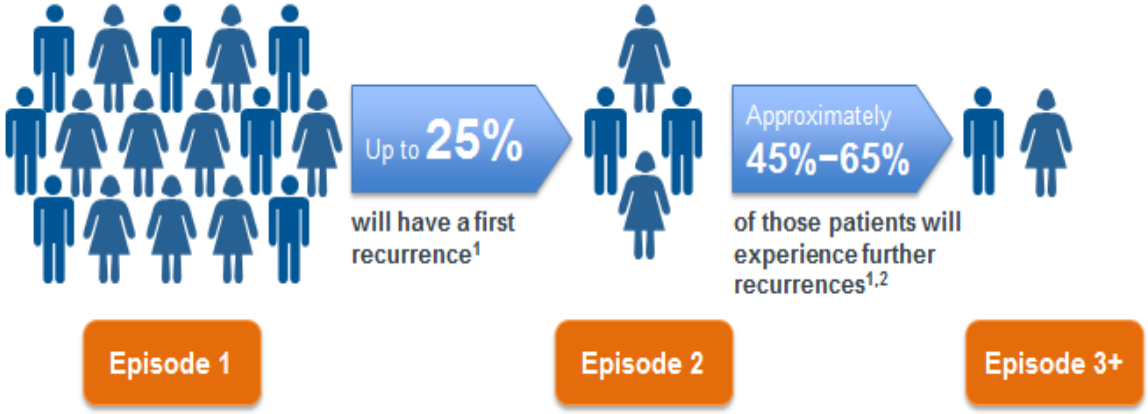
Table 3: **Clinical characteristics of first episodes of inpatients with available clinical outcome results with use of the result of the CTA and NAAT tests to define**

was published in 2002 that addressed this issue. Johansen et al. [2] found that nurses were able to predict correctly the presence of CDAD in 31 of 37 cases (sensitivity, 84%; specificity, 77%), using a mixture of patient signs, symptoms, and history, including stool odor. The positive and negative predictive values of the characteristic odor for CDAD were 77% and 82%, respectively. Burdette and Bernstein found a high negative predictive value (92%) but a much lower positive predictive value (35%) [1].

CLIFF is better!!!!!!!

Recidiva CDI: “Unmet Medical Need”

- La recidiva viene definita come episodio di CDI che si ripresenta nelle 8 settimane dopo l’insorgenza dell’episodio precedente, a condizione che i sintomi dell'episodio precedente siano risolti dopo il completamento del trattamento dell’episodio iniziale
- Fino al 25% dei pazienti sviluppa un episodio di recidiva.
- Questo tasso sale al 45-65 % negli episodi successivi.



Clin Microbiol Infect. 2012; Suppl 6:5-12 ; JAMA. 1994;271(24):1913−1918. *Am J Gastroenterol*. 2002;97(7):1769−1775. *Clin Microbiol Infect*. 2014;20(suppl 2):1−26. *IDSA Guidelines 2010*

Recurrent CDI: FADOI-PRACTICE

Cioni et al. BMC Infectious Diseases (2016) 16:656
DOI 10.1186/s12879-016-1961-9

BMC Infectious Diseases

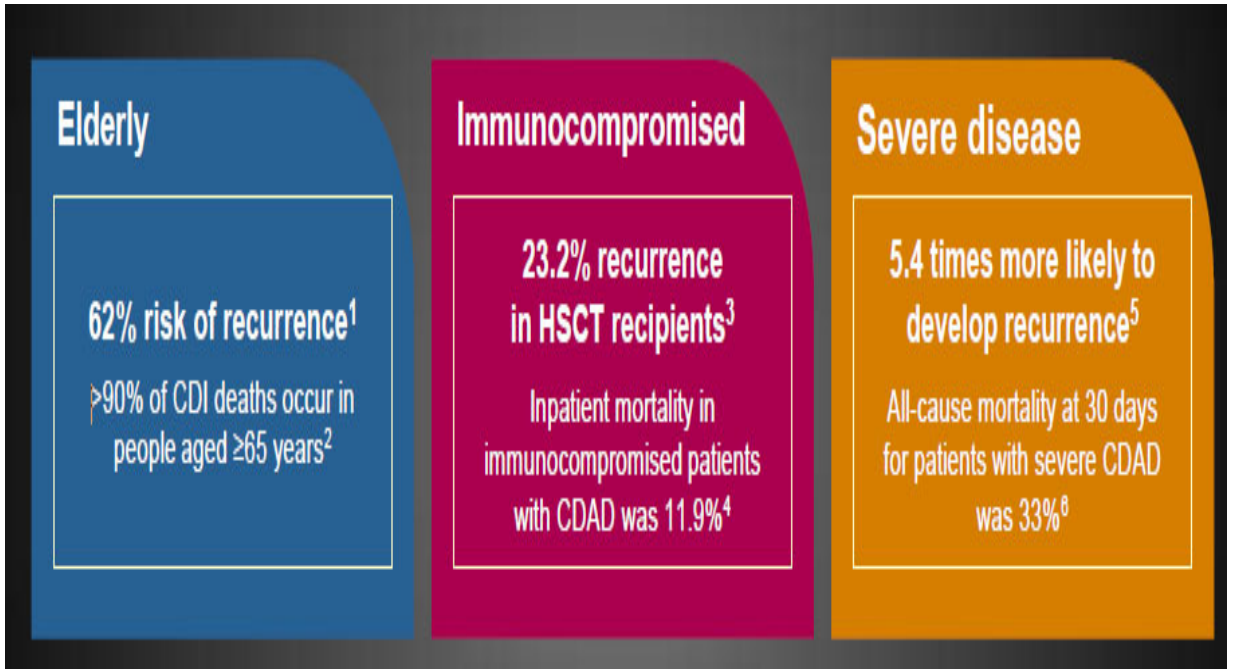
RESEARCH ARTICLE Open Access

Epidemiology and outcome of *Clostridium difficile* infections in patients hospitalized in Internal Medicine: findings from the nationwide FADOI-PRACTICE study

Giorgio Cioni[1], Pierluigi Viale[2], Stefania Frasson[3], Francesco Cipollini[4], Francesco Menichetti[5], Nicola Petrosillo[6], Sergio Brunati[7], Patrizia Spigaglia[8], Chiara Vismara[9], Alessandra Bielli[9], Fabrizio Barbanti[8], Giancarlo Landini[10], Grazia Panigada[11], Gualberto Gussoni[3*], Erminio Bonizzoni[12], Giovanni Pietro Gesu[9] and for the Research Department of FADOI

- **10,780 patients**:
  103 (0.96 %) had CDI
- **Recurrent CDI = 14.6 %**
- **Overall Incidence**
  5.3/10,000 patient-days
- **In-hospital mortality**
  → 16.5 % CD group
  → 6.7% No-CD group
  ($p < 0.001$)
- **Median length of hospital stay**
  →16 days (IQR = 13; CDI)
  →8 days (IQR = 8; No CDI)

Recurrence Is a Major Healthcare Concern, Especially in High-Risk Subgroups



1. Garey KW et al. J Hospital Infect. 2008;70(4):298–304. 2. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2013. 3. Huang AM et al. Transpl Infect Dis. 2014;16(5):744–750. 4. Magee G et al. Am J Infect Control. 2015;43(11):1148–1153. 5. Abou Chakra CN et al. PLoS One. 2014;9(6):e98400. doi:10.1371/journal.pone.0098400. 6. Hardt C et al. World J Gastroenterol. 2008;14(27):4338–4341.

ZAR Score

Wilcox MH et al 2017; 376: 305-317

Scala di punteggio: (1-8)

1. Età >60 anni	1 punto
2. Temperatura corporea >38,3 C°	1 punto
3. Livello di albumina <2,5 g/dl	1 punto
4. Conta dei globuli bianchi periferici >15.000 / mm^3	1 punto
5. Evidenza endoscopica di colite pseudomembranosa	2 punti
6. Trattamento in reparto di terapia intensiva	2 punti

Infezione grave se Zar score ≥2

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Recidiva di CDI: Terapia
Linee Guida ESCMID & IDSA

	ESCMID[1]	IDSA[2]
First recurrence	Vancomycin or metronidazole	Vancomycin or fidaxomicin
Second or multiple recurrence	Vancomycin or fidaxomicin	Vancomycin or fidaxomicin
Prevention of recurrence	**No pharmacologic treatment recommendation**	**No pharmacologic treatment recommendation**

- Vancomicina/Metronidazolo: CDI lieve moderata
- Vancomicina/Fidaxomicina: CDI grave

1)Debast SB et al. Clin Microbiol Infect. 2014
2) McDonald L et al. Cli Infect Dis. 2018

Table 2. Recommendations for the Treatment of *Clostridium difficile* Infection in Children

Clinical Definition	Recommended Treatment	Pediatric Dose	Maximum Dose	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low Weak/Low
Initial episode, severe/ fulminant	• Vancomycin × 10 days (PO or PR) with or without metronidazole × 10 days (IV)[a]	• 10 mg/kg/dose qid • 10 mg/kg/dose tid	• 500 mg qid • 500 mg tid	Strong/Moderate Weak/Low
First recurrence, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen[b], OR • Vancomycin for 10 days followed by rifaximin[c] for 20 days, OR • Fecal microbiota transplantation	• 10 mg/kg/dose qid • Vancomycin: 10 mg/kg/dose qid; rifaximin: no pediatric dosing • …	• 125 mg qid • Vancomycin: 500 mg qid; rifaximin: 400 mg tid • …	Weak/Low Weak/Low Weak/Very low

Abbreviations: IV, intravenous; PO, oral; PR, rectal; qid, 4 times daily; tid, 3 times daily.

[a]In cases of severe or fulminant *Clostridium difficile* infection associated with critical illness, consider addition of intravenous metronidazole to oral vancomycin.

[b]Tapered and pulsed regimen: vancomycin 10 mg/kg with max of 125 mg 4 times per day for 10–14 days, then 10 mg/kg with max of 125 mg 2 times per day for a week, then 10 mg/kg with max of 125 mg once per day for a week, and then 10 mg/kg with max of 125 mg every 2 or 3 days for 2–8 weeks.

[c]No pediatric dosing for rifaximin; not approved by the US Food and Drug Administration for use in children <12 years of age.

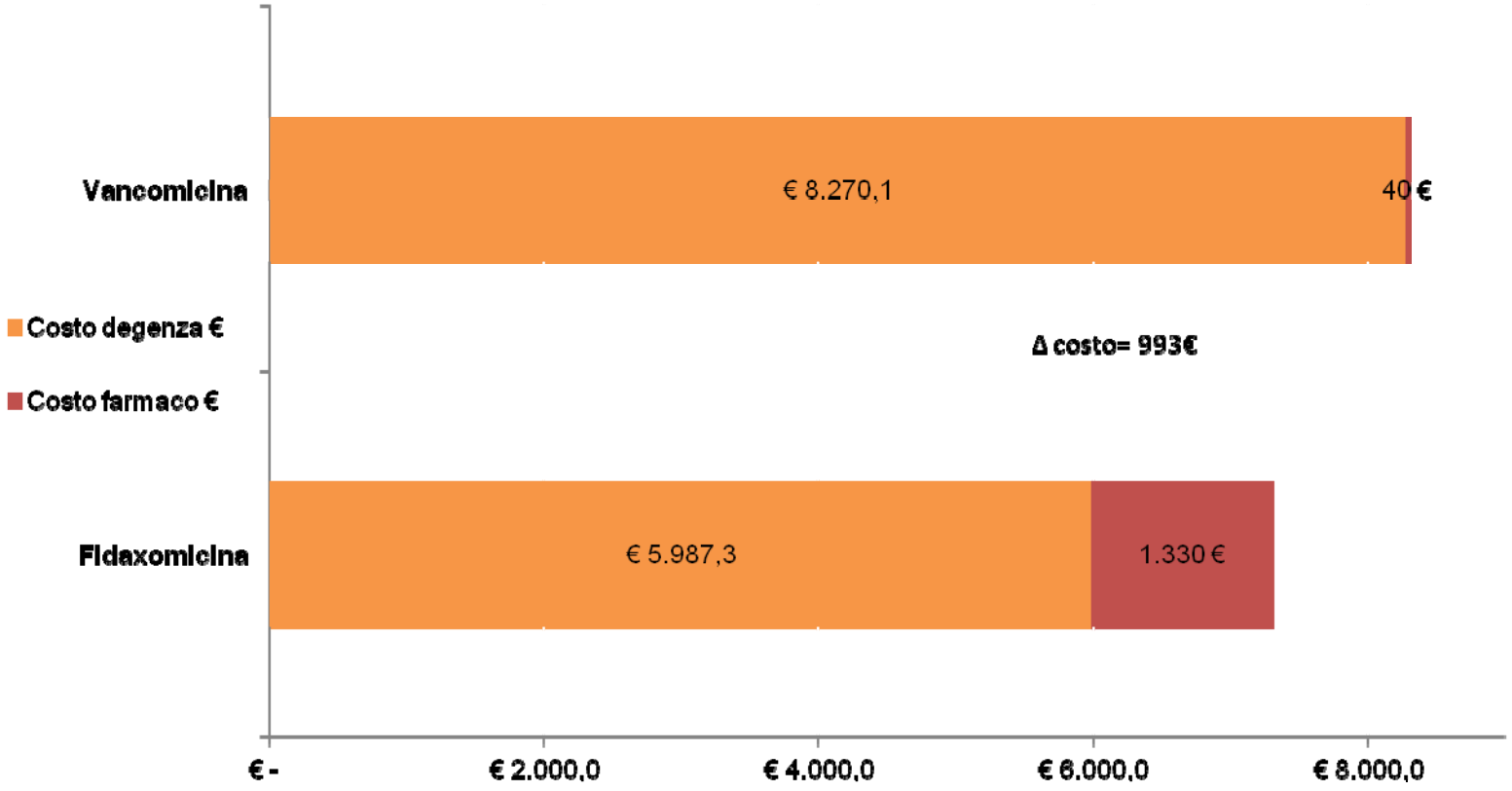
Fidaxomicin microbiology: targeted spectrum of activity against *C. difficile*

Bacteria	Fidaxomicin MIC_{90}
C. difficile	0.25
Anaerobic Gram- negatives	>1024
Anaerobic Gram-positive NSF bacilli	32
Anaerobic Gram-positive cocci	2
Streptococci	32
Enterococci	8
Staphylococci	2

NSF= Non spore forming

Finegold et al. Antimicrob Agents Chemother 2004;48:4898–902

Costi *C. difficile*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

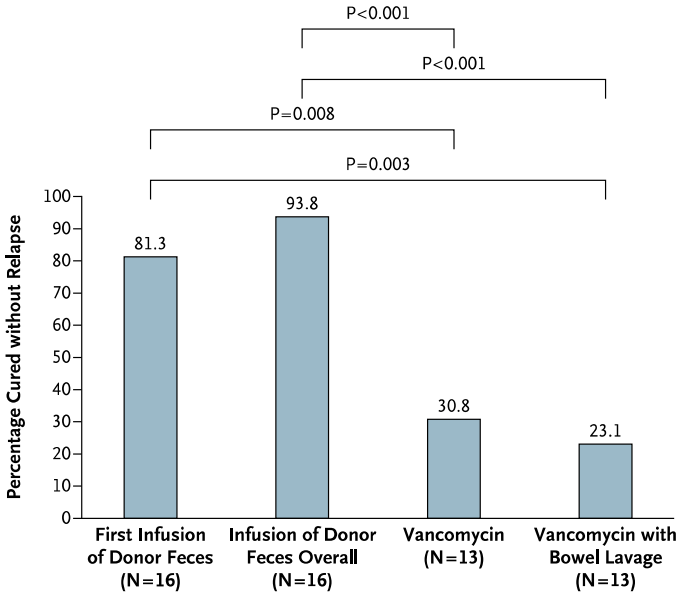


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Conseguenze del trapianto di feci

Weight Gain After Fecal Microbiota Transplantation

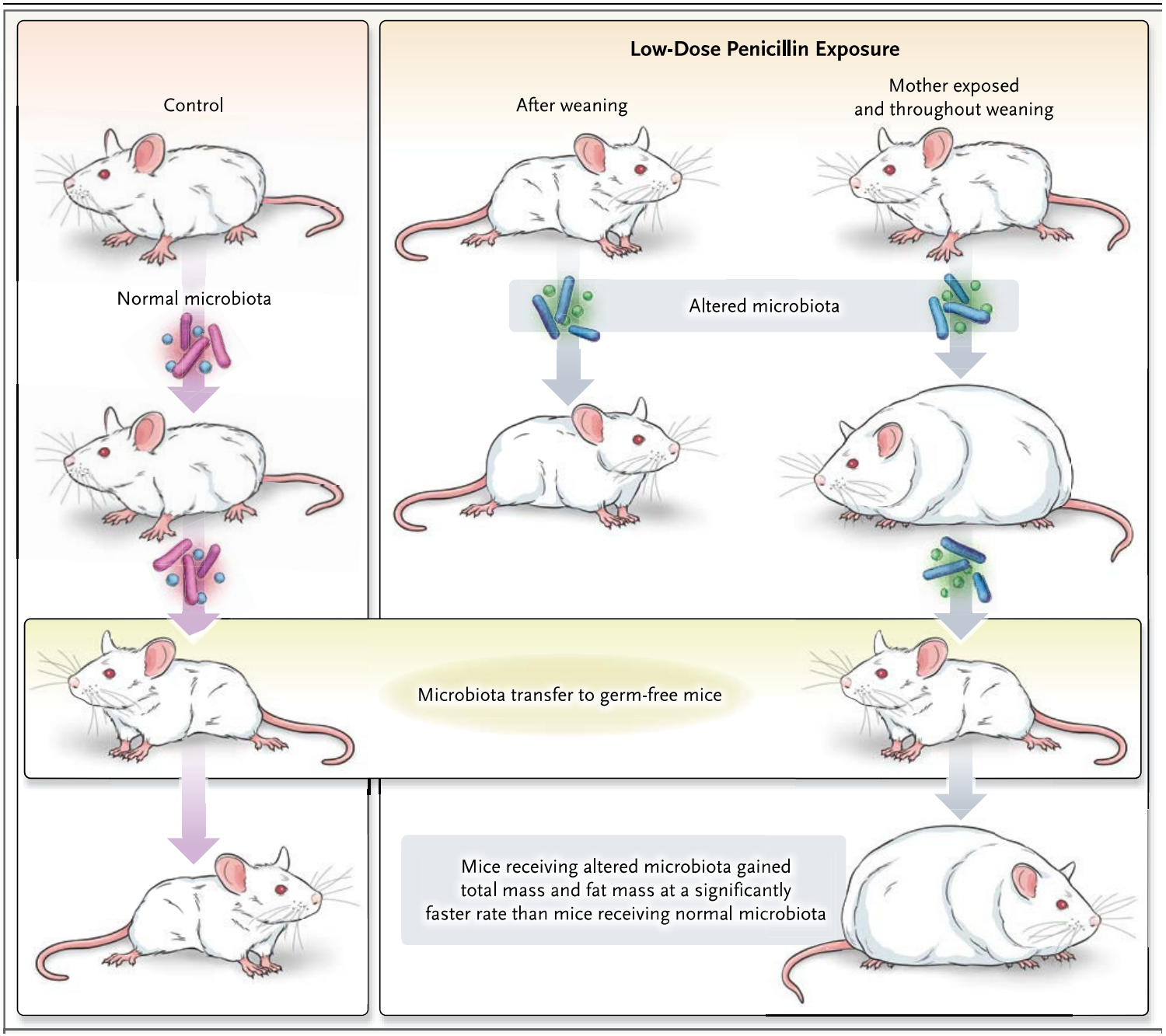
Neha Alang[1] and Colleen R. Kelly[2]

[1]Department of Internal Medicine, Newport Hospital, and [2]Division of Gastroenterology, Center for Women's Gastrointestinal Medicine at the Women's Medicine Collaborative, The Miriam Hospital, Warren Alpert School of Brown University, Providence, Rhode Island

Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor. This case may stimulate further studies on the mechanisms of the nutritional-neural-microbiota axis and reports of outcomes in patients who have used non-ideal donors for FMT.

Keywords. *Clostridium difficile* infection; fecal microbiota transplantation; gut microbiota; obesity.

The patient presented again 16 months after FMT, and reported an unintentional weight gain of 34 pounds. She weighed 170 pounds and had become obese (BMI of 33). She had not lost any weight over the months she was being treated for CDI. She had been unable to lose weight despite a medically supervised liquid protein diet and exercise program. Her serum cortisol and thyroid panel were normal. She has continued to gain weight despite efforts to diet and exercise, and at 36 months post-FMT her weight was 177 pounds (BMI of 34.5). She has also developed constipation and unexplained dyspeptic symptoms.


Low-Dose Penicillin Exposure
Control
After weaning
Mother exposed
and throughout weaning
Normal microbiota
Altered microbiota
Microbiota transfer to germ-free mice
Mice receiving altered microbiota gained
total mass and fat mass at a significantly
faster rate than mice receiving normal microbiota

Conseguenze del trapianto di feci

GASTROENTEROLOGY 2011;141:599–609

The Intestinal Microbiota Affect Central Levels of Brain-Derived Neurotropic Factor and Behavior in Mice

PREMYSL BERCIK,* EMMANUEL DENOU,* JOSH COLLINS,* WENDY JACKSON,* JUN LU,* JENNIFER JURY,* YIKANG DENG,* PATRICIA BLENNERHASSETT,* JOSEPH MACRI,‡ KATHY D. McCOY,* ELENA F. VERDU,* and STEPHEN M. COLLINS*

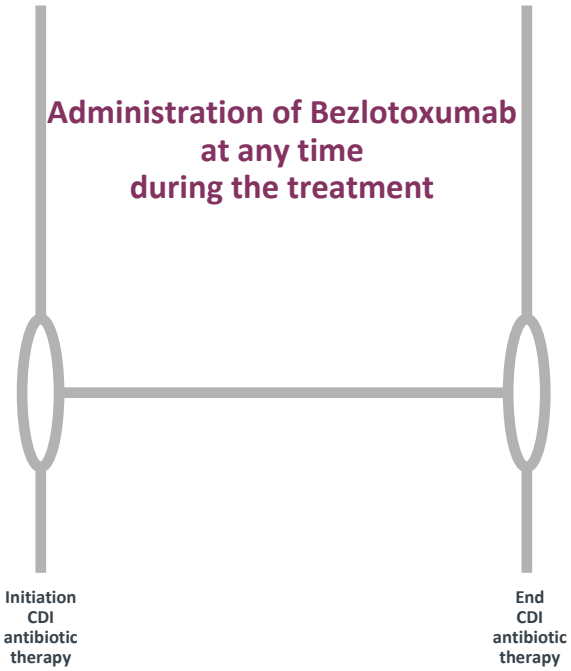
**The Farncombe Family Digestive Health Institute, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada; ‡Clinical Research Trials and Proteomics Laboratory, Hamilton Health Sciences, Hamilton, Ontario, Canada*

Bezlotoxumab

Anticorpo monoclonale (IgG1/kappa) di derivazione completamente umana:
- **Tecnologia di DNA ricombinante che neutralizza la tossina B**
- **Immunità passiva anti-B**

- **No attività antimicrobica diretta**
- **Somministrato insieme alla terapia**
- Prevenzione delle **recidive**

Somministrazione durante il ciclo di terapia CDI
Singola infusione endovenosa di 10 mg/kg



FDA Briefing Document Bezlotoxumab Injection Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC) June 9, 2016). Leav BA, et al. Vaccine 28 (2010) 965–969; RCP Zinplava, RCP Zinplava

2019 update of the WSES guidelines for management of Clostridioides (Clostridium) difficile infection in surgical patients

Sartelli et al. World Journal of Emergency Surgery 2019

- Coadjuvant treatment with monoclonal antibodies (bezlotoxumab) may prevent recurrences of CDI, particularly in patients with CDI due to the 027 epidemic strain, in immunocompromised patients and in patients with severe CDI (**Recommendation 1 A**).

Management of *Clostridioides difficile* infection (CDI) in Solid Organ Transplant Recipients: Guidelines from the American Society of Transplantation Community of Practice

Mullane et al. Clin Transpl 2019

- Bezlotoxumab in addition to standard of care CDI treatment antibiotics, is recommended for SOT recipients at risk for recurrent CDI (**strong, low**).

Analisi Integrata degli Studi di Fase 3: MODIFY I e MODIFY II

Wilcox MH et al NEJM 2017; 376: 305-17

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*

ABSTRACT

BACKGROUND

Clostridium difficile is the most common cause of infectious diarrhea in hospitalized patients. Recurrences are common after antibiotic therapy. Actoxumab and bezlotoxumab are human monoclonal antibodies against *C. difficile* toxins A and B, respectively.

METHODS

We conducted 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; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis. 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.

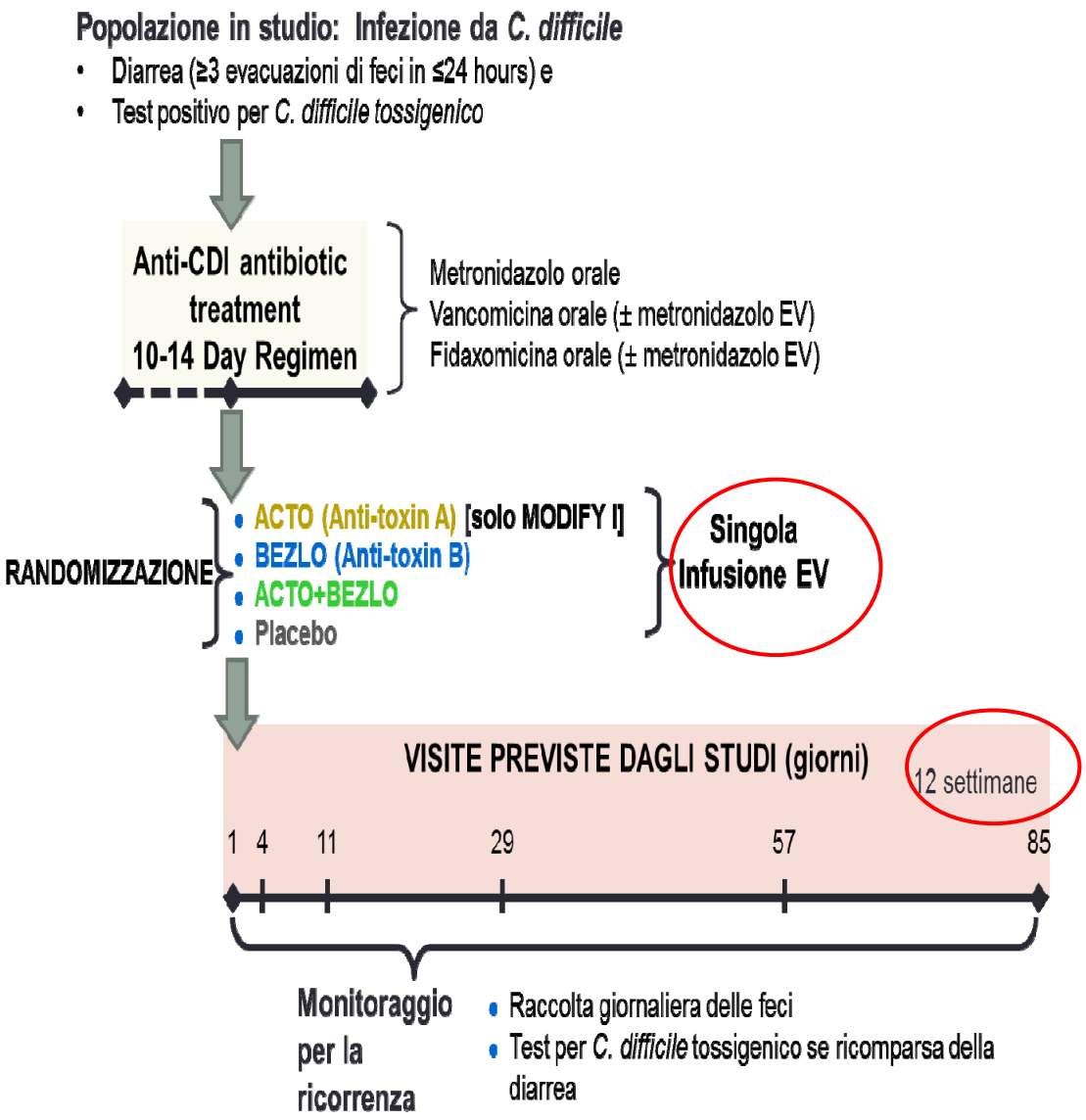
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wilcox at the Division of Microbiology, Old Medical School, Leeds General Infirmary, Leeds LS1 3EX, United Kingdom, or at mark.wilcox@nhs.net.

*A complete list of investigators in the MODIFY I and MODIFY II trials is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:305-17.
DOI: 10.1056/NEJMoa1602615

MODIFY I e MODIFY II: Disegno dei Trials Clinici di fase III

Wilcox MH et al NEJM 2017; 376: 305-17



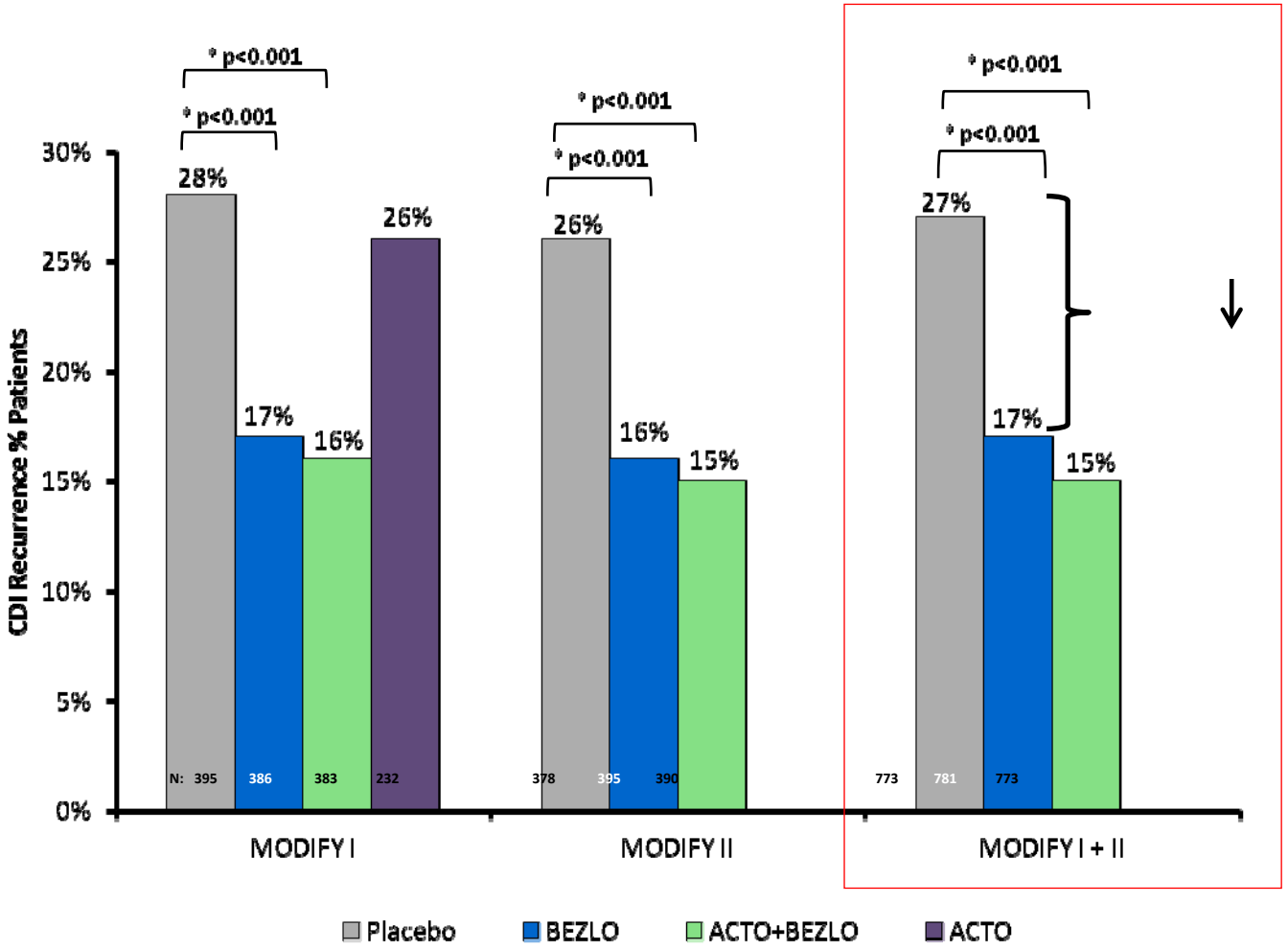
I trials clinici di fase 3 MODIFY I e MODIFY II sono studi randomizzati, placebo-controllati in doppio cieco. **Coinvolti 322 Centri in 30 Stati**

Primary endpoint:
Percentuale di pazienti con recidiva di CDI (definita come nuovo episodio di infezione da C. diff. dopo la cura clinica iniziale dell'episodio basale) durante 12 settimane di follow-up.

Secondary endpoint:
Global Cure: initial clinical cure dell'episodio basale e nessuna recidiva durante le 12 sett. di follow-up

Endpoint primario: Recidiva di CDI

Endpoint primario; mITT, MODIFY l and MODIFY ll; percentuale di pazienti con recidiva di CDI durante 12 sett. di follow-up



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ABSTRACT

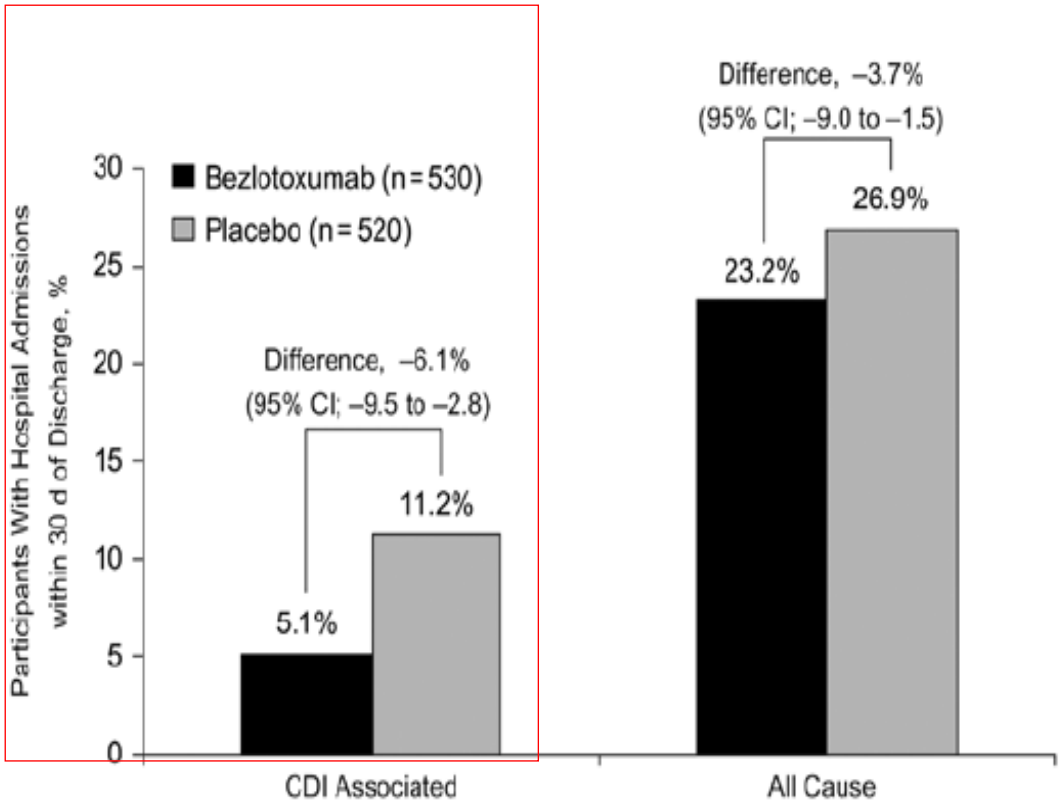
CONCLUSIONS

Among participants receiving antibiotic treatment for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo. The addition of actoxumab did not improve efficacy. (Funded by Merck; MODIFY I and MODIFY II ClinicalTrials.gov numbers, NCT01241552 and NCT01513239.)

Bezlotoxumab & Hospital Readmission for CDI

Riduzione dei ricoveri ospedalieri in un'analisi post hoc su 1.050 pazienti ricoverati

Riduzione del -53% rischio di ri-ospedalizzazione a 30 giorni (5,1% vs 11,2%)



Vimalanand S. Prabhu et al. *Clinical Infectious Diseases* 2017

Clinical AEs Comparabili al Placebo

Wilcox NEJM 2017

Time Period and Event	Actoxumab plus Bezlotoxumab (N=777)	Bezlotoxumab (N=786)	Actoxumab (N=235)	Placebo (N=781)
		number of participants (percent)		
During the 24 hours after infusion				
Infusion-specific reaction*	62 (8.0)	81 (10.3)	26 (11.1)	59 (7.6)
Treatment stopped because of an adverse event	0	1 (0.1)	1 (0.4)	0
During the 4 weeks after infusion				
One or more adverse events	455 (58.6)	485 (61.7)	158 (67.2)	478 (61.2)
Serious adverse event	123 (15.8)	156 (19.8)	65 (27.7)	167 (21.4)
Death	28 (3.6)	32 (4.1)	14 (6.0)	32 (4.1)
Drug-related adverse event†	50 (6.4)	59 (7.5)	17 (7.2)	46 (5.9)
Serious drug-related adverse event‡	5 (0.6)	4 (0.5)	3 (1.3)	2 (0.3)
Most common adverse events§				
Abdominal pain	32 (4.1)	34 (4.3)	15 (6.4)	34 (4.4)
Diarrhea	46 (5.9)	47 (6.0)	13 (5.5)	45 (5.8)
Death	51 (6.6)	56 (7.1)	27 (11.5)	59 (7.6)

8 patients in the bezlotoxumab group experienced congestive heart failure, versus two in the placebo group. This difference was not statistically significant.

However, caution in patients with cardiovascular disease, and congestive heart failure in particular, should be warranted.

* The adverse events reported on the day of or day after infusion that might have been a sign of an acute hypersensitivity reaction were nausea, vomiting, chills, fatigue, feeling hot,
infusion-site conditions, pyrexia, arthralgia, myalgia, dizziness, headache, dyspnea, nasal congestion, pruritus, rash, urticaria, flushing, hot flush, hypertension, and hypotension.

† Causality was assessed by the investigator, who was unaware of the study-group assignments.

‡ A list of serious drug-related events is provided in Table S12 in the Supplementary Appendix.

§ This category includes events with an incidence of at least 4% in at least one study group reported during the first 4 weeks after infusion.

¶ C. difficile infection (the primary efficacy end point) was to be reported as an adverse event only if it was serious.

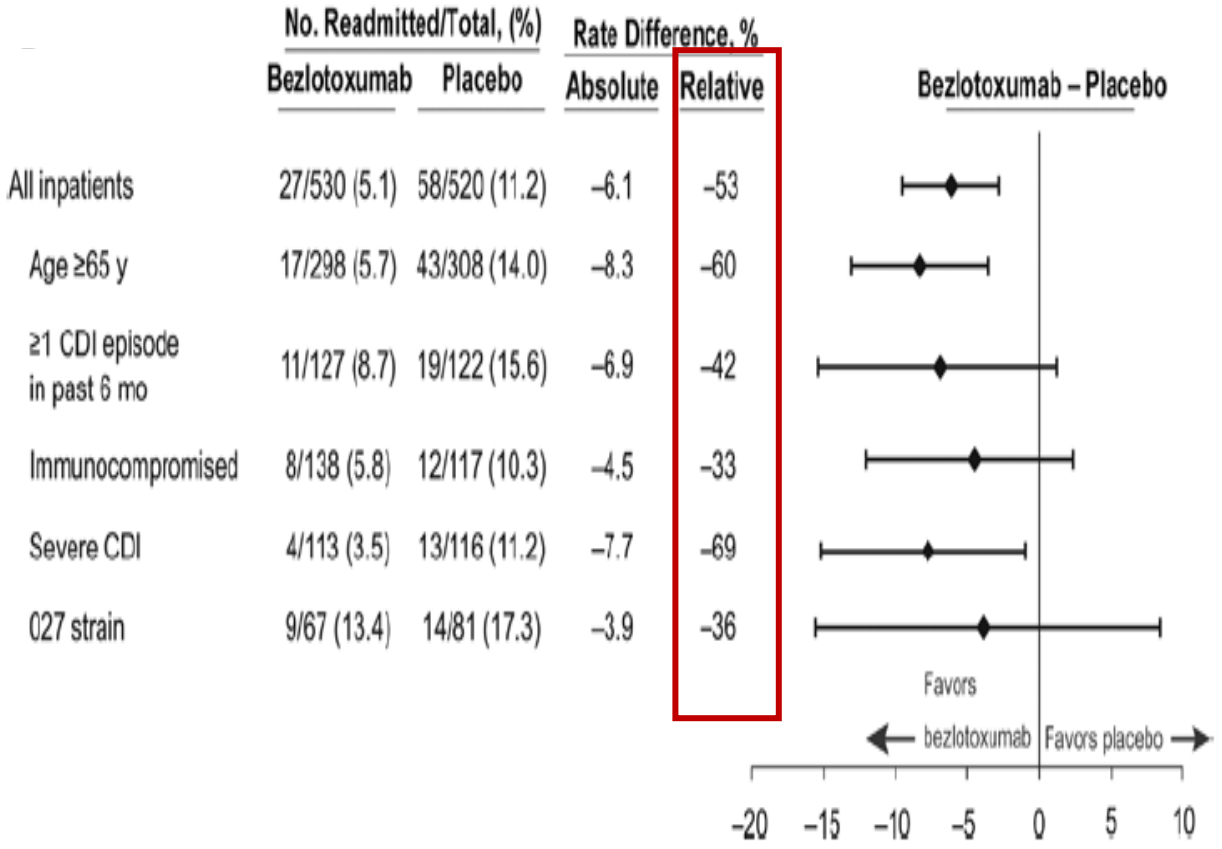
MODIFY1 e MODIFY2

Wilcox MH et al NEJM 2017; 376: 305-17

	Bezolotoxumab plus SOC (N=781)	SOC alone (N=773)
Inpatient	68%	67%
Aged ≥65 years	50%	52%
CDI in past 6 months	28%	28%
≥2 previous CDI episodes	13%	16%
Severe CDI (Zar score ≥2)[a]	16%	16%
Immunocompromised[b]	23%	20%
PCR ribotype[c]	(n=490)	(n=486)
Most common strained	43%	48%
027 strain	18%	21%
Concomitant systemic antibiotic use	37%	41%

77% dei pazienti: ≥1 fattore di rischio per recidiva di CDI

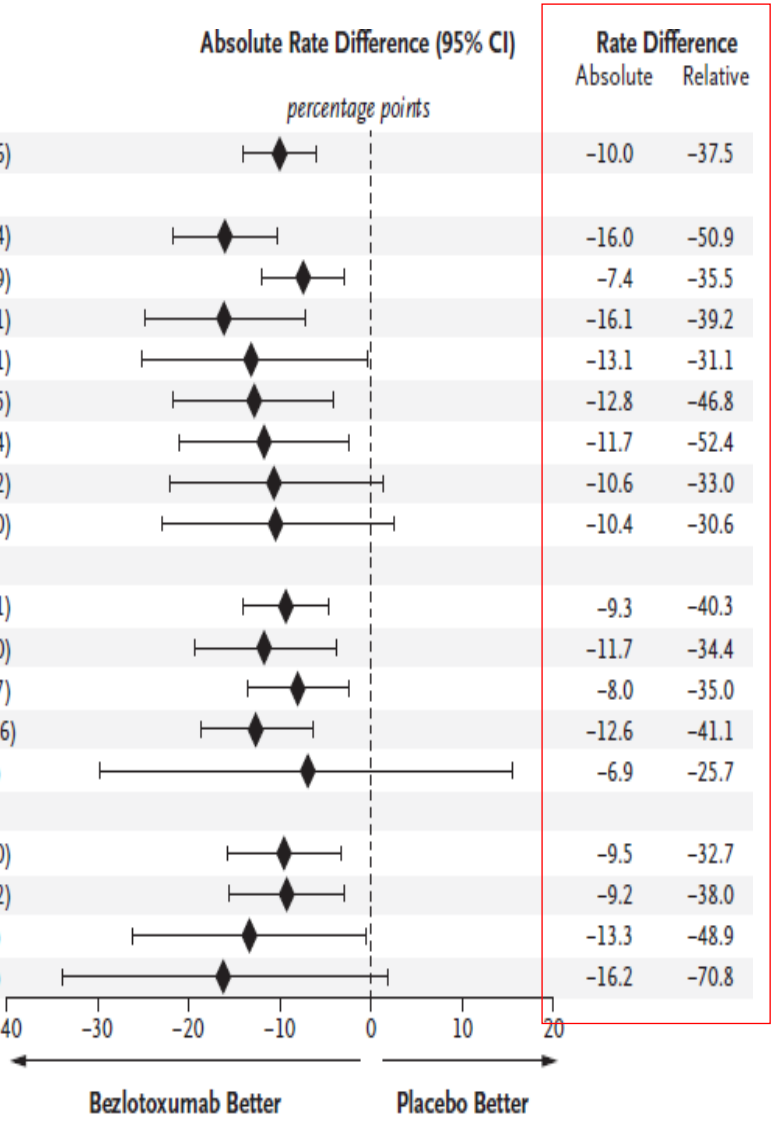
Bezlotoxumab Reduced the Risk of Recurrence in Select High-Risk Subgroups



Vimalanand S. Prabhu et al. Thirty-Day Readmissions in Hospitalized Patients Who Received Bezlotoxumab With Antibacterial Drug Treatment for *Clostridium difficile* Infection. Clinical Infectious Diseases 2017

Recidiva di CDI per Sottogruppi
Durante 12 sett. di follow-up; MODIFY I + II; mITT

Subgroup	Bezlotoxumab	Placebo	Rate Difference Absolute	Rate Difference Relative
	no./total no. (%)			
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 *core ≥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



Wilcox M.H. et al. N Engl J Med 2017;376:305-17 and supplementary appendix

Bezlotoxumab in Haematologic Malignancies

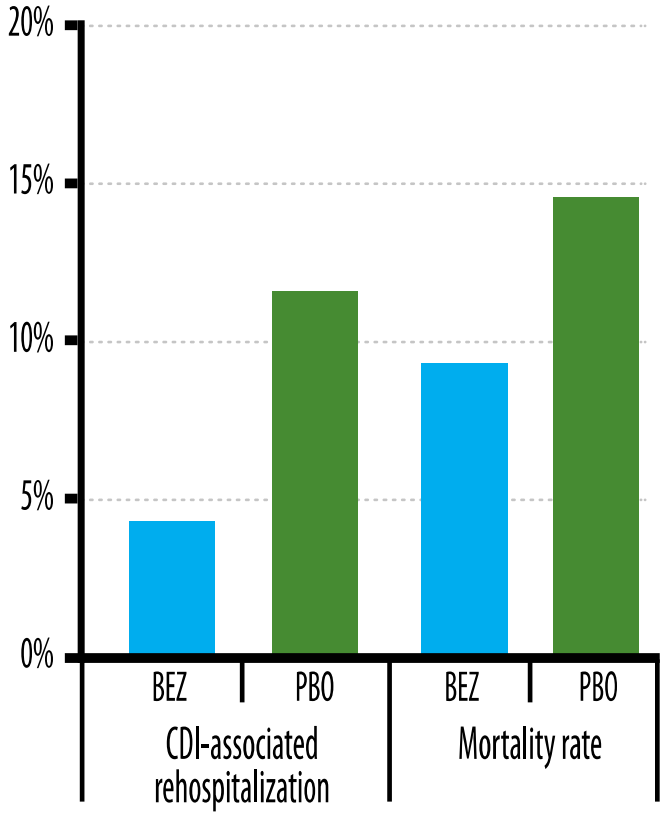
Post-hoc analysis of the Phase 3 MODIFY I/II trials to determine if bezlotoxumab affected the rCDI rate in MODIFY I/II participants with a haematologic malignancy

Characteristics	BEZ N=53 n (%)	PBO N=54 n (%)
Clinical characteristics		
Inpatient	46 (86.8)	43 (79.6)
Female	30 (56.6)	21 (38.9)
Mean age, years (SD)	57.3 (16.9)	66.3 (14.4)
≥65 years of age	18 (34.0)	32 (59.3)
≥1 CDI episodes in past 6 months	8 (15.1)	19 (35.2)
Severe CDI (Zar score ≥2)[a]	11 (20.8)	13 (24.1)
Immunocompromised[b]	50 (94.3)	46 (85.2)
Received a stem cell transplant	8 (15.1)	10 (18.5)
Antibiotic use during antibacterial drug treatment for CDI[c]	38 (71.1)	27 (50.0)
Antibiotic use after antibacterial drug treatment for CDI[c]	32 (60.4)	29 (53.7)
At least 1 of the 5 predefined risk factors*	53 (100.0)	52 (96.3)
Charlson Comorbidity Index ≥3	29 (54.7)	32 (59.3)
Albumin <2.5 g/dL	9 (17.0)	9 (16.7)
Anti-CDI antibiotic		
Metronidazole	28 (52.8)	22 (40.7)
Vancomycin	22 (41.5)	28 (51.9)
Fidaxomicin	3 (5.7)	4 (7.4)
PCR ribotype[d]		
Participants with a positive culture	28	38
027, 078 or 244 strain	4 (14.3)	15 (39.5)
027 strain	3 (10.7)	13 (34.2)

- ✓ 107 participants included:
  - 53 in the bezlo (BEZ) group
  - 54 in the placebo (PBO) group.
  - ✓ Majority = inpatients at randomization
- ✓ Almost all ≥1 prespecified risk factor for rCDI
- ✓ A higher proportion of participants in the PBO group experienced ≥1 CDI episodes in the previous 6 months

Hospitalization and Mortality in Patients with Haematologic Malignancies

- **A lower proportion of BEZ-treated participants had a CDI-associated re-hospitalization** compared with PBO (4.3% *vs* 11.6%)
- During the 12-week follow-up period, **the mortality rate was 9.3% in participants receiving BEZ and 14.5% in participants receiving PBO**



Bezlotoxumab reduced the rate of rCDI compared with placebo in participants with haematologic malignancy.

#P0358 - Cornely OA, et al. Impact of bezlotoxumab in recurrent *Clostridium difficile* infection in MODIFY I/II participants with haematologic malignancy

Bezlotoxumab in Patients with Solid Tumours

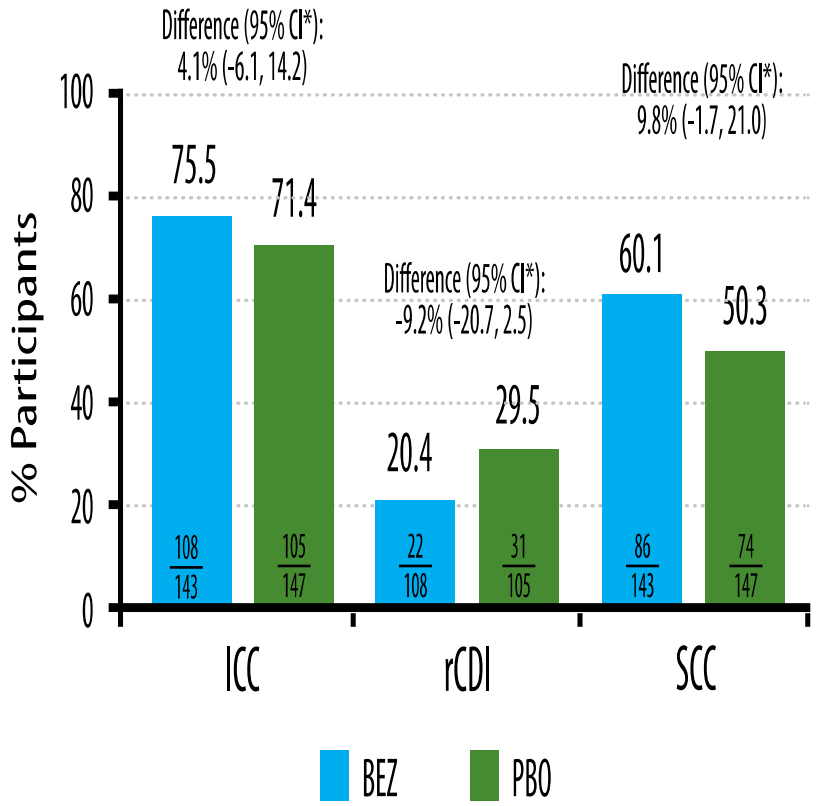
Post-hoc analysis of the Phase 3 MODIFY I/II trials to determine if bezlotoxumab affected the rCDI rate in MODIFY I/II participants with a solid tumour as a comorbid condition.

Characteristics	BEZ N=143 n (%)	PBO N=147 n (%)
Clinical characteristics		
Inpatient	109 (76.2)	108 (73.5)
Female	69 (48.3)	79 (53.7)
≥65 years of age	94 (65.7)	91 (61.9)
≥1 CDI episodes in past 6 months	46 (32.2)	32 (21.8)
Severe CDI (Zar score ≥2) [a]	27 (18.9)	34 (23.1)
Immunocompromised [b]	33 (23.1)	29 (19.7)
Antibiotic use during antibacterial drug treatment for CDI [c]	57 (39.9)	57 (38.8)
Antibiotic use after antibacterial drug treatment for CDI [c]	56 (39.2)	42 (28.6)
At least 1 of the 5 predefined risk factors*	123 (86.0)	114 (77.6)
Charlson Comorbidity Index ≥3	109 (76.2)	113 (76.9)
Albumin <2.5 g/dL	22 (15.4)	30 (20.4)
Anti-CDI antibiotic		
Metronidazole	72 (50.3)	64 (43.5)
Vancomycin	66 (46.2)	76 (51.7)
Fidaxomicin	5 (3.5)	7 (4.8)
PCR ribotype [d]		
Participants with a positive culture	100	96
027, 078 or 244 strain	29 (29.0)	29 (30.2)
027 strain	26 (26.0)	26 (27.1)

- ✓ 290 participants were included in the solid tumour subgroup:
  - 143 in the bezlo (BEZ) group (48.3% female; median age 69 years)
  - 147 in the placebo (PBO) group (53.7% female; median age 68 y)
- ✓ A higher proportion of BEZ-treated participants had ≥1 prespecified risk factor for rCDI compared with PBO (86.0% *vs* 77.6%), including a higher incidence of participants who had ≥1 CDI episode in the past 6 months (32.2% *vs* 21.8%)

Patients with Solid Tumours with ICC, rCDI and SCC

- Initial clinical cure (ICC) rates were similar between both treatment groups.
- Although **a lower proportion of BEZ-treated participants experienced an rCDI** than PBO-treated participants, the difference was not significant.
- Among participants who experienced rCDI, **a lower proportion of severe rCDI** (Zar score ≥2) **was reported in the BEZ group** compared with the PBO group (4.5% *vs* 12.9%).
- A similar proportion of participants achieved sustained clinical cure (SCC) in BEZ and PBO groups.



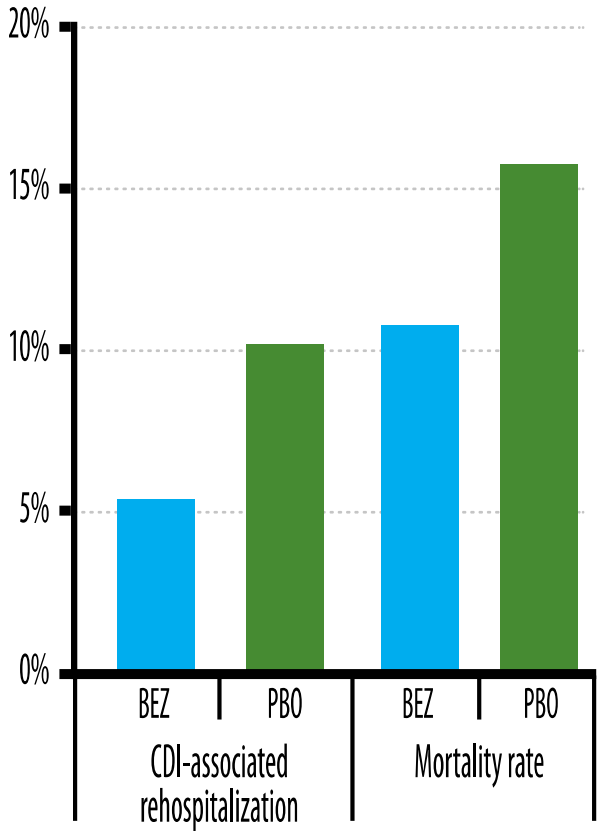
*Based on the Miettinen and Nurminen method.

ICC, initial clinical cure; rCDI, recurrent *Clostridium difficile* infection; SCC, sustained clinical cure

Hospitalization & Mortality in Patients with Solid Tumors

- The rate of 30-day CDI-associated re-hospitalization was lower in the BEZ group than in the PBO group (5.5% *vs* 10.2%).

- Mortality rates during 12-week follow-up were lower in the BEZ group (10.5% *vs* 15.6% in the BEZ and PBO groups, respectively)



Bezlotoxumab led to a proportionally lower rCDI rate in solid tumour participants compared with placebo.

#P0359 - Mullane K, et al. Reduction of recurrent *Clostridium difficile* infection in solid tumour participants treated with bezlotoxumab.

In Medicina Interna

- Donna, 91 anni
- APR: Ipotiroidismo in terapia sostitutiva, Ipertensione arteriosa, Cardiopatia ipertrofica ipertensivo-valvolare, IRC grado moderato, Osteoporosi severa con pregresse fratture
- **Ricovero c/o Medicina Interna** dal 13/08 al 24/08/2018**:** per disidratazione e ipokaliemia in **diarrea da C. Difficile**
  - **1°Episodio** (trattata con Vancomicina) sottoposta inizialmente a terapia empirica con Ciprofloxacina.
- **Ricovero c/o Geriatria** dal 10/09 al 18/09/2018
  - **1° recidiva di enterite da C. Difficile** trattata con vancomicina (dimessa con schema tapered di Vancomicina fino al 11/11/2018).
- **Ricovero c/o Geriatria** dal 16/11 al 21/11 con prosecuzione cure c/o Ospedalizzazione a domicilio fino al 28/11/2018:
  - **2° recidiva di enterite da C. Difficile** trattata con metronidazolo, dapprima ev e poi per os fino al 2/12/2018.

- **Ricovero a gennaio 2019: diarrea e nuova positività per CDI**
  - Impostata terapia antibiotica con vancomicina per os con buona risposta clinica e risoluzione delle evacuazioni diarroiche.
  - **Consulenza infettivologica: terza recidiva di C. difficile, indicazione a terapia con anticorpo monoclonale Bezlotoxumab**

Conclusioni

- Indicazioni: prevenzione delle recidive di CDI in pazienti ad alto rischio
  - Rimborsabilità: diagnosi microbiologica di recidiva, gia' in trattamento con terapia antibiotica, >1 condizioni: eta' > 65 anni; ZAR-score ≥ 2; immunocompromessi.
- Efficacia dimostrata in sottogruppi di pazienti a rischio (insufficienza renale, fattori di rischio combinati, paziente ematologico, neoplasia solida…)
- Possibili applicazioni:
  - **paziente fragile, SOT, HSCT… (almeno 1 FR)**
  - **Recidiva CDI**
  - **Primo episodio ma previsione terapia antibiotica/ospedalizzazione protratta**