L'infezione da *Clostridium difficile* (CDI)
Quadri clinici e nuovi approcci terapeutici

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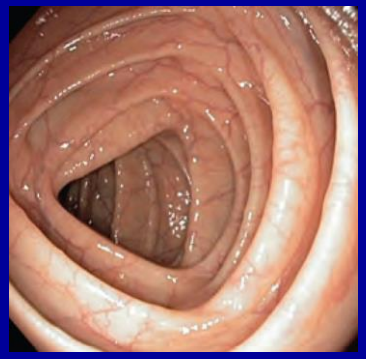
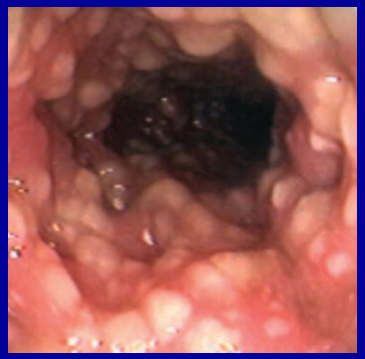
Clinical presentation of infection with *C. difficile*

- Asymptomatic colonisation
- Diarrhoea without colitis
  - Watery
  - Mucus but no blood
- Colitis without pseudomembrane formation
- Pseudomembranous colitis
- Fulminant colitis

Normal, healthy colon

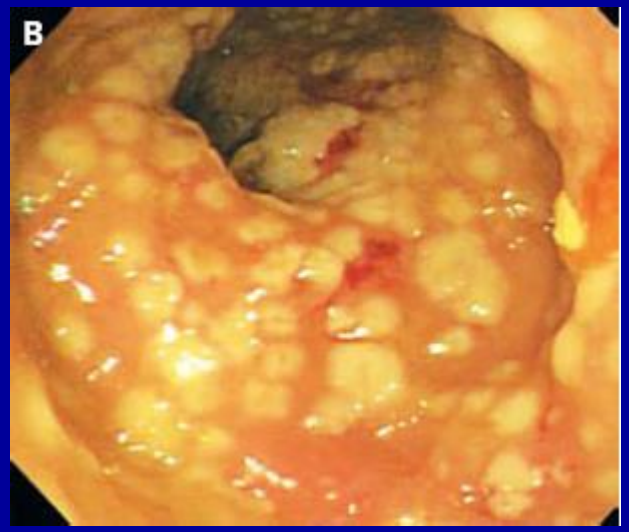


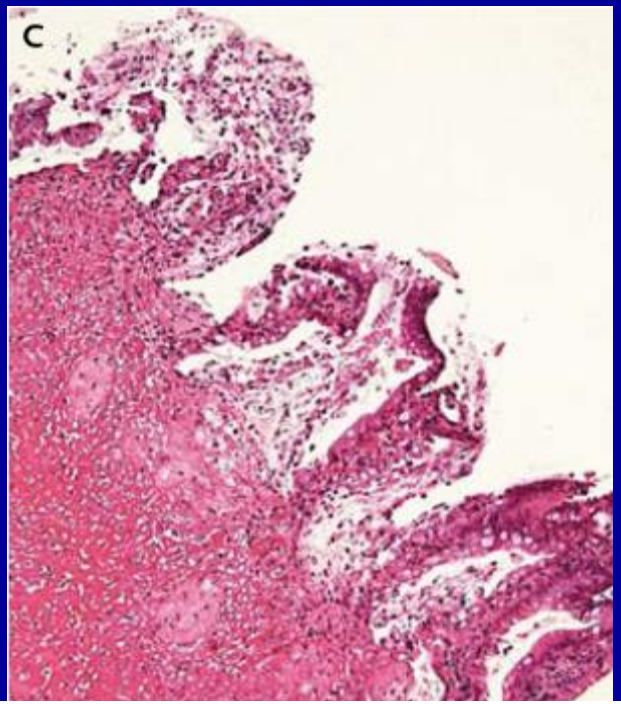
Pseudomembranous colitis

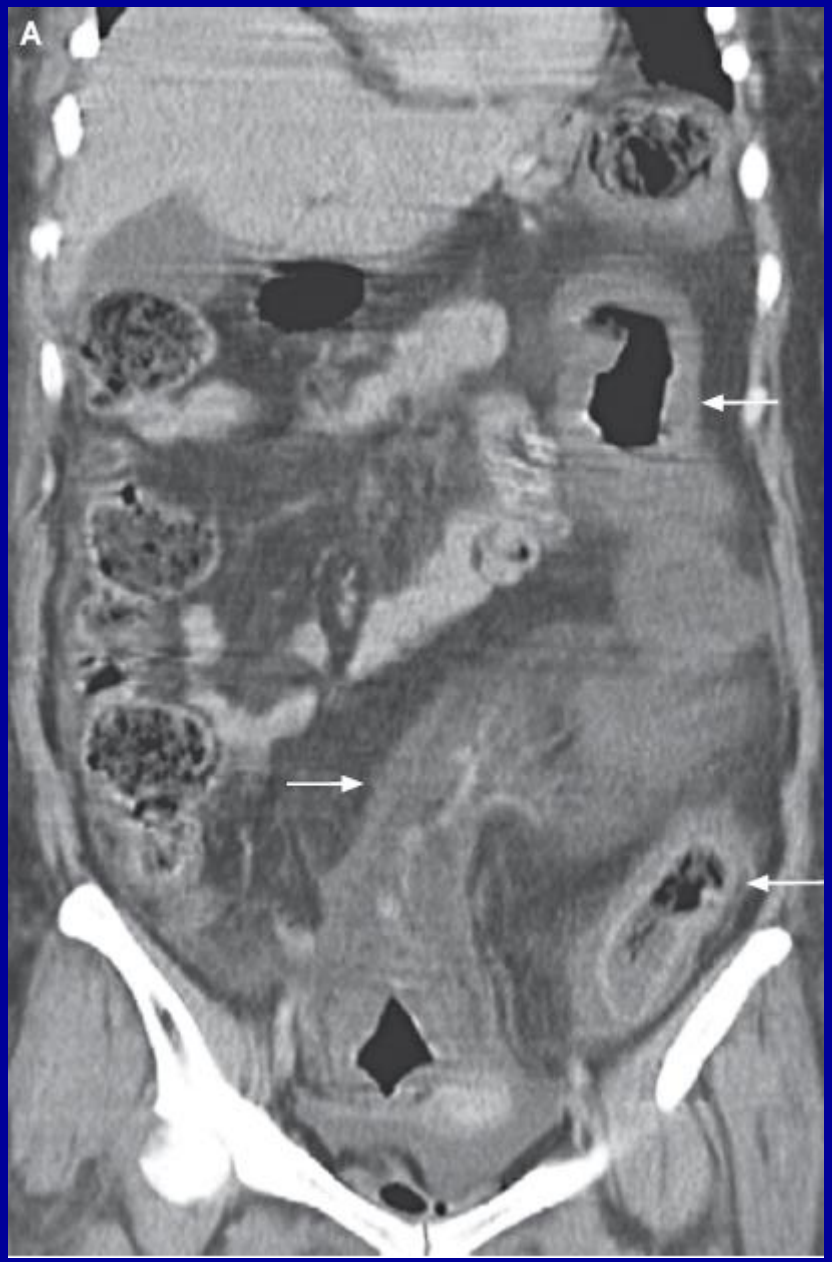


Increasing severity

Bauer et al. Clin Microbiol Infect 2009;15:1067–79;
Bartlett & Gerding. Clin Infect Dis 2008;46:S12–8.







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IMAGES IN CLINICAL MEDICINE

Risk factors for CDI

- Exposure to antibiotics, especially broad-spectrum antibiotics
- Exposure to the organism, usually through admission to health care facility (prolonged H)

- Others: older age, gastrointestinal surgery, naso –gastric tube feeding, reduced gastric acid, concurrent disease including inflammatory bowel disease

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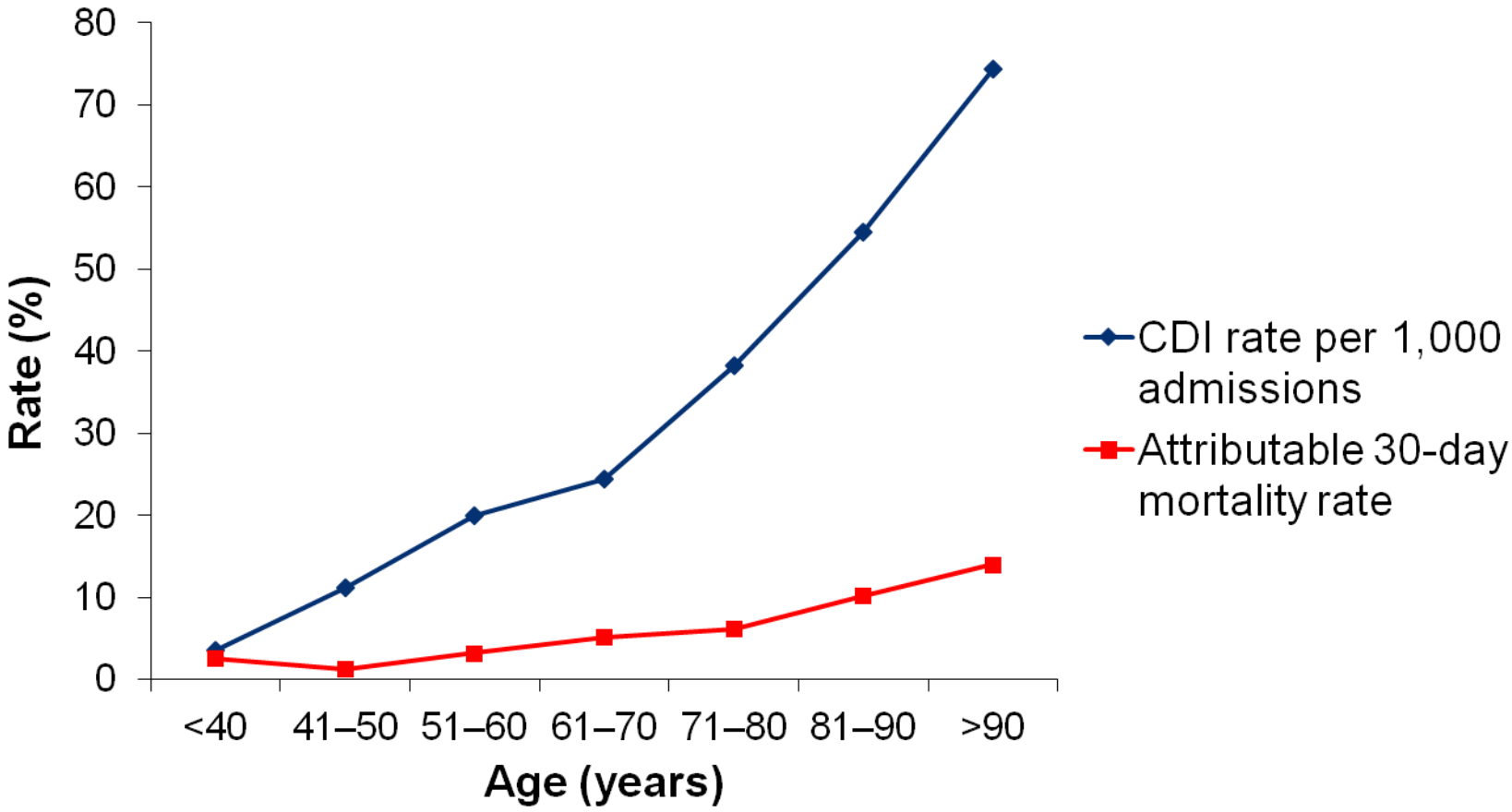
Age-specific incidence of CDI and attributable mortality



Loo et al. N Engl J Med 2005;353:442–9.

Costs associated with treating CDI

- The management of patients with CDI may necessitate:
  - Isolation and therapy of infected patients
  - Rigorous hand hygiene
  - Environmental decontamination
- In cases of outbreaks, cohort isolation and ward closure may be necessary

- CDI patients, when compared with non-infected matched controls:[1–3]
  - Spend on average an extra 7–21 days in hospital
  - Have increased median treatment costs of €7,147

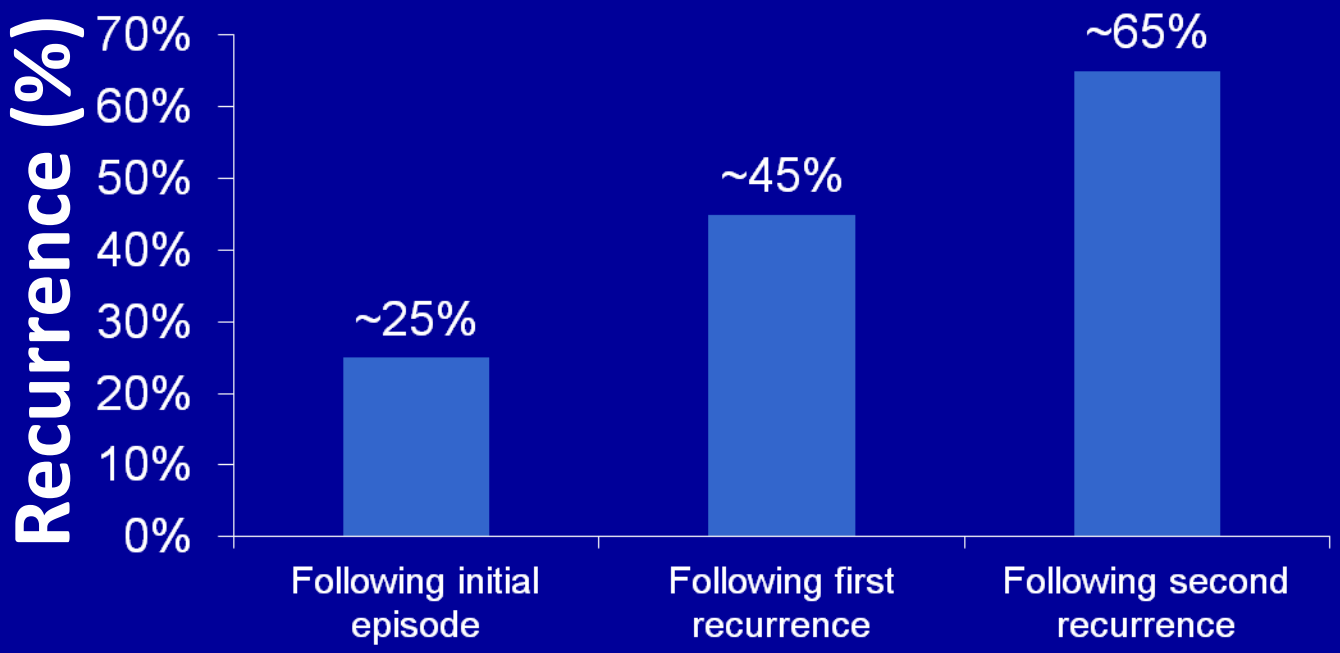
1. Vonberg et al. J Hosp Infect 2008;70:15–20;
2. Dubberke et al. Infect Control Hosp Epidemiol 2009;30:57–66;
3. Wilcox et al. J Hosp Infect 1996;34:23–30.

Recurrence of CDI

- Recurrence of CDI has been identified by ESCMID as the most important problem in the treatment of CDI[1]
- CDI recurrence is common, occurring in up to 25% of cases within 30 days following treatment[2–4]
- Recurrence appears to be related to a combination of:[5]
  - A failure to re-establish the colonic microflora
  - The presence in the intestines of spores of *C. difficile*
  - A sub-optimal host immune response to the infecting organism and its toxins

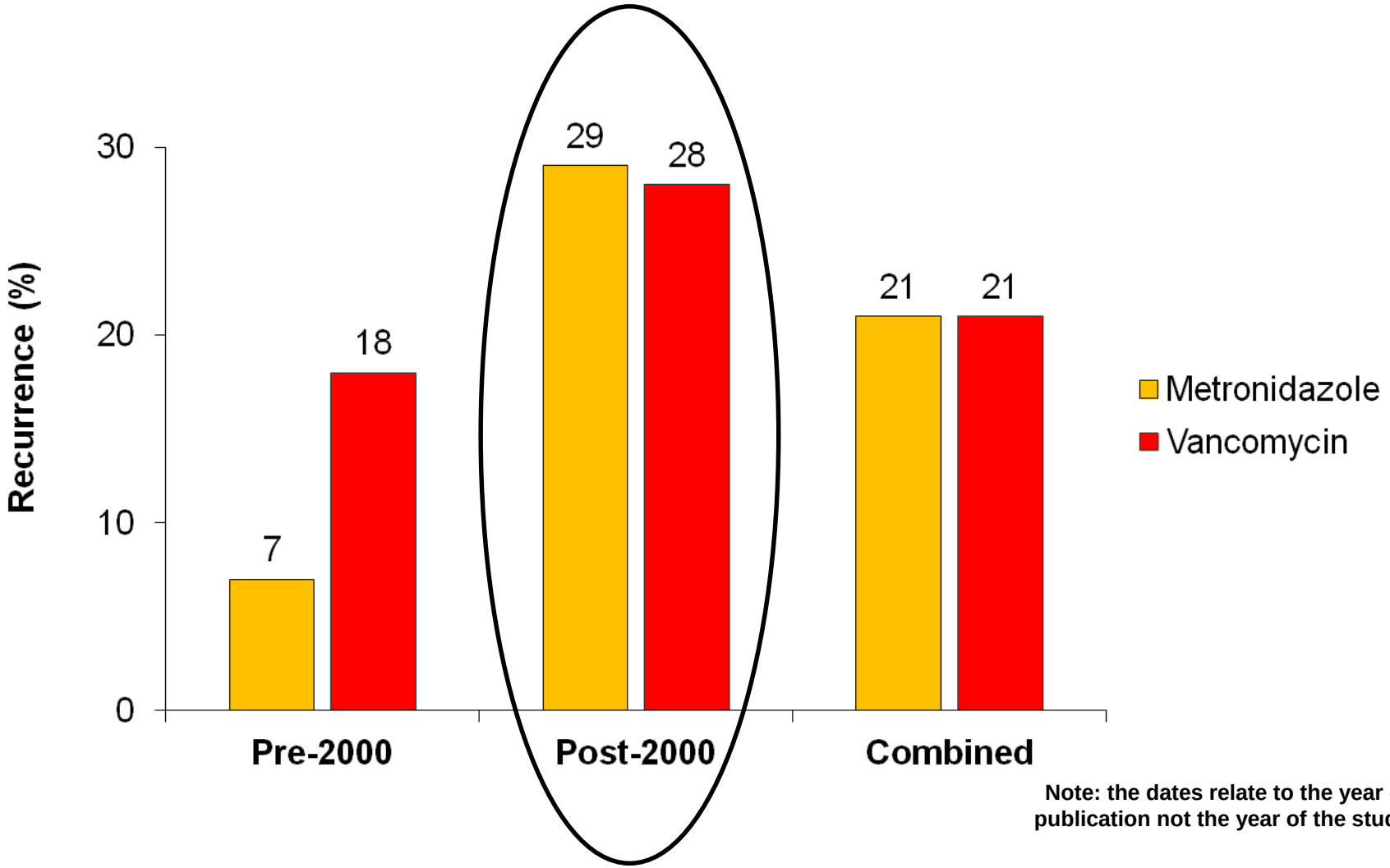
1. Bauer et al. Clin Microbiol Infect 2009;15:1067–79;
2. Louie et al. N Engl J Med 2011;364:422–31;
3. Lowy et al. N Engl J Med 2010;362:197–205;
4. Bouza et al. Clin Microbiol Infect 2008;14(Suppl 7):S103–4;
5. DuPont. N Engl J Med 2011;364:473–4.

CDI RECURRENCE (within 30 days following treatment)



1. Louie et al. N Engl J Med 2011;364:422–31;
2. Lowy et al. N Engl J Med 2010;362:197–205;
3. Bouza et al. Clin Microbiol Infect 2008;14(Suppl 7):S103–4;
4. McFarland et al. Am J Gastroenterol 2002;97:1969-75;
5. McFarland et al. JAMA 1994;271:1913-8.
6. Pepin et al. Clin Infect Dis 2005;40:1591-7

Rates of disease recurrence with metronidazole and vancomycin



Note: the dates relate to the year of publication not the year of the study

Adapted from Aslam et al. Lancet Infect Dis 2005;5:549–57.

Risk factors for a recurrence of CDI

- Immunocompromised patients[1]
- Exposure to other antibacterial agents that disrupt the normal colonic microflora[2–5]
- Previous episode of CDI[2,4,6]
- Renal impairment[7,8]
- Aged 65 years or over[2,4,9]
- Impaired immune response to *C. difficile* toxin A[2]
- Severe underlying disease[2]
- Prolonged hospitalisation[9]
- ICU stay[5]

1. Cohen. J Ped Gastroenterol Nutr 2009;48:63–5;
2. Kyne et al. Lancet 2001;357:189–93;
3. Bauer et al. Clin Microbiol Infect 2009;15:1067–79;
4. Bauer et al. Lancet 2011;377:63–73;
5. Hu et al. Gastroenterology 2009;136:1206–14;
6. McFarland et al. Am J Gastroenterol 2002;97:1769–75;
7. Do et al. Clin Infect Dis 1998;26:954–9;
8. Bauer et al. Clin Microbiol Infect 2011;17(Suppl 4):A1–A4;
9. Pépin et al. Clin Infect Dis 2005;40:1591–7.

Pharmacotherapy of CDI: First episode

- Aim of treatment is to eradicate *C. difficile* from the intestines and promote restoration of the normal colonic microflora
- Cessation of antibacterial therapy, if possible, is usually the first step

Diagnosis	ESCMID recommended treatment
Non-severe first episode	• Metronidazole 500 mg tid orally for 10 days*
Severe first episode	• Vancomycin 125 mg qid orally for 10 days • IV metronidazole 500 mg tid for 10 days plus intracolonic vancomycin 500 mg in 100 mL saline every 4–12 hours and/or vancomycin 500 mg qid by nasogastric tube if oral therapy impossible

***IV if oral therapy is not possible**

Bauer et al. Clin Microbiol Infect 2009;15:1067–79.

CME

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Christina M. Surawicz, MD[1], Lawrence J. Brandt, MD[2], David G. Binion, MD[3], Ashwin N. Ananthakrishnan, MD, MPH[4], Scott R. Curry, MD[5], Peter H. Gilligan, PhD[6], Lynne V. McFarland, PhD[7,8], Mark Mellow, MD[9] and Brian S. Zuckerbraun, MD[10]

Management of mild, moderate, and severe CDI

6. If a patient has strong a pre-test suspicion for CDI, empiric therapy for CDI should be considered regardless of the laboratory testing result, as the negative predictive values for CDI are insufficiently high to exclude disease in these patients. (Strong recommendation, moderate-quality evidence)
7. Any inciting antimicrobial agent(s) should be discontinued, if possible. (Strong recommendation, high-quality evidence)
8. Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally three times per day for 10 days. (Strong recommendation, high-quality evidence)
9. Patients with severe CDI should be treated with vancomycin 125 mg four times daily for 10 days (Conditional recommendation, moderate-quality evidence)
10. Failure to respond to metronidazole therapy within 5–7 days should prompt consideration of a change in therapy to vancomycin at standard dosing. (Strong recommendation, moderate-quality evidence)
11. For mild-to-moderate CDI in patients who are intolerant/allergic to metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard dosing. (Strong recommendation, high-quality evidence)
12. In patients in whom oral antibiotics cannot reach a segment of the colon, such as with Hartman's pouch, ileostomy, or colon diversion, vancomycin therapy delivered via enema should be added to treatments above until the patient improves. (Conditional recommendation, low-quality evidence)
13. The use of anti-peristaltic agents to control diarrhea from confirmed or suspected CDI should be limited or avoided, as they may obscure symptoms and precipitate complicated disease. Use of anti-peristaltic agents in the setting of CDI must always be accompanied by medical therapy for CDI. (Strong recommendation, low-quality evidence)

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Pharmacotherapy of CDI: First recurrence

- ESCMID has identified recurrence as being the most important problem in the treatment of CDI
  - Up to 25% of patients suffer a recurrence within 30 days following treatment
- ESCMID recommends treating a first recurrence as a first episode unless the disease has progressed from non-severe to severe

Diagnosis	ESCMID recommended treatment
Non-severe first recurrence	• Metronidazole 500 mg tid orally for 10 days*
Severe first recurrence	• Vancomycin 125 mg qid orally for 10 days • IV metronidazole 500 mg tid for 10 days plus intracolonic vancomycin 500 mg in 100 mL saline every 4–12 hours and/or vancomycin 500 mg qid by nasogastric tube if oral therapy impossible

***IV if oral therapy is not possible**

Bauer et al. Clin Microbiol Infect 2009;15:1067–79.

Table 3. CDI severity scoring system and summary of recommended treatments

Severity	Criteria	Treatment	Comment
Mild-to-moderate disease	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria	Metronidazole 500 mg orally three times a day for 10 days. If unable to take metronidazole, vancomycin 125 mg orally four times a day for 10 days	If no improvement in 5–7 days, consider change to vancomycin at standard dose (vancomycin 125 mg four times a day for 10 days)
Severe disease	Serum albumin <3 g/dl plus ONE of the following: WBC ≥15,000 cells/mm^3, Abdominal tenderness	Vancomycin 125 mg orally four times a day for 10 days	
Severe and complicated disease	Any of the following attributable to CDI: Admission to intensive care unit for CDI Hypotension with or without required use of vasopressors Fever ≥38.5 °C Ileus or significant abdominal distention Mental status changes WBC ≥35,000 cells/mm^3 or <2,000 cells/mm^3 Serum lactate levels >2.2 mmol/l End organ failure (mechanical ventilation, renal failure, etc.)	Vancomycin 500 mg orally four times a day and metronidazole 500 mg IV every 8 h, and vancomycin per rectum (vancomycin 500 mg in 500 ml saline as enema) four times a day	Surgical consultation suggested
Recurrent CDI	Recurrent CDI within 8 weeks of completion of therapy	Repeat metronidazole or vancomycin pulse regimen	Consider FMT after 3 recurrences

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Pharmacotherapy of CDI: Second and later recurrences

- ESCMID recommends treating second or later recurrences in the same way as severe first recurrence
  - With the option of using tapered or pulsed dosing regimens

Diagnosis	ESCMID recommended treatment

Second and later recurrences	• Vancomycin 125 mg qid orally for at least 10 days
	  • Consider tapering vancomycin dose by decreasing daily dose with 125 mg every 3 days
	  • Consider pulse dosing with vancomycin 125 mg every 3 days for 3 weeks
	• IV metronidazole 500 mg tid for 10–14 days plus retention enema of vancomycin 500 mg in 100 mL saline every 4–12 hours and/or vancomycin 500 mg qid by nasogastric tube if oral therapy impossible

Bauer et al. Clin Microbiol Infect 2009;15:1067–79.

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Management of recurrent CDI (RCDI)

19. The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)

20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)

21. There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)

22. No effective immunotherapy is currently available. Intravenous immune globulin (IVIG) does not have a role as sole therapy in treatment of RCDI. However, it may be helpful in patients with hypogammaglobulinemia. (Strong recommendation, low-quality evidence)

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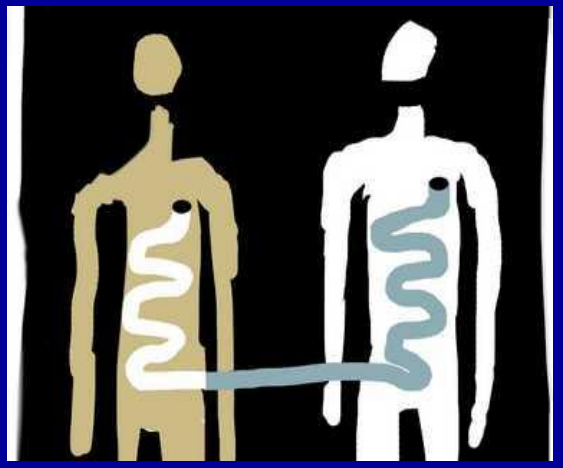
The NEW ENGLAND JOURNAL of MEDICINE

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.



METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Donor-Feces Infusion (N=16)	Vancomycin Only (N=13)	Vancomycin and Bowel Lavage (N=13)	P Value†
Age — yr	73±13	66±14	69±16	0.39
Body-mass index‡	22±3	22±4	24±4	0.41
Female sex — no. (%)	8 (50)	7 (54)	3 (23)	0.22
Karnofsky performance status§	50±18	50±17	56±21	0.62
Median Charlson comorbidity index (range) — score¶	3 (0–4)	1 (0–8)	1 (0–6)	0.53
Median recurrences of CDI (range) — no.	3 (1–5)	3 (1–4)	2 (1–9)	0.69
Previous failure of tapered vancomycin therapy — no. (%)	10 (62)	8 (62)	6 (46)	0.63
Reported antibiotic use before CDI — no. (%)	16 (100)	12 (92)	13 (100)	0.62

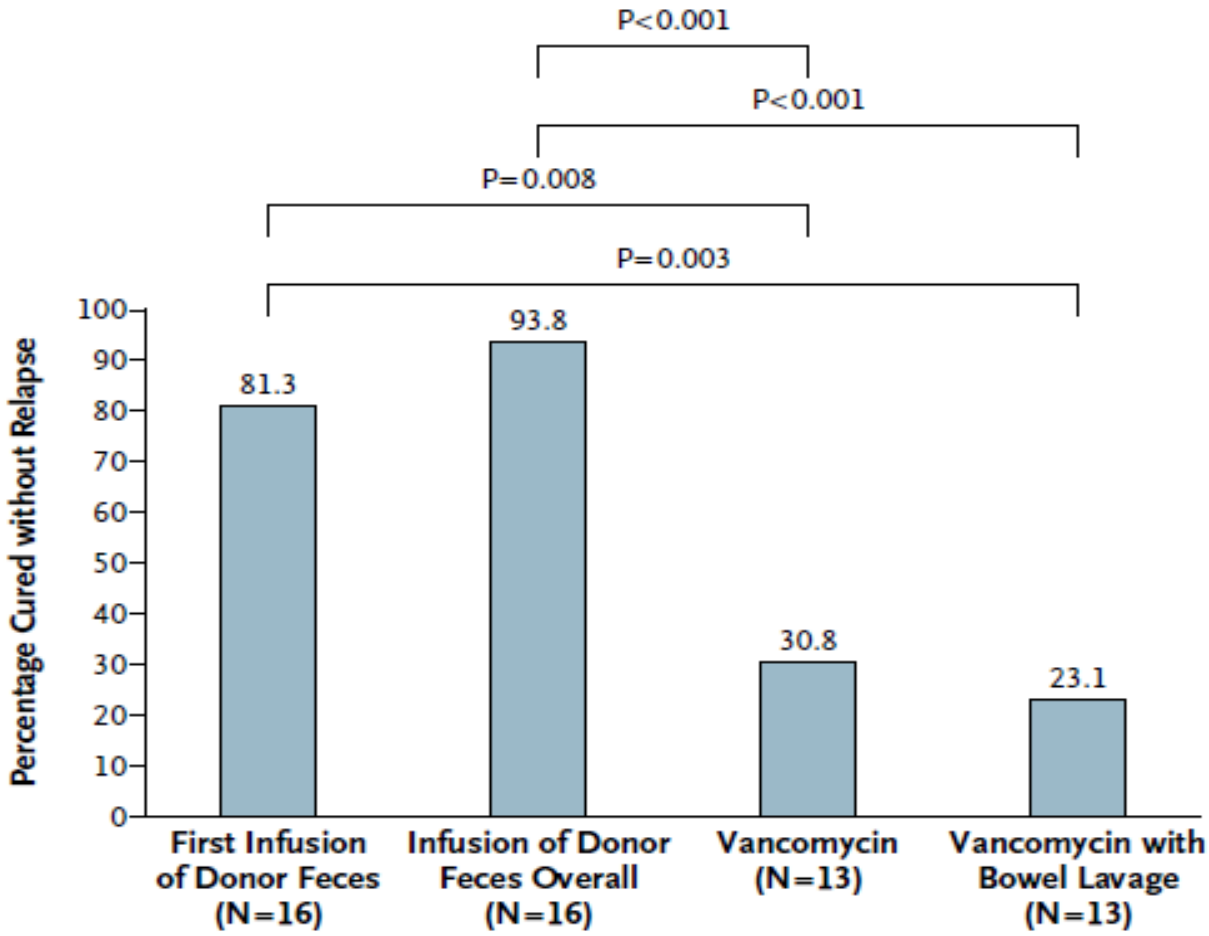
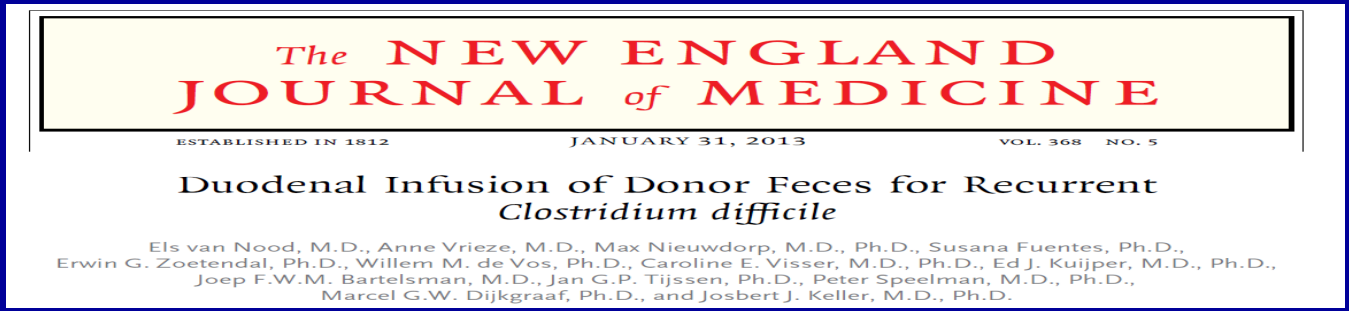


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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.



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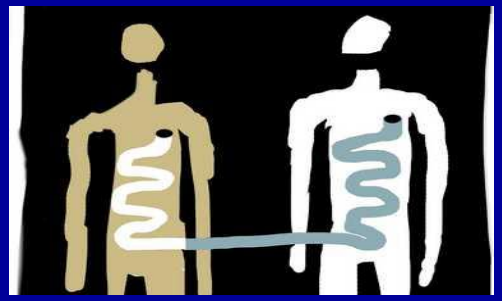


- The infusion of donor feces was significantly more effective than the use of vancomycin
- Improvement in the microbiota diversity due to feces infusion persisted over time
- Infectious complications were not observed after donor infusion in our study (and not reported in the literature)
- What about other promising strategies, such as fidaxomycin or infusion of CD monoclonal antibodies ?

Rationale for a new CDI treatment

- Metronidazole and vancomycin are the mainstay treatments for CDI[1] and both have limitations
  - Up to 25% disease recurrence[2–4]
  - Not selective for *C. difficile* and therefore may disrupt normal colonic microflora[7,8]
  - Evidence of reduced susceptibility to metronidazole[9]
    - Potentially declining efficacy[9,10]
  - Unsuitability of metronidazole for severe CDI[1]
  - Concern of overgrowth with VRE[11]

1. Bauer et al. Clin Microbiol Infect 2009;15:1067–79
2. Louie et al. NEJM 2011;364:422–31
3. Lowy et al. NEJM 2010;362:197–205
4. Bouza et al. Clin Microbiol Infect 2008;14(Suppl 7): S103
5. Vancocin (vancomycin) SmPC October 2008
6. Flagyl (metronidazole) SmPC, March 2011
7. Finegold et al. Antimicrob Agents Chemother 2004;48:4898–902
8. Louie et al. Antimicrob Agents Chemother 2009;53:261–3
9. Baines et al. J Antimicob Chemother 2008;62:1046–52
10. McFarland. Curr Opin Gastroenterol 2008;25:24–35
11. Al-Nassir et al. Antimicrob Agents Chemother 2008;52:2403–6

CURRENT OPINION

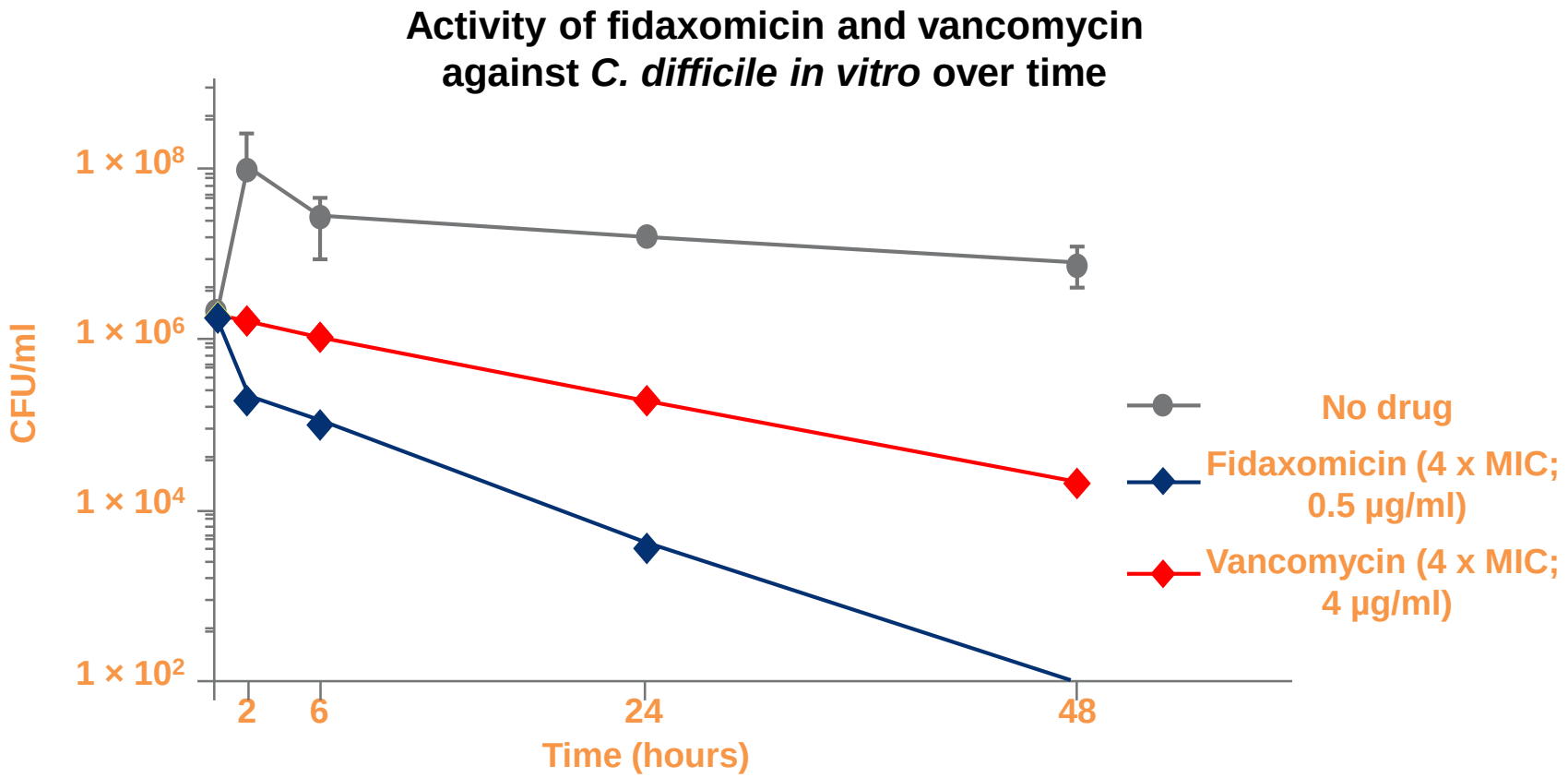
New developments in chemotherapeutic options for *Clostridium difficile* colitis

Alaina S. Ritter and William A. Petri Jr.

Table 1. Comparison of standard and emerging antibiotic therapies for *Clostridium difficile* infection

Antibiotic	Comments	Dose (mg)	Route	Doses per day	Length of treatment (days)	Price/dose (U.S.)[a]		Common drug side-effects[b]	Current treatment status of drug	References
						Generic	Brand-name			
Metronidazole		250	oral	4	10–14	$0.86	$4.53	GI intolerance, metallic taste, headache, peripheral neuropathy (prolonged use)	Recommended for mild CDI	[11]
		500	oral	3	10–14					[11]
Vancomycin	Severe CDI	125	oral	4	10–14	$31.39	$41.79	GI intolerance	FDA approved	[15▪▪]
	Fulminant CDI	500	oral	4	Variable					[12]
	Impaired intestinal motility	500[c]	Enema	4	Variable					[1]
Fidaxomicin		200	oral	2	10	–	$156.46	GI intolerance, neutropenia, anemia	FDA approved (2011)	[16]
Rifaximin		400	oral	2	14	–	$35.49	GI intolerance, headache	Additional clinical trials needed	[17▪]
	as chaser	400	oral	3	Variable					[18]
Tigecycline	100 mg loading dose	50	i.v.	2	Variable	–	$93.99	GI intolerance, hyperbilirubinemia, BUN increase	Clinical trial (NCT01401023)[d]	[19–22]
Teicoplanin[e]		100	oral	2	Variable	–	–	i.v. only: rash, Red man syndrome	Limited use in U.S.	[21]
Doxycycline		100	oral	2	10	$0.41	$6.06	Staining of teeth (children <8 years), GI intolerance, photosensitivity, arthralgia	Additional clinical trials needed	[23,24▪]
Linezolid	600 mg oral loading dose	600	oral	2	7–14	–	$151.99	Reversible bone marrow suppression, GI intolerance, headache, peripheral/optic neuritis, serotonin syndrome in combination with SSRIs	Additional clinical trials needed	[25]
	600 mg i.v. loading dose	600	i.v.	2	7–14					[25]
Nitazoxanide		500	oral	2	7–10	–	$35.29	GI intolerance, headache	Additional clinical trials needed	[26]

Fidaxomicin: bactericidal activity against *C. difficile*



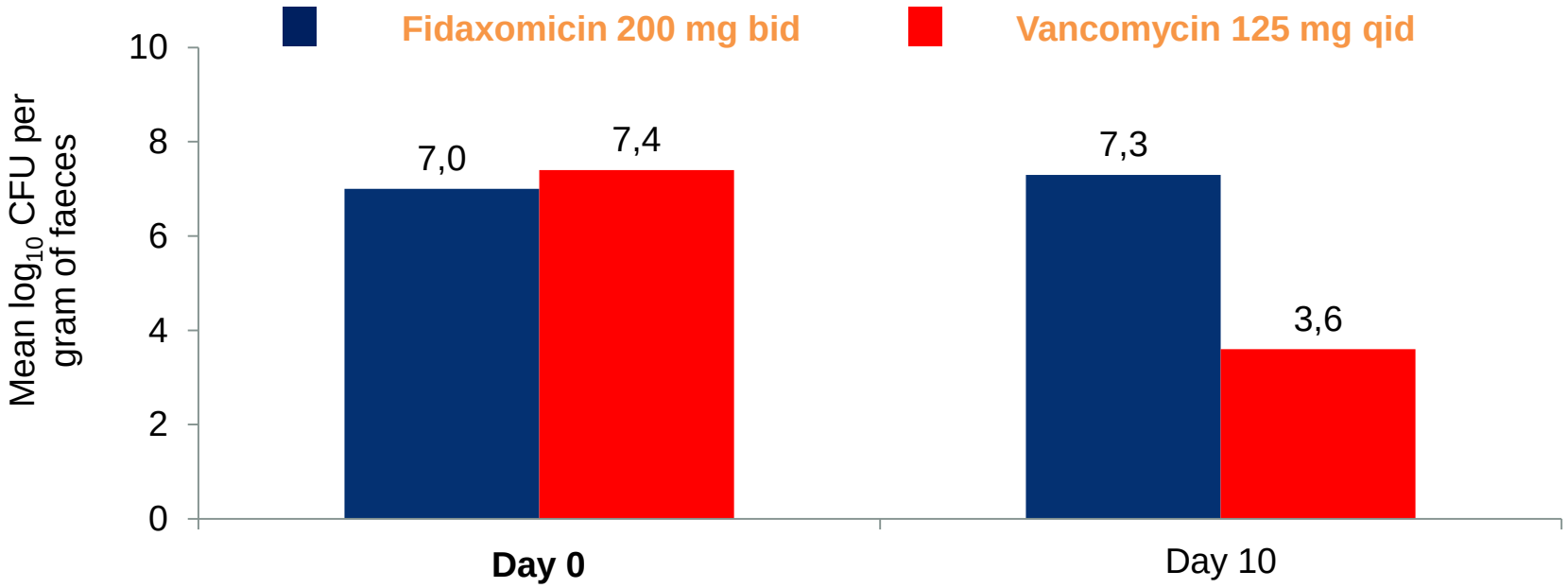
- Bactericidal activity is defined as a 3 $\log_{10}$ reduction in CFU

Babakhani et al. J Med Microbiol 2011;60:1213–7

CFU, colony-forming units

Fidaxomicin: effects on colonic microflora

Colonic levels of *B. fragilis* before (Day 0) and after treatment (Day 10)



- Data from the fidaxomicin phase 2a clinical trials in patients treated for *C. difficile* infection

Adapted from Louie et al. Antimicrob Agents Chemother 2009;53:261–3

CFU, colony-forming units

Fidaxomicin: summary of key pharmacokinetic properties

- Convenient twice-daily dosing regimen[1]
- Minimal systemic absorption[1]
- High faecal concentrations[2]
  - Faecal concentrations exceed MIC_{90} of *C. difficile* throughout the dosing interval
- Near-complete faecal recovery of fidaxomicin or the active metabolite[3]
- No clinically-relevant increases in fidaxomicin plasma concentrations observed in patients with colitis[4]

1. Astellas Pharma Europe. DIFICLIR (fidaxomicin) SmPC
2. Louie et al. Antimicrob Agents Chemother 2009;53:223–8
3. Shue et al. Antimicrob Agents Chemother 2008;52:1391–5
4. Data on file (AI/11/0007/EU)

Fidaxomicin: clinical development programme

Trial	Description	Fidaxomicin	Vancomycin
Phase 3 (101.1.C.003)[1]	North American multicentre, double-blind, randomised, parallel group study of 10 days' duration	200 mg twice daily (N=302)	125 mg four times daily (N=327)
Phase 3 (101.1.C.004)[2]	Multinational, multicentre, double-blind, randomised, parallel group study of 10 days' duration	200 mg twice daily (N=264)	125 mg four times daily (N=260)

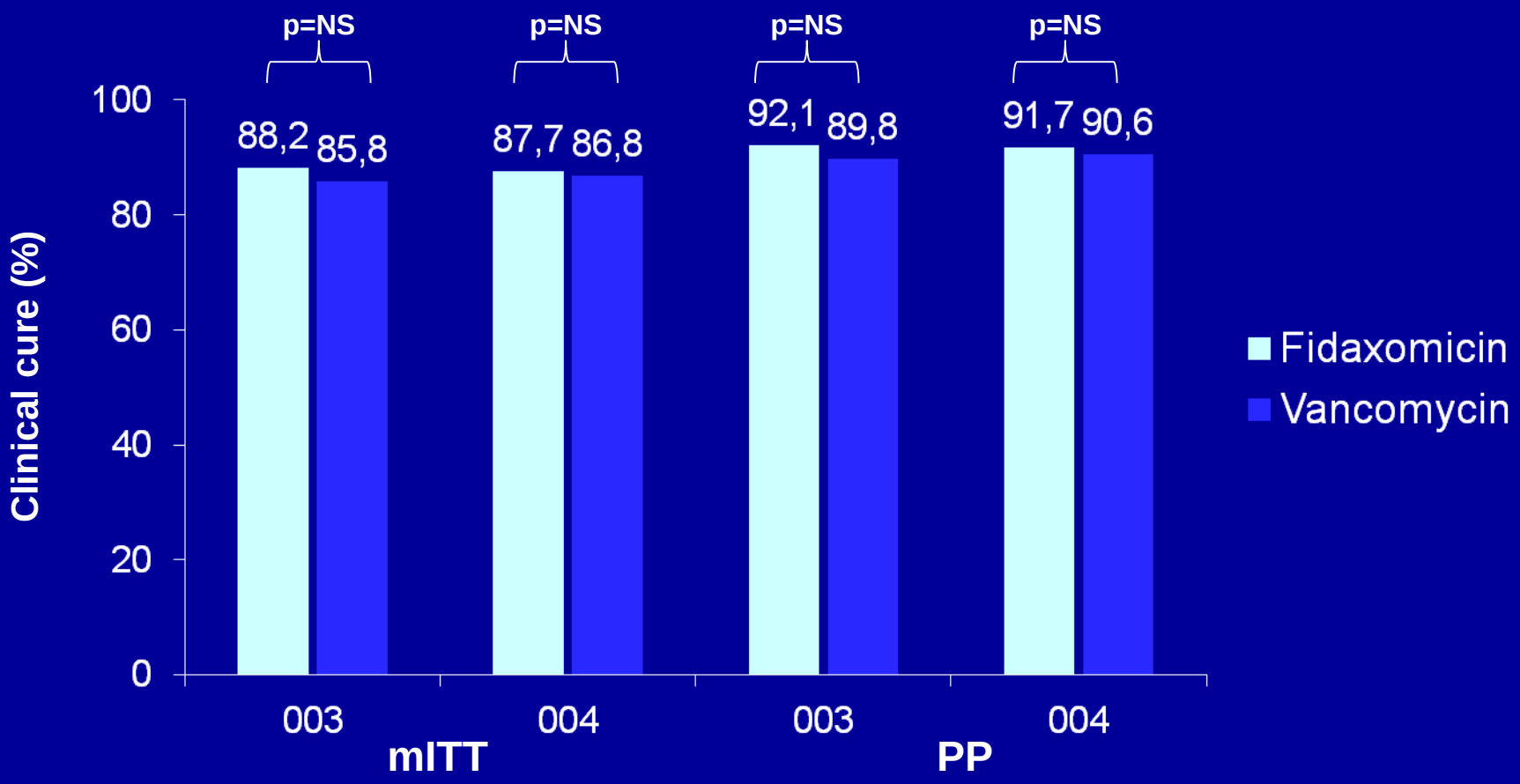
1. Louie et al. NEJM 2011; 364:422–31
2. Cornely OA et at. Lancet ID 2012; 12:281-9

Phase 3 trials: inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adult male or female (≥16 years) • Confirmed diagnosis of CDI – Diarrhoea defined as change in bowel habits with ≥3 UBM in a 24-hour period – Presence of *C. difficile* toxin A or B in stool within 48 hours of randomisation • Primary episode or first recurrence of CDI • Treatment with metronidazole or vancomycin for <24 hours	• Life-threatening or fulminant CDI • Toxic megacolon • Previous exposure to fidaxomicin • >1 recurrence or relapse within 3 months • Antibacterial therapy with likely effectiveness in treating CDI such as bacitracin or fusidic acid • Crohn's disease or ulcerative colitis • Use of antidiarrhoeal drugs such as loperamide

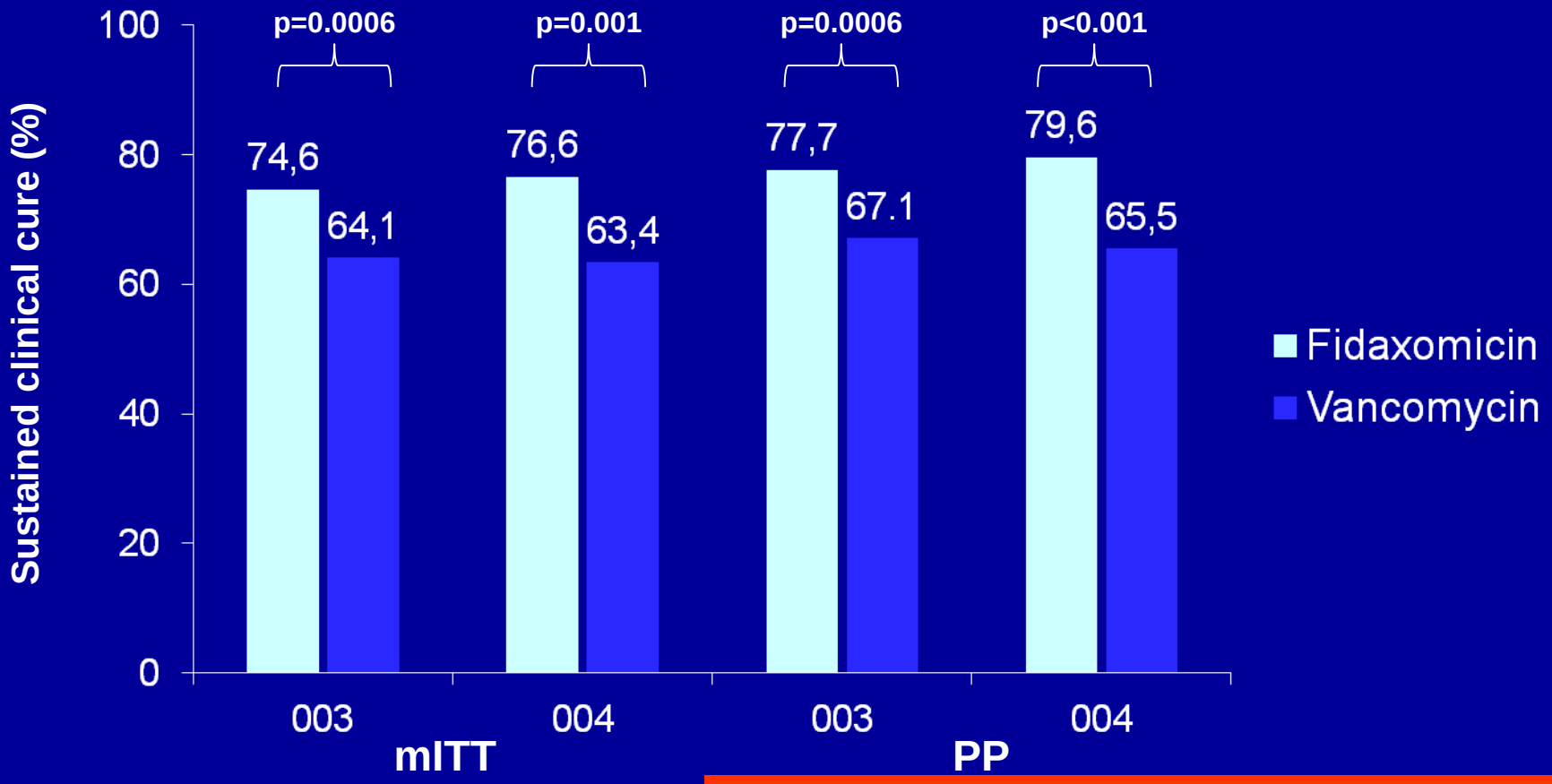
UBM, unformed bowel movements

Rates of clinical cure



Louie et al. N Engl J Med 2011;364:422–31;
Cornely et al. Lancet Infect Dis 2012; epub ahead of print (doi:10.1016/S1473-3099(11)70374-7)

Rates of sustained clinical cure



Sustained clinical cure: Clinical cure with no recurrence during the 30-day follow-up period

Louie et al. N Engl J Med 2011;364:422–31;
Cornely et al. Lancet Infect Dis 2012;doi:10.1016/S1473-3099(11)70374-7)

Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection: Meta-analysis of Pivotal Randomized Controlled Trials

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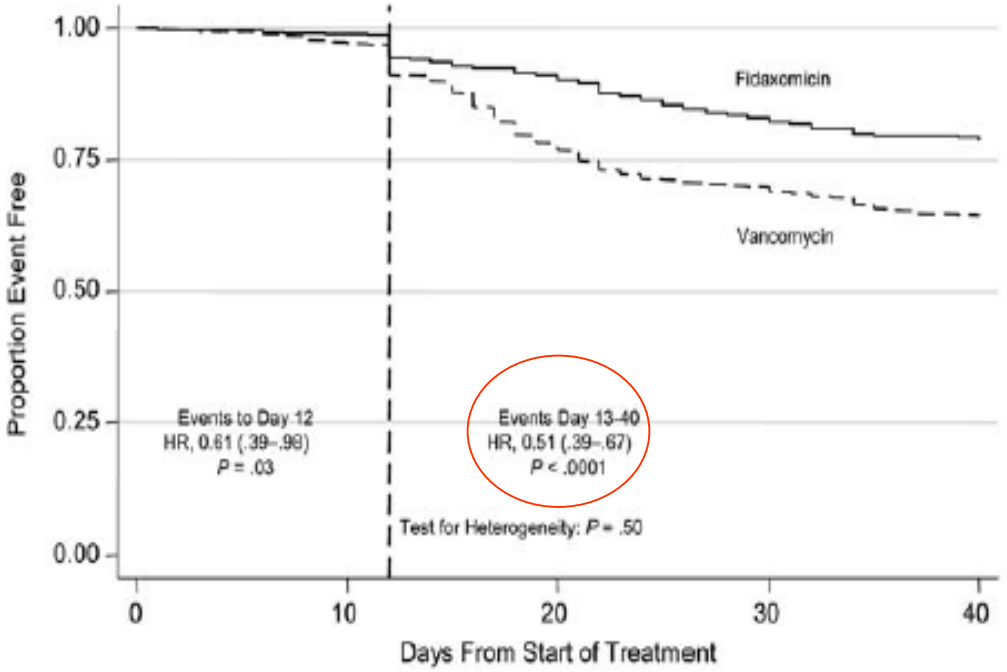
Two recently completed phase 3 trials (003 and 004) showed fidaxomicin to be noninferior to vancomycin for curing *Clostridium difficile* infection (CDI) and superior for reducing CDI recurrences. In both studies, adults with active CDI were randomized to receive blinded fidaxomicin 200 mg twice daily or vancomycin 125 mg 4 times a day for 10 days. Post hoc exploratory intent-to-treat (ITT) time-to-event analyses were undertaken on the combined study 003 and 004 data, using fixed-effects meta-analysis and Cox regression models. ITT analy-

Crook DW et al., CID 2012



Number at Risk	(events)								
Fidaxomicin	572	(6)	515	(41)	472	(42)	427	(21)	405
Vancomycin	592	(14)	527	(104)	416	(44)	365	(27)	334

Note: Patients first assessed for persistent diarrhea 8 to 12 days after start of treatment: those with diarrhea considered as events on day 12.

Figure 2. Persistent diarrhea, recurrence, or death. Study treatment was administered for 10 days and clinical cure was assessed at 12 days, at which time persistent diarrhea (>3 stools/24 hours and toxin A and/or B positive or requiring anti–*Clostridium difficile* infection [CDI] treatment) was defined as clinical failure. The events occurring before day 12 are deaths and the step increase in events at day 12 represents cases assessed to have persistent diarrhea at the posttreatment assessment. Events from day 13 to day 40 represent CDI recurrence or deaths. Abbreviation: HR, hazard ratio.

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Table 4. Cost of antibiotic therapy for *C. difficile* infection

	Cost per dose	Regimen	Cost per 10-day regimen
Metronidazole 500 mg	$0.73	500 mg three times a day	$22.00
Vancomycin 125 mg pills	$17.00	125 mg four times a day	$680.00
Vancomycin 125 mg IV compounded for oral	$2.50–$10.00	125 mg four times a day	$100.00–$400.00
Fidaxomicin 200 mg	$140.00	200 mg twice a day	$2,800.00

IV, intravenous.
Vancomycin IV form can be compounded for oral use as well as used for enema therapy.

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Terapia della CDI
Considerazioni conclusive (personali)

- Le attuali terapie sono adeguate nel ~ 75% dei casi

- Le recidive appaiono associate all'impossibilità di ristabilire il normale microbiota intestinale (protrarsi di antibioticoT), alla persistenza di spore intestinali (insufficiente infection control) e/o al deficit della risposta immune

- Fidaxomicina possiede le caratteristiche per essere raccomandata nel trattamento della CDI dopo la prima recidiva, in particolare nel paziente con i fattori di rischio sopracitati.


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