Programma del Corso di Farmacologia
Corso integrato di Medicina Interna

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- Infezioni gastrointestinali ……1 ottobre 2018
- Terapia dell'ulcera ……8 ottobre 2018
- Terapia del dolore……15 ottobre 2018
- Terapia della gotta……22 ottobre 2018

INFEZIONI INTRADDOMINALI

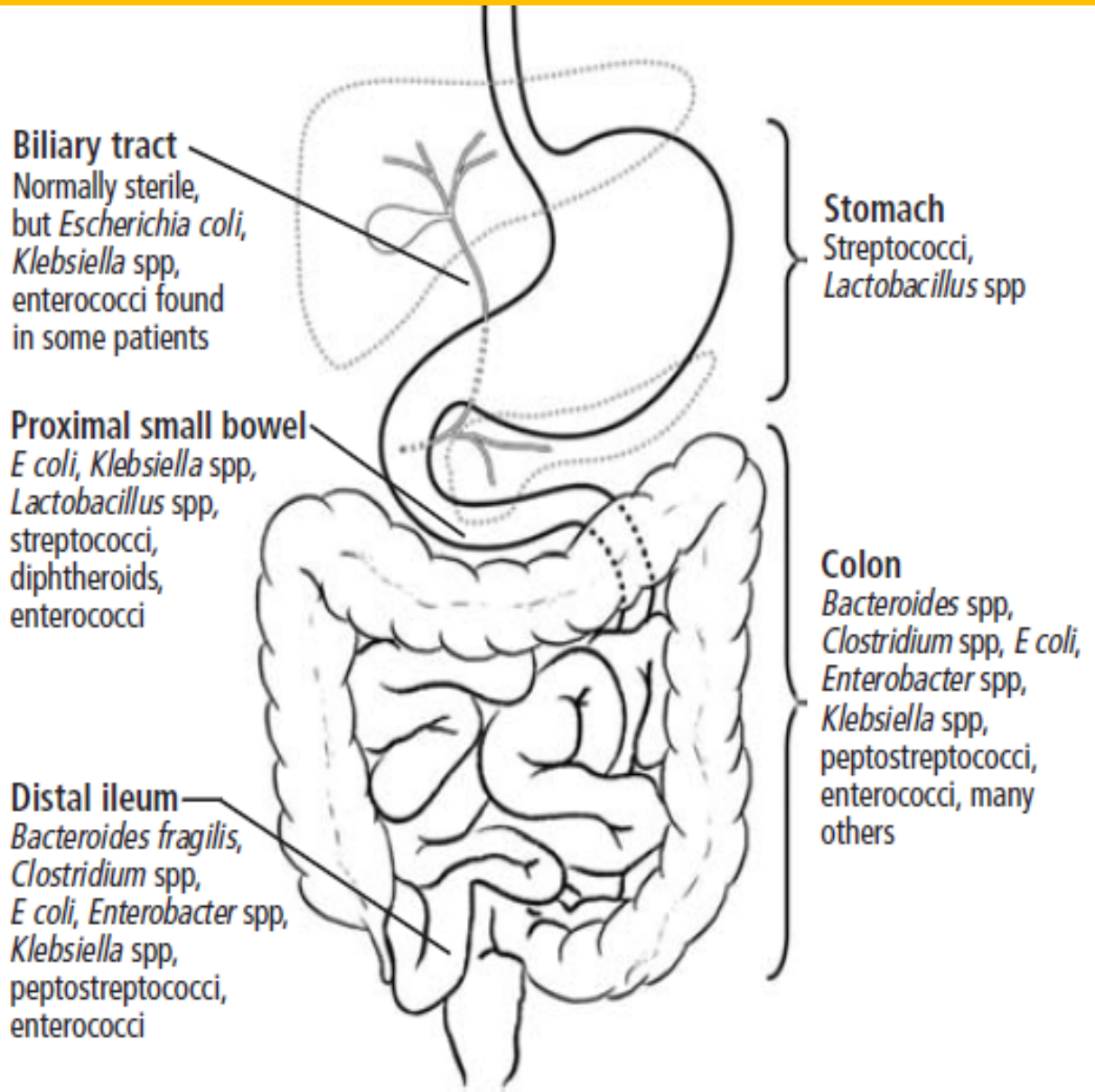
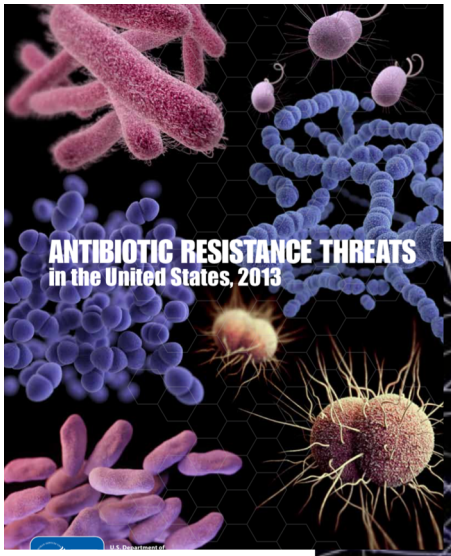


FIGURE 1. Usual microflora of the gastrointestinal tract.



CLOSTRIDIUM DIFFICILE

250,000 INFECTIONS PER YEAR

14,000 DEATHS

$1,000,000,000 IN EXCESS MEDICAL COSTS PER YEAR

THREAT LEVEL **URGENT**

This bacteria is an immediate public health threat that requires urgent and aggressive action.

Clostridium difficile (C. difficile) causes life-threatening diarrhea. These infections mostly occur in people who have had both recent medical care and antibiotics. Often, *C. difficile* infections occur in hospitalized or recently hospitalized patients.

RESISTANCE OF CONCERN

- Although resistance to the antibiotics used to treat *C. difficile* infections is not yet a problem, the bacteria spreads rapidly because it is naturally resistant to many drugs used to treat other infections.
- In 2000, a stronger strain of the bacteria emerged. This strain is resistant to fluoroquinolone antibiotics, which are commonly used to treat other infections.
- This strain has spread throughout North America and Europe, infecting and killing more people wherever it spreads.

PUBLIC HEALTH THREAT

- 250,000 infections per year requiring hospitalization or affecting already hospitalized patients.
- 14,000 deaths per year.
- At least $1 billion in excess medical costs per year.
- Deaths related to *C. difficile* increased 400% between 2000 and 2007, in part because of a stronger bacteria strain that emerged.
- Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older.
- About half of *C. difficile* infections first show symptoms in hospitalized or recently hospitalized patients, and half first show symptoms in nursing home patients or in people recently cared for in doctors' offices and clinics.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

ORIGINAL ARTICLE

Burden of *Clostridium difficile* Infection in the United States

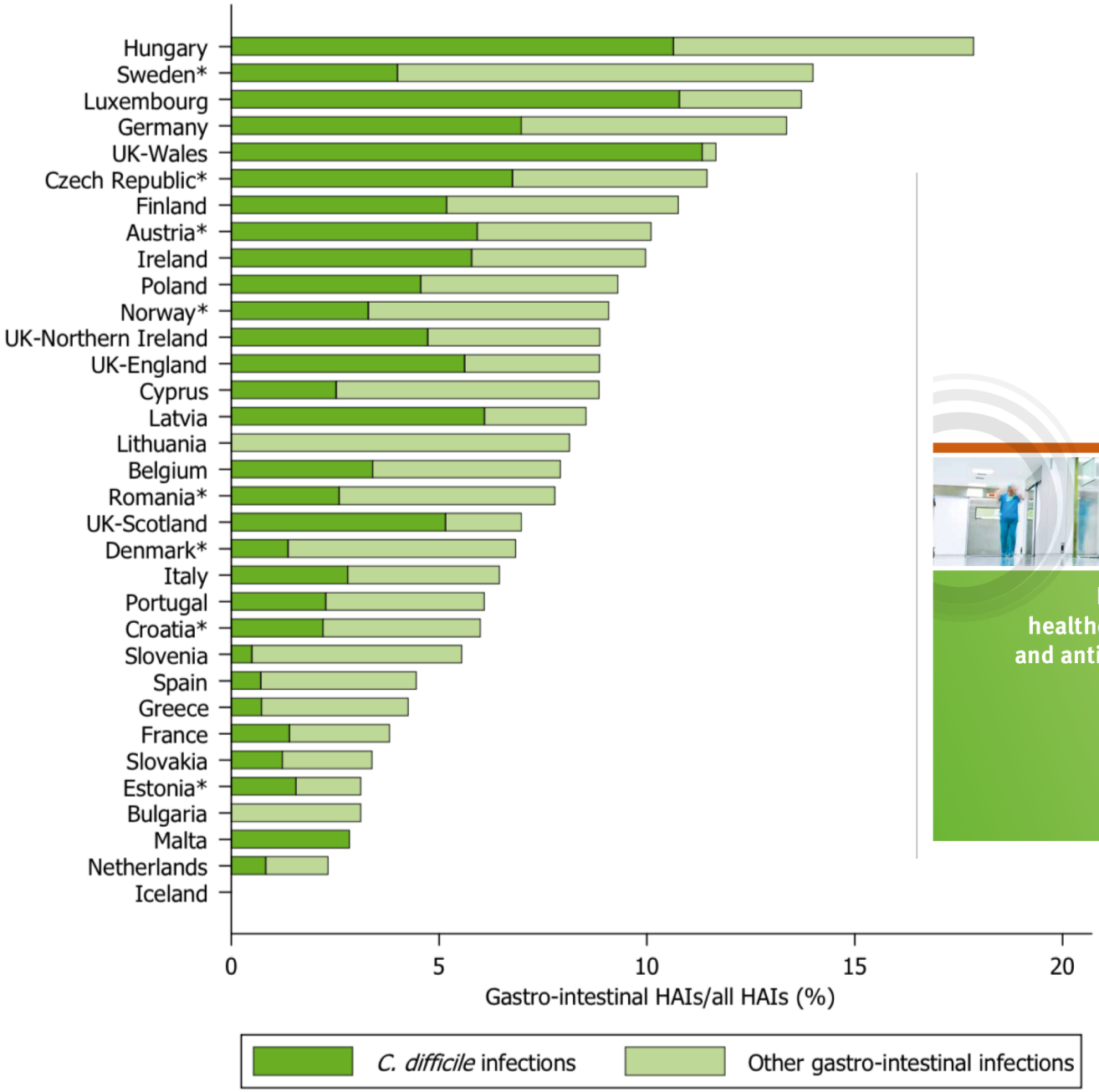
Fernanda C. Lessa, M.D., M.P.H., Yi Mu, Ph.D., Wendy M. Bamberg, M.D., Zintars G. Beldavs, M.S., Ghinwa K. Dumyati, M.D., John R. Dunn, D.V.M., Ph.D., Monica M. Farley, M.D., Stacy M. Holzbauer, D.V.M., M.P.H., James I. Meek, M.P.H., Erin C. Phipps, D.V.M., M.P.H., Lucy E. Wilson, M.D., Lisa G. Winston, M.D., Jessica A. Cohen, M.P.H., Brandi M. Limbago, Ph.D., Scott K. Fridkin, M.D., Dale N. Gerding, M.D., and L. Clifford McDonald, M.D.

RESULTS

A total of 15,461 cases of *C. difficile* infection were identified in the 10 geographic areas; 65.8% were health care–associated, but only 24.2% had onset during hospitalization. After adjustment for predictors of disease incidence, the estimated number of incident *C. difficile* infections in the United States was 453,000 (95% confidence interval [CI], 397,100 to 508,500). The incidence was estimated to be higher among females (rate ratio, 1.26; 95% CI, 1.25 to 1.27), whites (rate ratio, 1.72; 95% CI, 1.56 to 2.0), and persons 65 years of age or older (rate ratio, 8.65; 95% CI, 8.16 to 9.31). The estimated number of first recurrences of *C. difficile* infection was 83,000 (95% CI, 57,000 to 108,900), and the estimated number of deaths was 29,300 (95% CI, 16,500 to 42,100). The North American pulsed-field gel electrophoresis type 1 (NAP1) strain was more prevalent among health care–associated infections than among community-associated infections (30.7% vs. 18.8%, P<0.001)

trol and Prevention.)

Figure 3. ***Clostridium difficile*** **infections and other gastro-intestinal infections (excluding hepatitis) as a percentage of all HAIs, by country, ECDC PPS 2011–2012**



**PPS data representativeness was poor in Austria, Croatia, Czech Republic, Estonia, Norway and Romania and very poor in Denmark and Sweden.*

Clostridium difficile

- Bacillo gram positivo, anaerobio, sporigeno, presente nel suolo, nel tratto intestinale degli animali e nel 3% degli adulti sani.
- Hanno interesse clinico i ceppi che producono **tossina A e/o B**
- fa parte dei **Microrganismi "alert"**; il suo ritrovamento in pazienti ricoverati prevede misure di isolamento e precauzioni aggiuntive

Management must also include implementation of infection control policies. Patients with suspected or proven *C. difficile* infection should be placed on contact precautions, and healthcare workers should wash hands before and after patient contact. Hand hygiene with soap and water may be more effective than alcohol-based hand sanitizers in removing *C. difficile* spores, since *C. difficile* spores are resistant to killing by alcohol. Therefore, use of soap and water is favored over alcohol-based hand sanitization in the setting of a CDI outbreak.

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Review

Risk factors for development of *Clostridium difficile* infection due to BI/NAP1/027 strain: a meta-analysis

Konstantinos Z. Vardakas [a,b], Athanasios A. Konstantelias [a,c], Giorgos Loizidis [a,d], Petros I. Rafailidis [a,b], Matthew E. Falagas [a,b,e,*]

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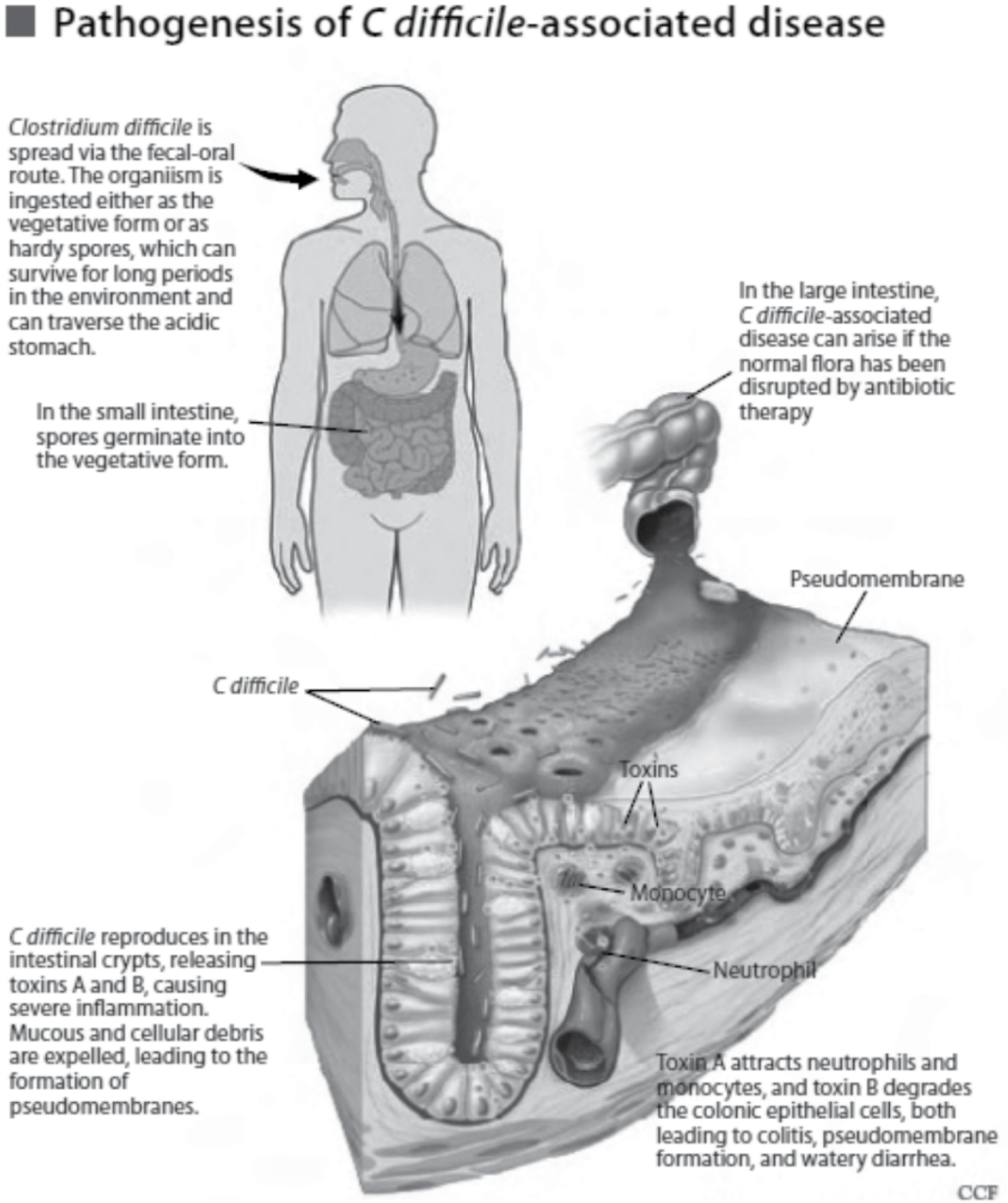
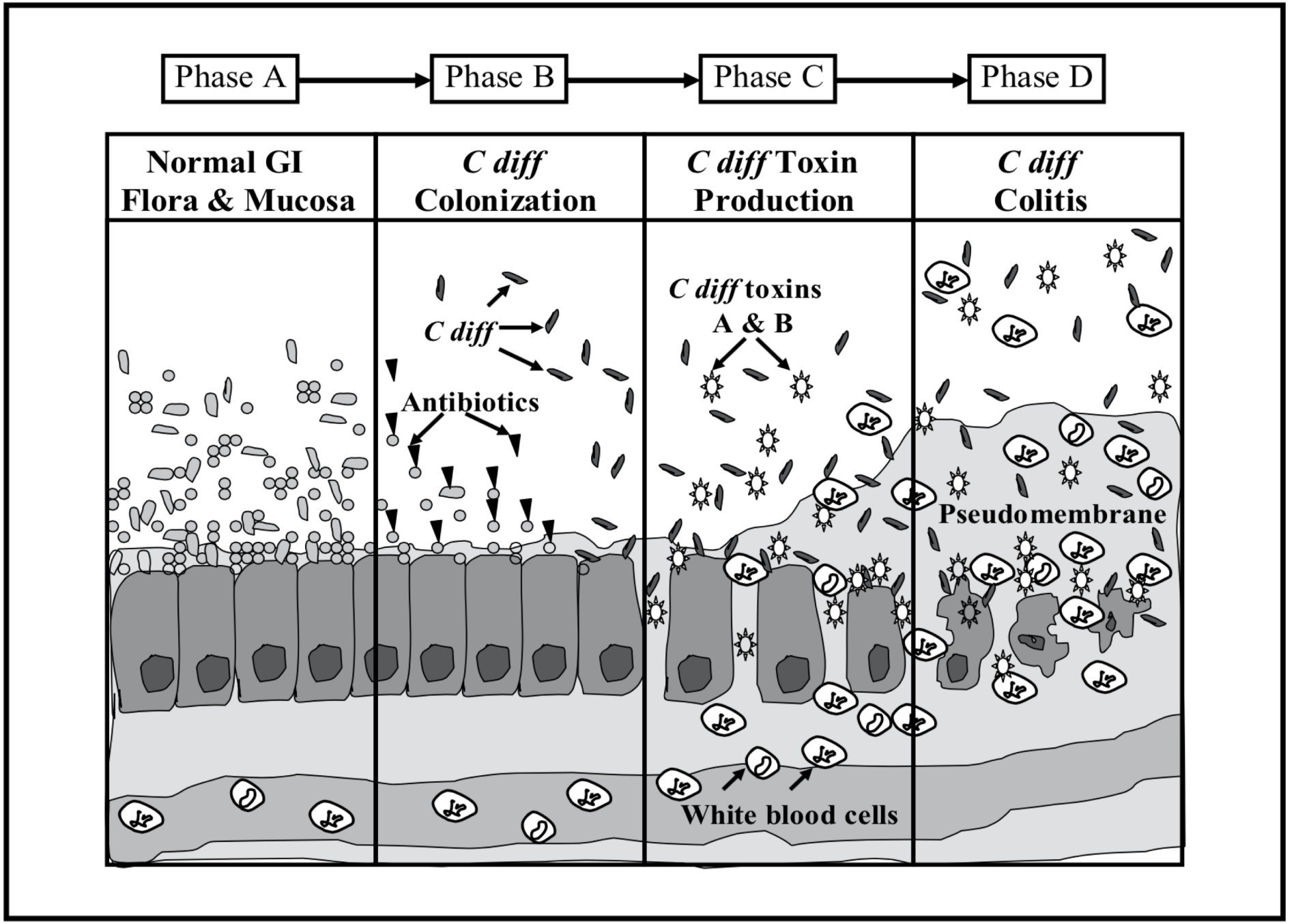
SUMMARY

Objective: To identify risk factors for the development of *Clostridium difficile* infection (CDI) due to *C. difficile* BI/NAP1/027 strain.
Methods: PubMed and Scopus databases were searched for studies that sought to identify risk factors for CDI due to the BI/NAP1/027 strain. The technique of meta-analysis was applied.
Results: Five studies compared CDI BI/NAP1/027 patients to CDI patients infected with non-BI/NAP1/027 strains, one compared CDI BI/NAP1/027 patients to non-CDI patients, and one provided data for both comparisons. The meta-analysis showed that fluoroquinolones were associated with a higher risk of CDI due to BI/NAP1/027 when compared to non-BI/NAP1/027 CDI (odds ratio (OR) 1.96, 95% confidence interval (95% CI) 1.37–2.80). A trend towards a lower risk for CDI due to BI/NAP1/027 was observed with cephalosporins when compared to non-BI/NAP1/027 CDI (OR 0.70, 95% CI 0.46–1.07). Prior macrolides were not associated with a higher risk for CDI BI/NAP1/027 when compared with non-BI/NAP1/027 CDI controls (OR 0.88, 95% CI 0.44–1.78). Clindamycin administration was associated with a lower risk for CDI due to BI/NAP1/027 when compared to non-BI/NAP1/027 CDI (OR 0.24, 95% CI 0.12–0.48). Age over 65 years was associated with an increased risk of CDI BI/NAP1/027 compared to non-BI/NAP1/027 CDI (OR 1.77, 95% CI 1.31–2.38).
Conclusions: Fluoroquinolones and age over 65 years were associated with a higher risk of CDI due to the BI/NAP1/027 strain. Clindamycin was associated with a lower risk of CDI due to BI/NAP1/027.



Modified from: Sunenshine RH, McDonald LC. *Clostridium difficile*-associated disease: new challenges from an established pathogen. *Cleve Clin J Med* 2006;73:187-197.

Figure 10.1. Phases of pathogenesis of *C. difficile* colitis.



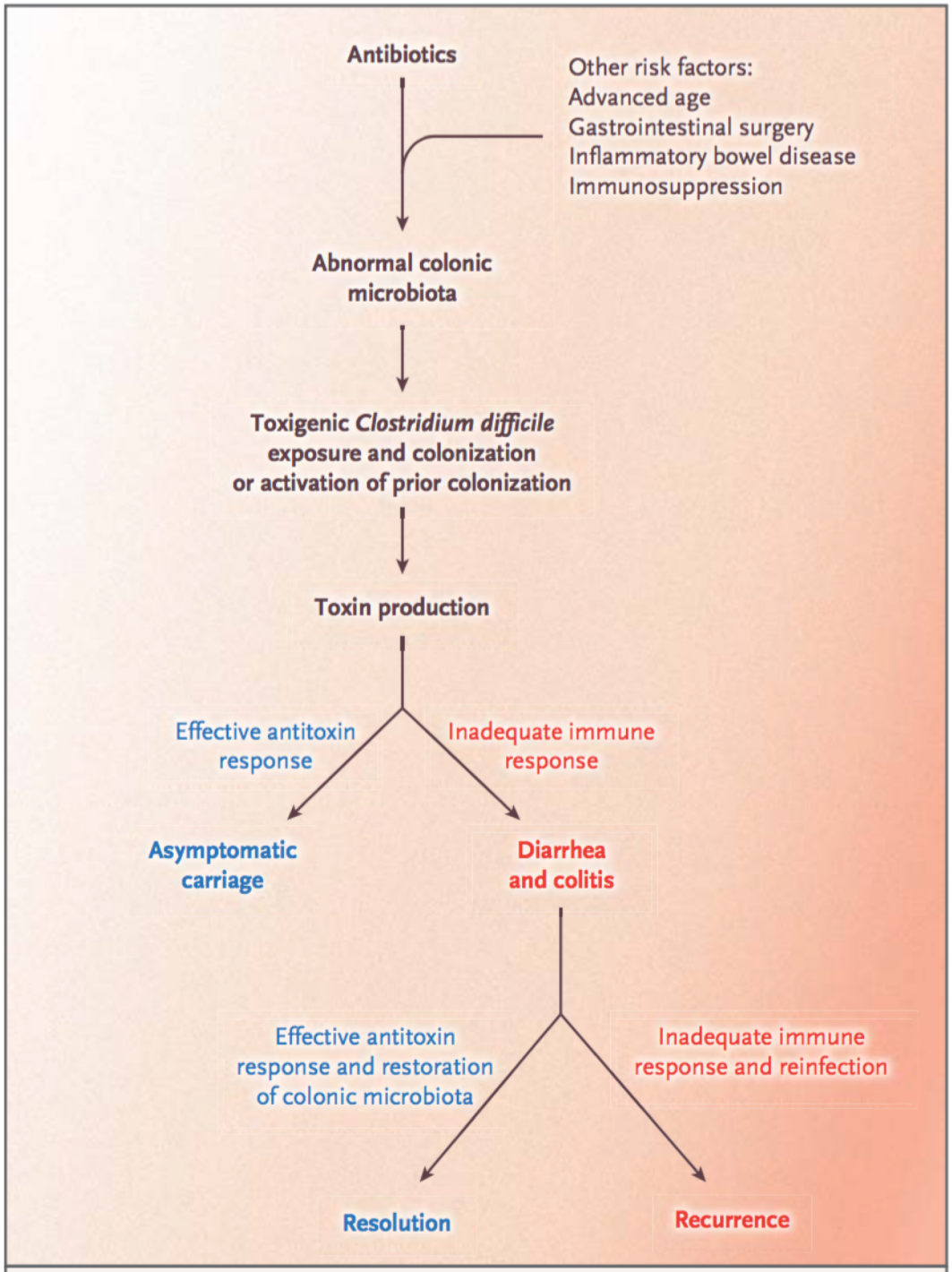


Figure 1. Pathogenesis of *Clostridium difficile* Infection.

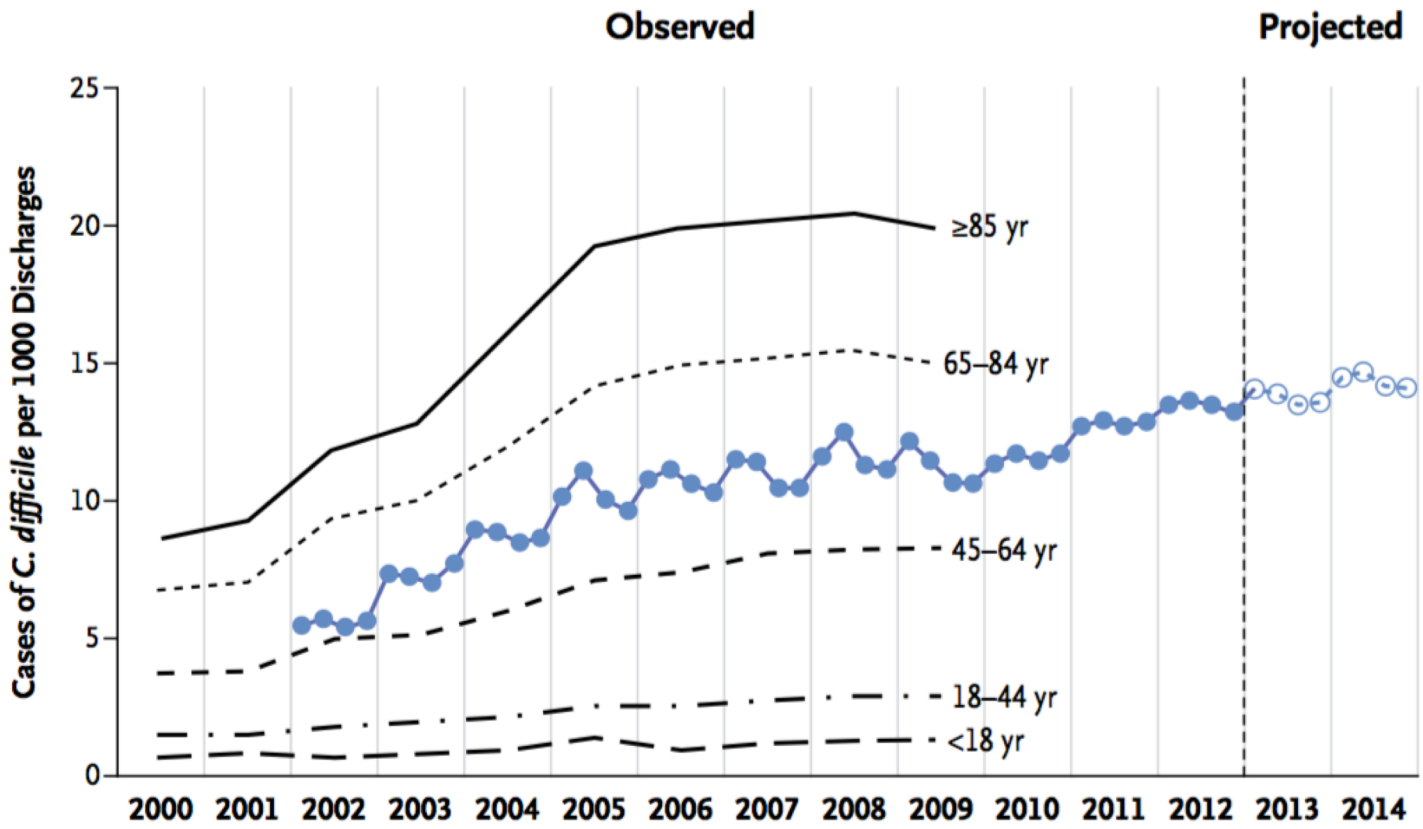


Figure 2. Incidence of Nosocomial *Clostridium difficile* Infection.

The overall incidence of nosocomial *C. difficile* infection is shown by year (blue), as is the incidence according to patient age (black). Data are from Steiner et al.[18] and Lessa et al.[24]

Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common
Macrolides	Somewhat common
Aminoglycosides	Uncommon
Bacitracin	Uncommon
Metronidazole	Uncommon
Teicoplanin	Uncommon
Rifampin	Uncommon
Chloramphenicol	Uncommon
Tetracyclines	Uncommon
Carbapenems	Uncommon
Daptomycin	Uncommon
Tigecycline	Uncommon

* Specific antibiotics are listed if their association with *C. difficile* infection differs from that of most other antibiotics in their class.

XXV. What is the role of antibiotic stewardship in controlling CDI rates?

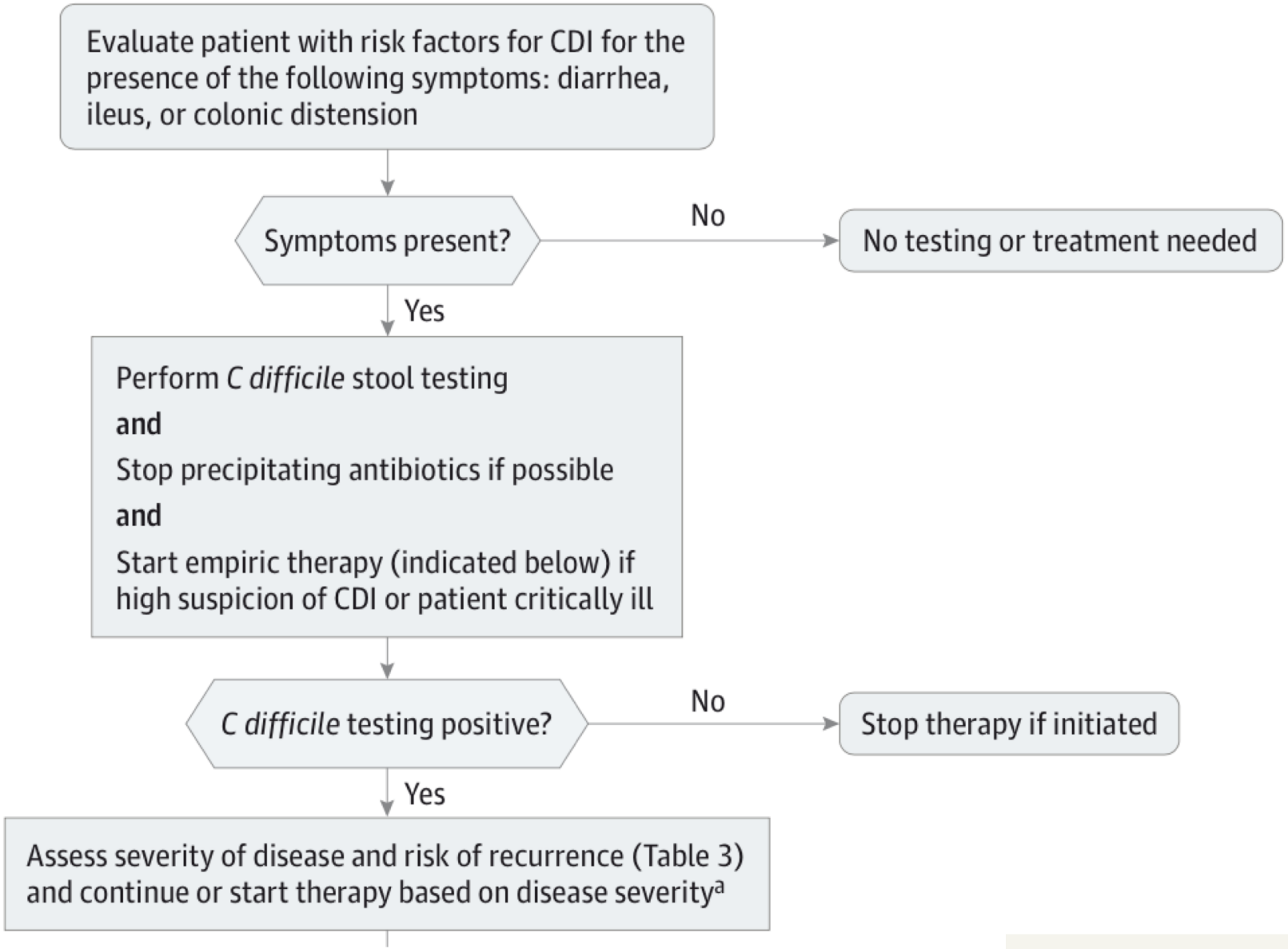
Recommendations

1. Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk *(strong recommendation, moderate quality of evidence)*.
2. Implement an antibiotic stewardship program *(good practice recommendation)*.
3. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered *(strong recommendation, moderate quality of evidence)*.

XXVI. What is the role of proton pump inhibitor restriction in controlling CDI rates?

Recommendation

1. Although there is an epidemiologic association between proton pump inhibitor (PPI) use and CDI, and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI *(no recommendation)*.



JAMA. 2015;313(4):398-408. doi:10.1001/jama.2014.17103

Clostridium difficile

La ricerca è indicata in:

pazienti ricoverati che presentano diarrea insorta dopo almeno 2 giorni di ricovero, oppure diarrea insorta entro le prime 48 ore, se dimessi da un ospedale

pazienti ambulatoriali con diarrea dimessi da un ospedale da non più di 4 settimane

pazienti con diarrea grave ndd.

Non effettuare la ricerca nei campioni di feci di soggetti asintomatici.

Sospendere la ricerca delle tossine di C. difficile su campioni fecali non appena viene accertata la diagnosi.

Non effettuare test dopo il trattamento a conferma della guarigione. Quando si sospetta una recidiva, ripetere il test per C. difficile, ma escludere anche altre cause possibili di diarrea.

Clostridium difficile

La diagnosi si basa sulla ricerca nelle feci di C. difficile e/o di suoi antigeni, tossine o acidi nucleici.

- Ricerca dell'antigene comune (glutammato deidrogenasi - GDH), indice di presenza di C. difficile. Il test è dotato di buona sensibilità, ma, in caso di positività, richiede conferma con un test in grado di evidenziare la presenza delle tossine A e B.

- Ricerca delle tossine A e B: sensibilità non elevata (75%), buona specificità (90%-100%); inoltre le tossine si degradano rapidamente se il campione non viene conservato a 2° - 8° C

- Amplificazione di acidi nucleici (NAT): sono disponibili in commercio test in PCR real-time in grado di identificare, a partire dal campione, anche i ceppi ipervirulenti. L'automazione delle fasi di estrazione, amplificazione e lettura, insieme al tempo di esecuzione (poco più di un'ora) ne fanno il test diagnostico ideale; il costo è più elevato.

Original Investigation

Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD

IMPORTANCE *Clostridium difficile* is a major cause of health care–associated infection, but disagreement between diagnostic tests is an ongoing barrier to clinical decision making and public health reporting. Molecular tests are increasingly used to diagnose *C difficile* infection (CDI), but many molecular test-positive patients lack toxins that historically defined disease, making it unclear if they need treatment.

OBJECTIVE To determine the natural history and need for treatment of patients who are toxin immunoassay negative and polymerase chain reaction (PCR) positive (Tox−/PCR+) for CDI.

DESIGN, SETTING, AND PARTICIPANTS Prospective observational cohort study at a single academic medical center among 1416 hospitalized adults tested for *C difficile* toxins 72 hours or longer after admission between December 1, 2010, and October 20, 2012. The analysis was conducted in stages with revisions from April 27, 2013, to January 13, 2015.

MAIN OUTCOMES AND MEASURES Patients undergoing *C difficile* testing were grouped by US Food and Drug Administration–approved toxin and PCR tests as Tox+/PCR+, Tox−/PCR+, or Tox−/PCR−. Toxin results were reported clinically. Polymerase chain reaction results were not reported. The main study outcomes were duration of diarrhea during up to 14 days of treatment, rate of CDI-related complications (ie, colectomy, megacolon, or intensive care unit care) and CDI-related death within 30 days.

RESULTS Twenty-one percent (293 of 1416) of hospitalized adults tested for *C difficile* were

CONCLUSIONS AND RELEVANCE Among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay test results. Patients with a positive molecular test result and a negative toxin immunoassay test result had outcomes that were comparable to patients without *C difficile* by either method. Exclusive reliance on molecular tests for CDI diagnosis without tests for toxins or host response is likely to result in overdiagnosis, overtreatment, and increased health care costs.

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Supplemental content at jamainternalmedicine.com

CME Quiz at jamanetworkcme.com and CME Questions page 1880

JAMA Intern Med. 2015;175(11):1792-1801. doi:10.1001/jamainternmed.2015.4114
Published online September 8, 2015.

Pathology and Laboratory Medicine, University of California Davis School of Medicine, Specialty Testing Center Bldg, 3740 Business Dr, Sacramento, CA 95820 (christopher.polage@ucdmc.ucdavis.edu).

Clostridium difficile

Sistema in uso:

- test immunocromatografico per la ricerca rapida dell'antigene GDH
- Real Time PCR per la ricerca combinata di tossina B, tossina binaria e del ceppo ipervirulento NAP1-027

Table 3. CDI Classification Based on Disease Severity

CDI Disease Category	Clinical and Laboratory Signs	Associated Risk Factors
Mild to moderate	Diarrhea without systemic signs of infection, white blood cell count <15 000 cells /mL, and serum creatinine <1.5 times baseline[15]	Antibiotic use, previous hospitalization, longer duration of hospitalization, use of proton pump inhibitors, receipt of chemotherapy, chronic kidney disease, and presence of a feeding tube[10-14]
Severe	Systemic signs of infection, and/or white blood cell count ≥15 000 cells/mL, or serum creatinine ≥1.5 times the premorbid level[15]	Advanced age, infection with BI/NAP1/027 strain[114,115]
Severe, complicated	Systemic signs of infection including hypotension, ileus, or megacolon[15]	See above,[a] plus recent surgery, history of inflammatory bowel disease, and intravenous immunoglobulin treatment[43]
Recurrent	Recurrence within 8 weeks of successfully completing treatment for CDI[16,20]	Patient age ≥65 y, concomitant antibiotic use, presence of significant comorbidities, concomitant use of proton pump inhibitors, and increased initial disease severity[16]

JAMA. 2015;313(4):398-408. doi:10.1001/jama.2014.17103

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 ≤15000 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 ≥15000 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

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

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Review

Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence

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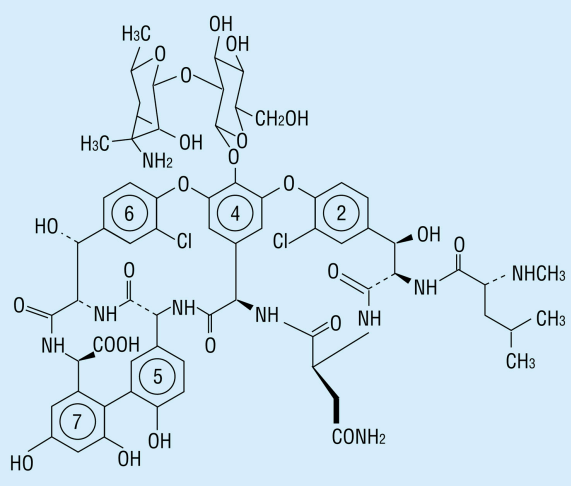
Metronidazole
Vancomycin
Randomised trial
Prospective
Retrospective
Cohort

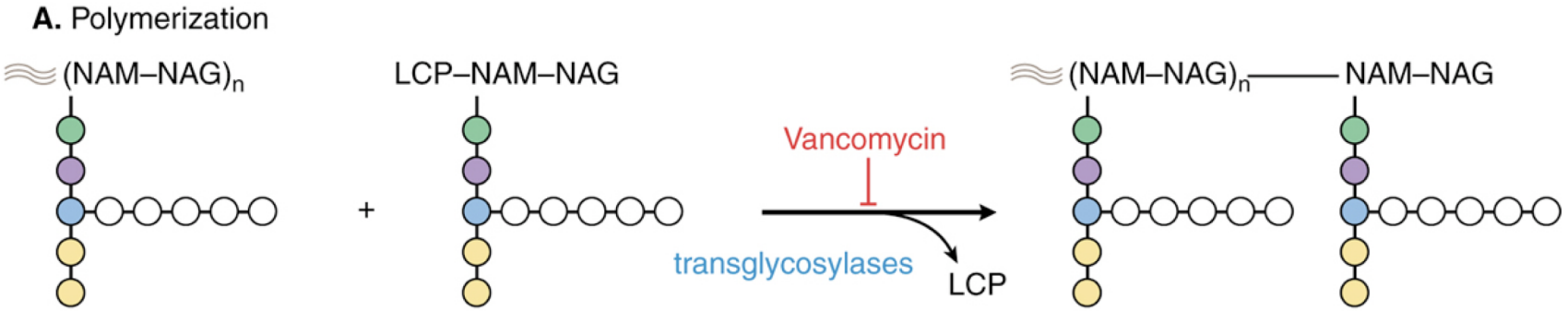
ABSTRACT

The objective of this review was to evaluate the frequency of treatment failure and recurrence of *Clostridium difficile* infection (CDI) following treatment with vancomycin or metronidazole in recently performed studies (last 10 years). Searches in PubMed and Scopus were performed by two reviewers independently. Data regarding treatment failure and recurrence following metronidazole and vancomycin treatment were extracted and analysed. In total, 39 articles (7005 patients) were selected for inclusion in the systematic review. The reported treatment failure was 22.4% with metronidazole (16 studies) and 14.2% with vancomycin (8 studies). Recurrence of CDI occurred in 27.1% of patients following metronidazole treatment (18 studies) and 24.0% of patients following vancomycin treatment (8 studies). Mean treatment failure and recurrence in the selected studies was 22.3% (24 studies) and 22.1% (37 studies). The reported outcomes depended on the study design (higher in prospective and retrospective cohort studies than in randomised controlled trials), geographic location of the study (higher in North America than in Europe and Asia), funding (higher in studies funded by non-profit organisations than pharmaceutical companies), mean age of the studied population (higher in older patients) and duration of follow-up (higher in studies with follow-up >1 month). In conclusion, infection with *C. difficile* is associated with 22.4% and 14.2% treatment failure and 27.1% and 24.0% recurrence after treatment with metronidazole and vancomycin, respectively. The variation in the reported outcomes amongst studies depends on the study design, location, funding, age and follow-up period.



vancomicina

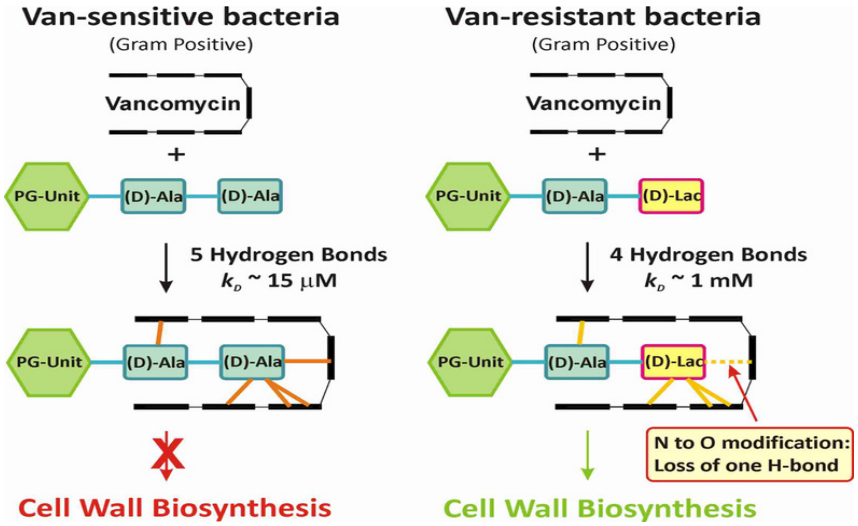
Vancocina®...



KEY

- L–Alanine
- D–Glutamate
- L–Lysine
- D–Alanine
- Glycine

NAM = N–Acetylmuramic acid
NAG = N–Acetylglucosamine
LCP = Lipid carrier bactoprenol
cell wall



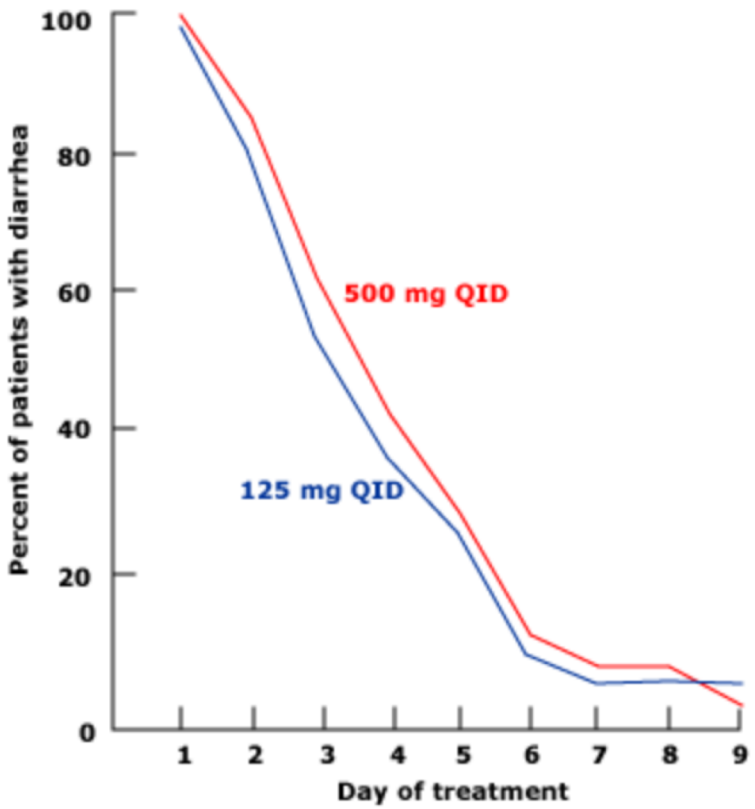
Glicopeptidi: spettro di attività

- Batteri Gram+
  - *Staphylococcus aureus m.s.*
  - *Staphylococcus aureus m.r.*
  - *Staphylococcus epidermidis*
  - *Streptococcus pyogenes*
  - *Streptococcus pneumoniae*
  - Viridans streptococci
  - *Enterococcus faecalis*
  - ***Clostridium difficile***
  - *Coryebacterium jeikeium*
- *Batteri Gram-:* ***sono resistenti***

Glicopeptidi: farmacocinetica

- **Non vengono assorbiti se somministrati per os**
- Si distribuiscono discretamente e attraversano anche la barriera ematoliquorale in presenza di flogosi
- Vengono eliminati quasi completamente per via renale
- Posologia 125 mg p.o. ogni 6 ore per 10 – 14 g
- Se il paziente è in terapia con altri antibiotici continuare il trattamento con vancomicina (o metronidazolo) per una settimana dopo la sospensione degli altri antibiotici.

High- and low-dose oral vancomycin are equally effective in acute *Clostridium difficile* colitis



Disappearance of diarrhea was identical in patients with acute *C. difficile* colitis who received either high- (500 mg four times daily, red line) or low- (125 mg four times daily, blue line) dose oral vancomycin for 10 days.

QID: four times daily.

Redrawn from Fekety R, Silva J, Kauffman C, et al. Am J Med 1989; 86:15.

Glicopeptidi: effetti collaterali

- **Tossicità scarsissima per somministrazione orale.**
- Ototossicità spesso irreversibile
- Nefrotossicità (rara, reversibile)
- La vancomicina è un liberatore di istamina:
  - Sindrome dell' uomo rosso
  - Sindrome del collo rosso
  - Ipotensione

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

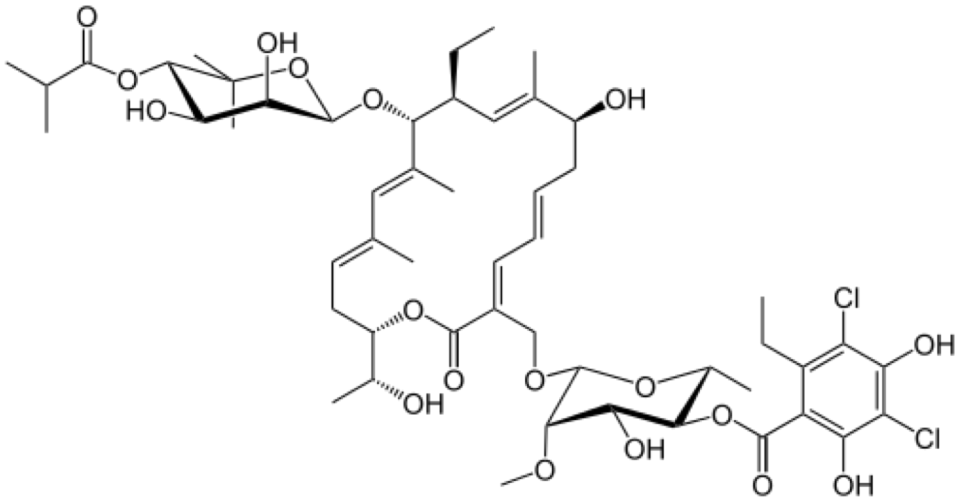
Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• 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 ≥15000 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

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.



Fidaxomicina

- Battericida, con azione selettiva su Gram + e in particolare Clostridium difficile, e minima attività sulla flora intestinale.
- Inibitore della RNA polimerasi dei Clostridi
- Non assorbita dopo somministrazione orale.
- Posologia 200 mg ogni 12 ore per 10 giorni

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 ≤15000 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 ≥15000 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

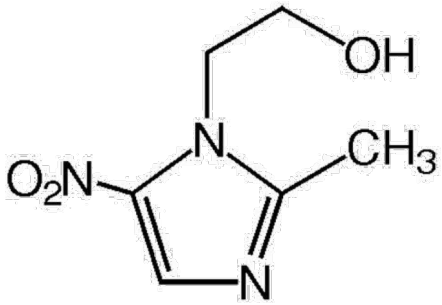
Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

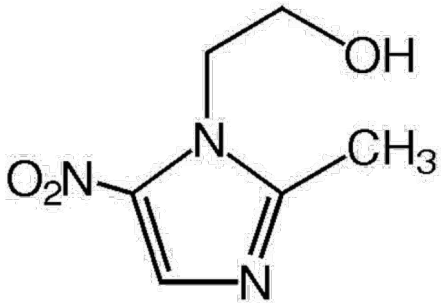
[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Metronidazolo



- Forma composti citotossici accettando elettroni sul nitro gruppo
- Spettro antibatterico: batteri anaerobi (*C. difficile*) e parassiti (*T. vaginalis, E. histolytica, G. lamblia*)
- Rarissima la resistenza del *C. difficile*.
- Biodisponibilità orale 100%, distribuzione ottima (inclusi CSF, osso, ascessi, metabolismo epatico)
- Posologia: 500 mg ogni 8 ore p.o. x 10 – 14 giorni
- Se dopo 7 giorni il paziente non risponde, passare alla vancomicina

Metronidazolo



- Tossicità:
  - Reazioni disulfiram-like
  - Disturbi G.I.
  - Sapore metallico
  - Colorazione rosso bruna delle urine
  - Vertigini e neuropatia periferica per trattamenti prolungati
- Non somministrare in gravidanza o allattamento

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

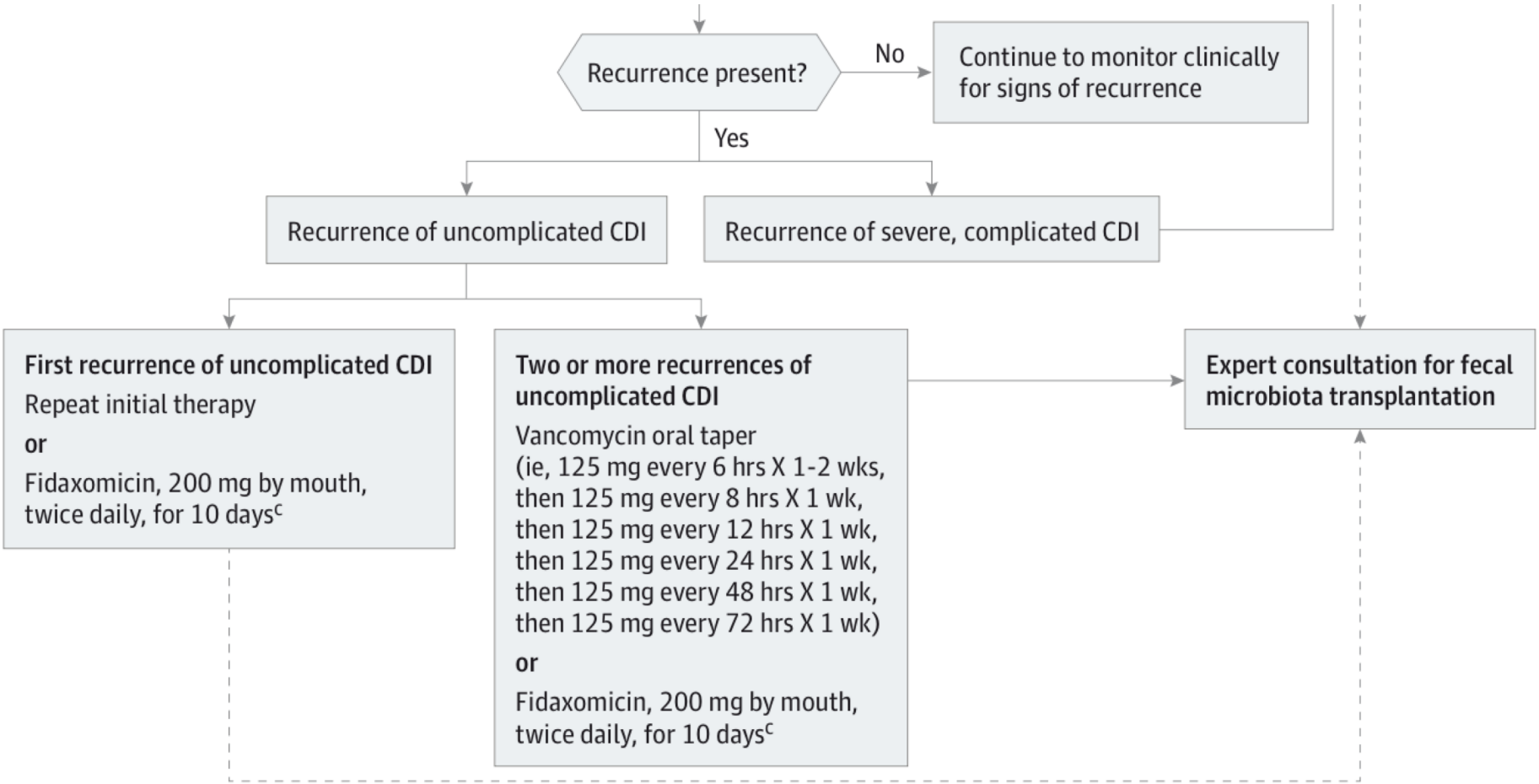
Clinical Definition	Recommended Treatment	Pediatric Dose	Maximum Dose	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low Weak/Low
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.



JAMA. 2015;313(4):398-408. doi:10.1001/jama.2014.17103

From The Medical Letter on Drugs and Therapeutics

Bezlotoxumab (Zinplava) for Prevention of Recurrent *Clostridium Difficile* Infection

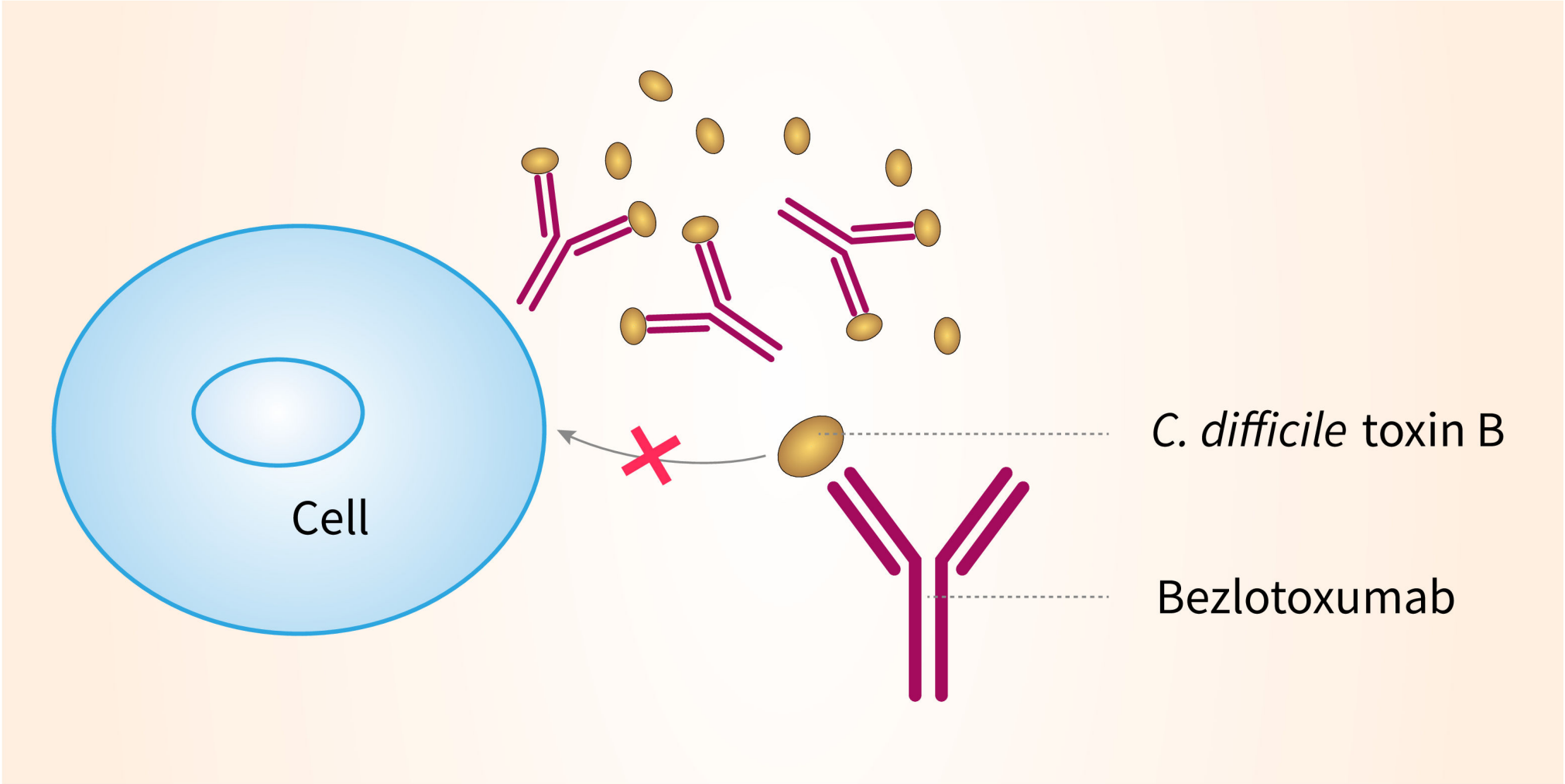
JAMA August 15, 2017 Volume 318, Number 7

The FDA has approved the fully human monoclonal antibody bezlotoxumab (Zinplava – Merck) for use with antibacterial drug treatment to reduce recurrence of *Clostridium difficile* infection (CDI) in adults with CDI at high risk for recurrence. It is the first drug to be approved for this indication.

Pronunciation Key

Bezlotoxumab: bez" loe tox' ue mab **Zinplava:** zin plah' va

- anticorpo monoclonale concepito per legarsi alla tossina B prodotta dal Clostridium difficile, neutralizzandone l'attività: in associazione alla terapia antibiotica per il Clostridium difficile, rappresenta un alleato in grado di consentire la prevenzione della recidiva di infezione. Il farmaco è, infatti, in grado di ridurre di circa il 40%6 le recidive, abbattendo del 53%7 il rischio di riospedalizzazioni correlate alla patologia.
- Approvato dall'AIFA luglio 2018


Cell
C. difficile toxin B
Bezlotoxumab

Costi del trattamento

Farmaco	Nome comm.	Posologia/die		Costo di un trattamento di 10 g
Metronidazolo	Flagyl®	500 mg x 3	20 cpr 250 mg€ 2,57	€ 7,71
Vancomicina	Levovanox® Maxivanil®	125 mg x 4	4 cps 250 mg € 18,19 Polvere per infusione e.v. 500 mg € 11,23	€ 181,9 € 112,3
Fidaxomicina	Dificlir®	200 mg x 2	20 cpr 200 mg € 2.487,44	€ 2.487,44
Bezlotoxumab	Zinplava®	1000 mg x 1 somministrazi		€ 4.393,99

Clinical Infectious Diseases

BRIEF REPORT

Efficacy of Oral Vancomycin in Preventing Recurrent *Clostridium difficile* Infection in Patients Treated With Systemic Antimicrobial Agents

Nicholas W. Van Hise,[1] Alex M. Bryant,[2] Erin K. Hennessey,[2,4] Andrew J. Crannage,[2,4] Jad A. Khoury,[3] and Farrin A. Manian[5]

[1]Department of Pharmacy, Edward-Elmhurst Hospitals, Naperville, Illinois; Departments of [2]Pharmacy, and [3]Medicine, Mercy Hospital St Louis, and [4]St Louis College of Pharmacy, Missouri; and [5]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston

(See the Editorial Commentary by Johnson on pages 654–5.)

We compared rates of recurrent *Clostridium difficile* infection in patients receiving or not receiving oral vancomycin prophylaxis with systemic antimicrobial therapy. The incidence of *C. difficile* infection was significantly lower in patients receiving prophylaxis (4.2% vs 26.6% in those without prophylaxis; odds ratio, 0.12; 95% confidence interval, .04–.4; $P < .001$).

Keywords. prophylaxis; *Clostridium difficile*; vancomycin; antimicrobial agents.

The Potential of Probiotics to Prevent *Clostridium difficile* Infection

Stephen J. Allen, MB ChB, MRCP(UK) Paediatrics, DTM&H, MD

KEYWORDS

- *C difficile* diarrhea • Probiotic • Lactobacilli • *Bifidobacteria*
- *Saccharomyces boulardii*

KEY POINTS

- In this article, the familiar term probiotic is used for microbial preparations being evaluated in clinical trials rather than for organisms with a proven health benefit.
- Probiotics evaluated in the prevention of *Clostridium difficile* diarrhea (CDD) have included bacteria (mostly lactobacilli and *Bifidobacteria*) either as single strains or as blends of strains and/or species, in variable doses (number of organisms) and in variable formulations, and the yeast *Saccharomyces boulardii*.
- The interpretation of the findings of meta-analysis of probiotic trials is complicated by the difficulty in pooling results for different probiotic preparations. As a result, there is insufficient evidence to recommend the use of any specific probiotic preparation.
- The falling incidence of CDD among the older people in hospitals because of control measures complicates the further evaluation of probiotics for CDD prevention.

XXVII. What is the role of probiotics in primary prevention of CDI?

Recommendation

1. There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials *(no recommendation)*.

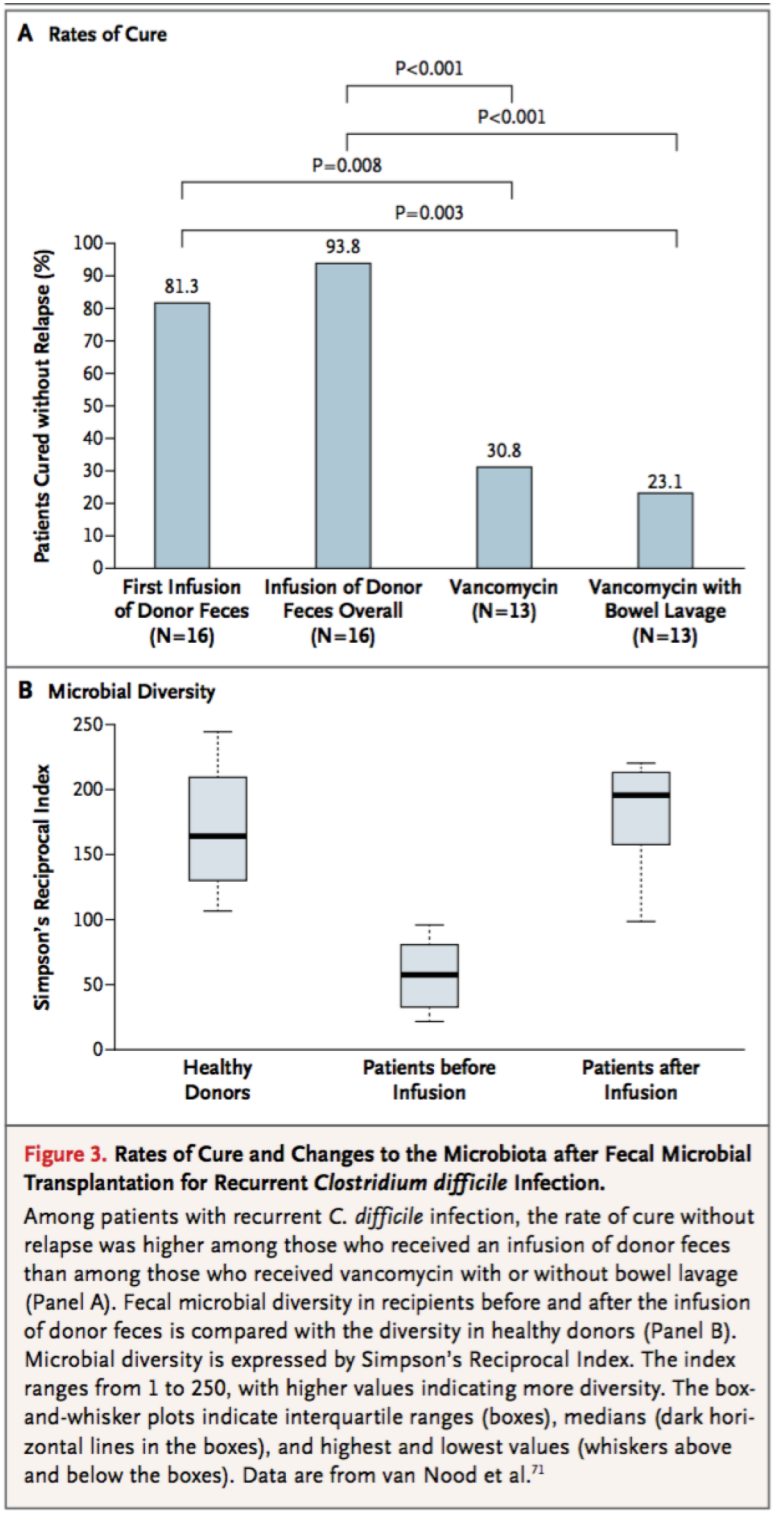


Figure 3. Rates of Cure and Changes to the Microbiota after Fecal Microbial Transplantation for Recurrent *Clostridium difficile* Infection.

Among patients with recurrent *C. difficile* infection, the rate of cure without relapse was higher among those who received an infusion of donor feces than among those who received vancomycin with or without bowel lavage (Panel A). Fecal microbial diversity in recipients before and after the infusion of donor feces is compared with the diversity in healthy donors (Panel B). Microbial diversity is expressed by Simpson's Reciprocal Index. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes). Data are from van Nood et al.[71]

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Research

Preliminary Communication

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection

Ilan Youngster, MD, MMSc; George H. Russell, MD, MSc; Christina Pindar, BA; Tomer Ziv-Baran, PhD; Jenny Sauk, MD; Elizabeth L. Hohmann, MD

Data supporting the use of fecal microbiota transplantation for recurrent CDI are increasing; however, the regulation and standardization of fecal microbiota transplantation is evolving. Studies are ongoing to develop synthetic stool for treating CDI or capsules for administrating fecal microbiota transplantation.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)

JAMA. 2014;312(17):1772-1778. doi:10.1001/jama.2014.13875
Published online October 11, 2014.

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OPEN ACCESS

European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,[1] Gianluca Ianiro,[1] Herbert Tilg,[2] Mirjana Rajilić-Stojanović,[3] Patrizia Kump,[4] Reetta Satokari,[5] Harry Sokol,[6] Perttu Arkkila,[7] Cristina Pintus,[8] Ailsa Hart,[9] Jonathan Segal,[9] Marina Aloi,[10] Luca Masucci,[11] Antonio Molinaro,[12] Franco Scaldaferri,[1] Giovanni Gasbarrini,[1] Antonio Lopez-Sanroman,[13] Alexander Link,[14] Pieter de Groot,[15] Willem M de Vos,[5,16] Christoph Högenauer,[4] Peter Malfertheiner,[14] Eero Mattila,[17] Tomica Milosavljević,[18] Max Nieuwdorp,[12,15,19] Maurizio Sanguinetti,[11] Magnus Simren,[20] Antonio Gasbarrini,[1] The European FMT Working Group

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For numbered affiliations see end of article.

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ABSTRACT

Faecal microbiota transplantation (FMT) is an important therapeutic option for *Clostridium difficile* infection. Promising findings suggest that FMT may play a role also in the management of other disorders associated with the alteration of gut microbiota. Although the health community is assessing FMT with renewed interest and patients are becoming more aware, there are technical and logistical issues in establishing such a non-standardised treatment into the clinical practice with safety and proper governance. In view of this, an evidence-based recommendation is needed to drive the practical implementation of FMT. In this European Consensus Conference, 28 experts from 10 countries collaborated, in separate working groups and through an evidence-based process, to provide statements on the following key issues: FMT indications; donor selection; preparation of faecal material; clinical management and faecal delivery and basic requirements for implementing an FMT centre. Statements developed by each working group were evaluated and voted by all members, first through an electronic Delphi process, and then in a plenary consensus conference. The recommendations were released according to best available evidence, in order to act as guidance for physicians who plan to implement FMT, aiming at supporting the broad availability of the procedure, discussing other issues relevant to FMT and promoting future clinical research in the area of gut microbiota manipulation. This consensus report strongly recommends the implementation of FMT centres for the treatment of *C. difficile* infection as well as traces the guidelines of technicality, regulatory, administrative and laboratory requirements.

INTRODUCTION

Faecal microbiota transplantation (FMT) consists of the infusion of faeces from a healthy donor to the GI tract of a recipient patient, in order to treat a specific disease associated with alteration of gut microbiota. A large body of evidence, including randomised controlled trials (RCTs), systematic reviews and meta-analyses, proved clear evidence that FMT is a highly effective treatment against recurrent *Clostridium difficile* infection (rCDI).[1–7] Due to the rising prevalence, severity and mortality of this infection, the therapeutic role played by FMT is therefore important to save human lives and to decrease the economic burden on healthcare systems.[8–11] Based on these data, both the European Society for Microbiology and Infectious Disease and the American College of Gastroenterology recommend FMT as a treatment for rCDI.[12 13]

Beyond the treatment of CDI, FMT has also been investigated in other disorders associated with the alteration of gut microbiota. In particular, studies in humans include RCTs in patients with UC and metabolic syndrome (MS).[14–16]

The global interest in FMT is increasing, and both doctors and patients are increasingly aware and informed. Although the dissemination of FMT in the clinical practice is restricted by regulatory and bureaucratic issues (principally related to costs, donor programme, safety control),[17–19] the FMT practice is booming, ranging from highly organised stool banking programmes to individual treatments with patient-identified directed donors, and even to individual and harmful do-it-yourself practices. Working groups (WGs) from the USA, Austria and France released recommendations on indications and methods of FMT.[20–22] Authoritative published guidelines and recommendations have been released as expert opinions rather than evidence-based consensus reports. A rigorous and formal evidence-based process to drive the wide range of FMT practice has not been performed yet.

The aim of this evidence-based consensus report is to define indications and methodology for the use of FMT in the treatment of CDI, to discuss the suitability of FMT for indications other than CDI and to address the minimum requirements needed to implement a FMT centre. The final aim is to encourage and drive the dissemination of the procedure and to promote further clinical research in the area.

METHODS

Consensus development process

The process of development of the consensus conference, aimed at drawing up evidence-based recommendations for the use of FMT in clinical practice, included the following steps: selection of

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- **DIVERTICOLITE ACUTA NON COMPLICATA**

- **Trattamento ambulatoriale** — possibile nei pazienti con diverticolite non complicata
- Criteri per il trattamento domiciliare

  - Disponibilità a consultare nuovamente il medico se la sintomatologia peggiora
  - Compliance con il piano terapeutico
  - Dolore addominale non grave
  - Temperatura corporea non molto elevata
  - Possibilità di tollerare l'assunzione orale di fluidi e cibo
  - Nessuna o minima comorbidità
  - Sistema di supporto disponibile

- **Diverticolite non complicata**
- Paziente non ospedalizzato
  - Antibiotici orali per 10 – 14 g, scelta dell'antibiotico basata sul patogeno probabile, cocchi Gram – e anaerobi (in particolare E. coli e B. fragilis).
  - Ciprofloxacina (500 mg PO due volte al giorno) più metronidazolo (500 mg PO tre volte al giorno).
  - Amoxicillina-clavulanato (875/125 mg due volte al giorno) è un'alternativa.
  - Per pazienti che non tollerano il metronidazolo, clindamicina. Per pazienti che non tollerano metronidazolo e beta lattamici la moxifloxacina ha un buon spettro contro G- e anaerobi.
- Paziente ospedalizzato
  - terapia empirica con antibiotici ad ampio spettro e.v. con attività contro cocchi G- e anaerobi, fino all'arrivo dei risultati del laboratorio da coltura di ascessi ottenuto per aspirazione percutanea o drenaggio chirurgico.
  - Rivalutare la terapia quando arriva l'antibiogramma. Se nella coltura cresce più di un organismo probabile infezione polimicrobica con anaerobi; anche se questi non vengono isolati in coltura, continuare con la copertura per gli anaerobi.

- **Raccomandazioni dietetiche**
  I pazienti ambulatoriali devono essere istruiti a consumare solo liquidi chiari. Il miglioramento clinico dovrebbe essere evidente dopo due o tre giorni, dopo di che la dieta può essere lentamente modificata. I pazienti che richiedono il ricovero possono essere trattati con liquidi chiari o completo riposo intestinale e idratazione per via endovenosa, a seconda della gravità dei sintomi.

- **Raccomandazioni dietetiche**
  Fibre - Il ruolo della terapia dietetica nella prevenzione delle recidive non è stato stabilita in studi clinici controllati randomizzati ben disegnati con-lungo termine di follow-up. Tuttavia, i pazienti dovrebbero essere generalmente consigliati di consumare una dieta ricca di fibre una volta che la fase acuta è risolta. Questa raccomandazione si basa soprattutto su studi non controllati, che hanno suggerito che la supplementazione di fibre a lungo termine può ridurre l'incidenza di recidive.
  Semi e noci – Ai pazienti con malattia diverticolare si è storicamente consigliato di evitare semi, mais e noci per la preoccupazione che i frammenti non digeriti possano rimanere incastrati all'interno di un diverticolo, inducendo in tal modo un episodio di diverticolite. Non c'è nessuna prova a questo proposito

Diarrea del viaggiatore

Pathogens causing travelers' diarrhea

Bacteria
Enterotoxigenic Escherichia coli
Enteroaggregative E. coli
Campylobacter jejuni
Salmonella species
Shigella species
Clostridium difficile
Vibrio parahaemolyticus (V. cholerae less common)
Aeromonas hydrophilia
Plesiomonas shigelloides
Yersinia enterocolitica
Viruses
Rotavirus
Enteric adenovirus
Parasites
Giardia lamblia
Cryptosporidium parvum
Cyclospora cayetanensis
Microsporidia
Isospora belli
Entamoeba histolytica (not common)

Diarrea del viaggiatore

- TRATTAMENTO
  - Idratazione
  - Antibiotici
  - Antidiarroici
  - La maggior parte dei casi risolvono da soli entro tre-cinque giorni di trattamento con la sola idratazione. La terapia antimicrobica accorcia la durata della malattia di circa un giorno e gli antidiarroici possono limitare i sintomi.
  - L'idratazione è il trattamento più importante in quanto il rischio più significativo è l'ipovolemia. I pazienti con diarrea lieve possono alternare sorsi di liquidi che contengono sale e fluidi che contengono zucchero (brodo, succo di frutta..)

Diarrea del viaggiatore

- TRATTAMENTO
  - Diarrea grave: soluzione di reidratazione orale, che fornisce elettroliti nelle concentrazioni adeguate e necessarie. L'intestino rimane in grado di assorbire l'acqua se sono presenti il glucosio e il sale.
    I pacchetti di soluzione di reidratazione orale sono disponibili nelle farmacie della maggior parte dei paesi, possono essere miscelati con acqua potabile. In alternativa, mezzo cucchiaino di sale, 1/2 cucchiaino di bicarbonato di sodio, e 4 cucchiai di zucchero in un litro di acqua. Le soluzioni come il Gatorade non sono equivalenti. L'utilizzo di fluidi è il fattore critico.
  - I pazienti possono essere inconsapevoli di quanto liquido stanno perdendo dall'intestino.

Oral agents for self-treatment of travelers' diarrhea

Agent	Adult dose	Pediatric dose•
Norfloxacin	400 mg twice daily for up to three days	Not recommended
Ciprofloxacin◇	500 mg twice daily for up to three days	20 to 30 mg/kg per day in two divided doses for up to three days; maximum dose 500 mg
Ofloxacin◇	200 mg twice daily for up to three days	7.5 mg/kg every 12 hours for up to three days; maximum dose 200 mg
Levofloxacin◇	500 mg once daily for up to three days	10 mg/kg once daily for up to three days; maximum dose 500 mg
Azithromycin§	1000 mg single dose	10 mg/kg once daily (single dose); maximum dose 1000 mg
Rifaxamin	200 mg three times daily for up to three days	≥12 years: 200 mg three times daily for up to three days

• Self-treatment of travelers' diarrhea in children is controversial.
◇ Not licensed for this indication in children younger than 18 years.
§ Preferred agent for children.

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- Antidarroici come la loperamide (Imodium) sono spesso utilizzati in combinazione con antibiotici per ridurre la frequenza delle scariche; non trattano la causa della diarrea. Una meta-analisi di 12 studi del 2008 suggerisce che loperamide combinato con la terapia antibiotica è utile nella diarrea del viaggiatore.
  Secondo alcuni studi questi farmaci possono prolungare alcuni tipi di dissenteria (ad esempio, Shigella), ma la maggior parte delle ricerche suggeriscono che possono essere utilizzati con sicurezza purché combinati con la terapia antibiotica (cautela nell'uso di questi farmaci nei casi di diarrea ematica).
- Se disponibile, racecadotril (Tiorfix), un inibitore encefalinasi, può essere un' aggiunta efficace. A differenza della loperamide, che riduce la motilità intestinale, ha una azione antisecretoria.

  Gli antidiarroici devono essere interrotti se il dolore addominale o altri sintomi peggiorano o se la diarrea continua ad essere intrattabile dopo due giorni.