Recurrent *Clostridium difficile* infection: how can we manage it?

Nicola Petrosillo

National Institute for Infectious Diseases

"Lazzaro Spallanzani", IRCCS, Roma

- **A first episode of Clostridium difficile infection (CDI) is followed by a symptomatic recurrence in approximately 19-20% of patients affected, following the resolution of the initial infection.**
- **In one study of 163 patients who already had at least one recurrence, the risk of a subsequent recurrence was 45%.**

Aslam S et al. Lancet Infect Dis 2005;5:549-57

McFarland LV et al. AJG 2002;97:1769-75

- **Recurrent CDI occurs either due to relapse (i.e. endogenous persistence of the same strain of *C. difficile*) or reinfection (i.e. acquisition of a new strain of *C. difficile* from an exogenous source)**

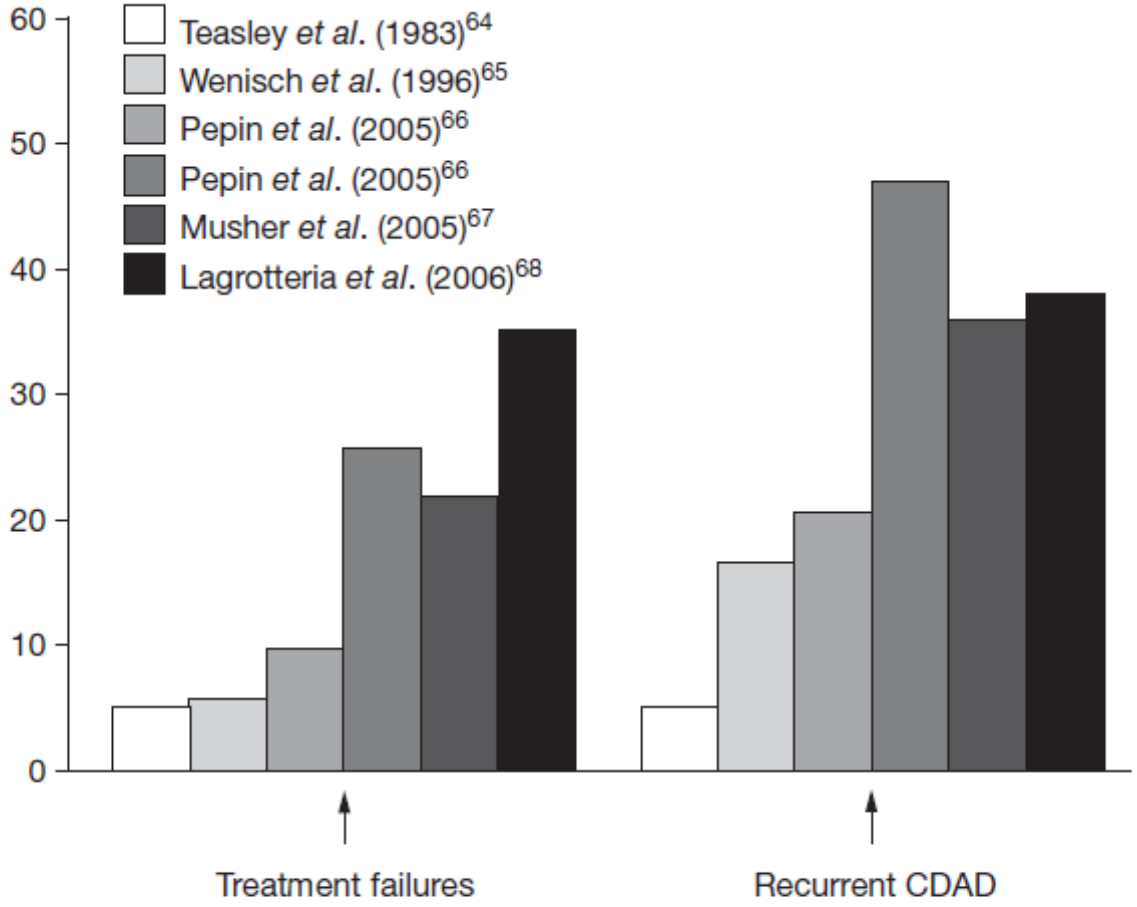


Figure 2 Treatment response rates (initial treatment failure and recurrences) before and after BI/NAP1/027 strain outbreaks. Arrows indicate the time when the new strain was detected in the outbreaks. Abbreviation: CDAD, *Clostridium difficile*-associated disease.

McFarland LV et al. *AJG 2002*

Risk factors for CDI recurrence

- Continued use of non-C. difficile antibiotics after diagnosis of CDI (OR: 4.23; P < 0.001), concomitant receipt of antacid medications (OR: 2.15; P = 0.019), and older age (OR: 1.62; P = 0.0012) were significantly associated with increased risk of recurrent CDI

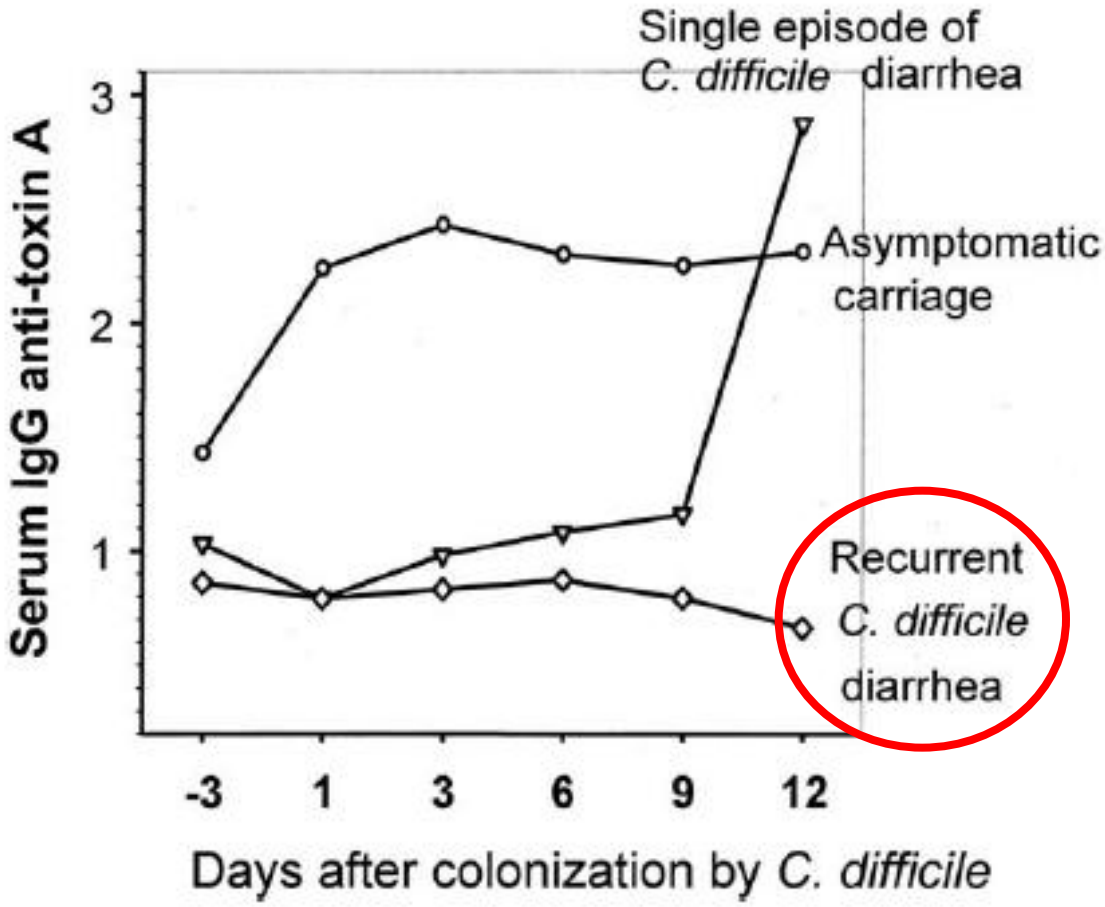
Garey KW et al. J Hosp Infect 2008;70:298-304

Table 1 Important risk factors for the development of recurrent *Clostridium difficile* infection.

- Inadequate antitoxin antibody response
- Persistent disruption of the colonic flora
- Advanced age
- Continuation of non-*C. difficile* antimicrobial therapy following a first episode of CDI
- Long hospital stays
- Concomitant receipt of antacid medications

CDI, *Clostridium difficile* infection.

Johnson S. J Infect. 2009;58:403-10



Maroo S, Lamont JT. Gastroenterology 2006;130:1311-6

- The most common BI/NAP1/027 group and the previous US epidemic REA group J/NAP2/001 had a significantly higher combined rate of recurrence with the same strain (relapse), compared with the other REA groups (39 of 42 [93%] vs 36 of 48 [75%], respectively; P = .023)

Figueroa I et al. CID 2012;55:S104-9.

Clostridium difficile 027 infection in Central Italy

- **10 patients with CDI from 027**

vs

- **7 patients with CDI from non-027 strains**

↓

- **12 recurrent episodes among the 027 group vs 0 recurrent episodes among the non-027 group (p = 0.04)**

Di Bella S et al. BMC Infect Dis 2012;12:370

how can we manage it?

- **Management of recurrent CDI is poorly studied, and the recently published SHEA/IDSA clinical practice guidelines for CDI give recommendations for recurrent CDI that are based on relatively poor quality of evidence.**

General recommendations include:

- **(1) treatment of the first recurrence with the same agent used initially but stratified by disease severity**

- **(2) avoiding prolonged or repeated courses of metronidazole because of the risk for neurotoxicity, and**

- **(3) treatment of multiple recurrences with vancomycin with use of a tapered and pulsed regimen.**

Cohen SH, et al. ICHE 2010;31:431-55

Tapered and pulsed vancomycin

2002: first evidences on tapered or pulsed course of vancomycin in patients with recurrent CDI

Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent *Clostridium difficile* Disease

- **163 CDI cases → 44.8% recurred.**
- **A tapering course of vancomycin resulted in significantly fewer recurrences (31%, *p 0.01), as did pulsed dosing of vancomycin* (14.3%, *p 0.02).***

McFarland LV et al. *AJG 2002*

Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent *Clostridium difficile* Disease

- ***A trend (p 0.09) for a lower recurrence*** **frequency was observed for high-dose (2 g/day) vancomycin and low-dose (1 g/day) metronidazole.**

- **Vancomycin was significantly more effective in clearing *C. difficile* culture and/or toxin by the end of therapy than metronidazole (89% *vs 59%, respectively; p 0.001).***

McFarland LV et al. *AJG 2002*

Other management strategies for multiple CDI recurrences

In addition to tapered and pulsed vancomycin regimens:

- **standard therapy followed by rifaximin,**
- **switching to nitazoxanide,**
- **intravenous immunoglobulin, and**
- **fecal transplantation**

UNCONTROLLED STUDIES

Fidaxomicin

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

- **A total of 629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis.**
- **The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively).**

Louie TJ et al. NEJM 2011;364:422-31

- **Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004).**
- **The lower rate of recurrence was seen in patients with non-North American Pulsed Field type 1 strains.**
- **The adverse-event profile was similar for the two therapies.**

Louie TJ, et al. NEJM. 2011;364:422-31

Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin

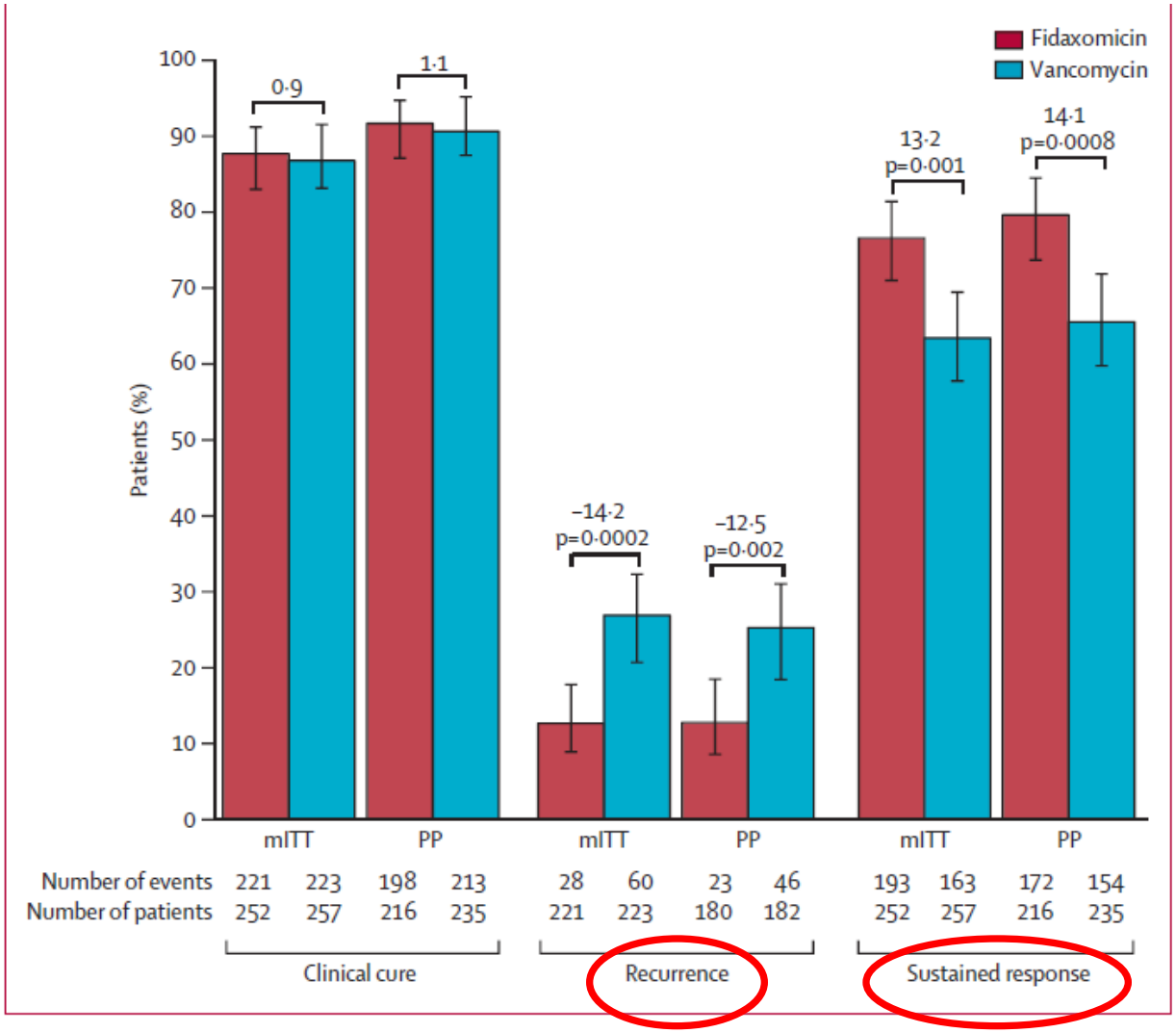


Figure 2: **Clinical outcomes by treatment group**

Cornely OA et al. Lancet Infect Dis 2012

The hypothesis of fidaxomicin as "Chaser" regimen

Table 1. Summary of Recurrent *Clostridium difficile* Infection Episodes, Treatments, and Outcomes in 3 Patients Following Fidaxomicin Administered as Post-Vancomycin "Chaser" Regimen

Patient	Age/ Sex	No. of CDI Episodes	Regimens	Duration of CDI Treatment up to Fidaxomicin Chaser[a]	Outcome (Follow-up)
1	67/M	4	M, M, V_t, V_t	8 mo (6 mo continuous V until FDX chaser)	Success (10 mo)
2	80/F	5	M, V, V, V_t, V&ivM followed by V_t	24 mo (5 mo of continuous V until FDX chaser)	CDI recurrence 3 mo later, but was treated for UTI just prior to recurrence
3	32/F	8	M, M, V_t, V_t, V/Rfx, V/ Rfx, V_t (IVIG), V_t	30 mo (5 mo of continuous V until FDX chaser)	Success (9 mo)

Abbreviations: CID, *Clostridium difficile* infection; FDX, fidaxomicin; IVIG, intravenous immunoglobulin; ivM, intravenous metronidazole; M, metronidazole; V, vancomycin; V_t, vancomycin taper; V/Rfx, vancomycin followed by rifaximin "chaser"; UTI, urinary tract infection.

[a] Following their last CDI episode, patients were "maintained" on a low-dose regimen of oral vancomycin until fidaxomicin became available.

Johnson S et al. CID. 2013;56:309-10

Rifaximin and rifampin

- Rifaximin exhibited high-level activity against 359 C difficile isolates, with MIC(50) <0.01 microg/ml and MIC(90) 0.25 microg/ml; rifampin had MIC(50) <0.002 microg/ml and MIC(90) 4 microg/ml. Among isolates analysed, 55 (15%) were positive for BT and tcdC-del.
- 28 (8% of 359) isolates were resistant to rifampin (> or = 32 microg/ml), of which 6 (2% of 359) were resistant to rifaximin and rifampin with MIC values > or = 32 microg/ml.

Jiang ZD, et al. J Clin Pathol. 2010;63:355-8

- **Most isolates (68%) had very low MIC-values for rifampin (<0.002 lg/mL) and the highest MIC value was 3.0 lg/mL.**
- **Isolates with a DNA profile compatible with the BI/NAP1/027 ribotype had, on the average, higher MICs of rifampin.**
- **After 12 weeks 17 (53%) patients had no relapse. The MIC value of rifampin seemed to predict the response to rifaximin treatment.**

Mattila E, et al. Aliment Pharmacol Ther. 2013;37:122-8

Table 2 | Susceptibilities *Clostridium difficile* isolates by strain type and antibiotic. Mann–Whitney *P*-values are of comparisons between BI/NAP1/027 and non-BI/NAP1/027 strain types

	N	Geometric Mean MIC (μg/mL)	MIC Range (μg/mL)	Mann–Whitney *P*-value
Rifampicin				0.002
BI/NAP1/027	7	0.46	>0.002–3.0	
Non-BI/NAP1/027	13	>0.002	>0.002	
Metronidazole				0.027
BI/NAP1/027	7	0.35	0.19–0.5	
Non-BI/NAP1/027	13	0.18	0.06–1.0	
Vancomycin				0.751
BI/NAP1/027	7	0.84	0.38–1.5	
Non-BI/NAP1/027	13	0.94	0.5–1.5	

Mattila E, et al. Aliment Pharmacol Ther. 2013;37:122-8

- Seven patients with multiple bacteriologic and symptomatic relapses of CDI were treated with vancomycin and rifampin in combination. Diarrhea and abdominal pain promptly resolved in all, and neither *C. difficile* nor its toxin could be recovered from their stools shortly after therapy. However, stools of all patients subsequently became culture-positive for *C. difficile* and occasionally had demonstrable cytotoxin. Except in one instance following oral antibiotic use, all patients remained free of symptoms. Resistance to either vancomycin or rifampin was not encountered.

Buggy BP, Fekety R, Silva J Jr. J Clin Gastroenterol. 1987;9:155-9.

Nitazoxanide

Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide

- **35 patients who failed treatment with metronidazole for CDI**
- **Nitazoxanide, 500 mg twice daily, was given for 10 days.**

Musher DM, et al. J Antimicrob Chemother. 2007;59:705-10

Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide

- **Twenty-six (74%) of 35 patients responded to nitazoxanide, of whom seven later had recurrent disease, yielding a cure rate of 19 of 35 (54%) from initial therapy.**

- **Three who initially failed and one who had recurrent disease were re-treated with, and responded to, nitazoxanide.**

- **Thus, the aggregate cure with nitazoxanide in this difficult-to-treat population was 23 of 35 (66%).**

Musher DM, et al. J Antimicrob Chemother. 2007;59:705-10

Tigecycline

Recently, *C. difficile* was reported to have low MIC values for tigecycline [6, 7]. Here, we describe 4 patients with severe refractory CDI who were successfully treated with intravenous tigecycline. The demographic and clinical characteristics of these 4 patients with severe refractory CDI are shown in table 1.

Table 1. Demographic and clinical characteristics of 4 patients with severe refractory *Clostridium difficile* infection who were treated with tigecycline.

Case	Sex	Age, years	Symptoms	Method of diagnosis[a]	Duration of previous standard therapy[a]	Duration of tigecycline therapy[a]	Date of relief of symptoms after start of tigecycline therapy	Date of negative toxin EIA result after start of tigecycline therapy	Relapse within 3 months?
1	Male	60	Diarrhea >8 times per day; temperature >38.5°C; hypovolemic shock; pseudomembranes; bloody stools	Toxin EIA (day 16); culture positive for ribotype 159	Mtz (days 16–20); Vm (days 21–25); Vm and Mtz (days 26–57)	3 weeks, in combination with Vm (days 58–78)	Day 3	Day 3	No
2	Female	36	Ileus; temperature >38.5°C; hypovolemic shock; pseudomembranes	Toxin EIA (day 22); culture	Vm (day 22–26); Vm and Mtz (days 27–35)	15 days (days 36–50)	Day 5	Day 5	No
3	Male	36	Diarrhea >8 times per day; temperature >38.5°C; hypovolemic shock	Toxin EIA (day 36); culture positive for ribotype 078	No standard therapy	7 days (days 36–42), followed by 4 weeks of Vm (days 43–70)	Day 5	Day 13	No
4	Female	82	Diarrhea >8 times per day; temperature >38.5°C; hypovolemic shock; pseudomembranes; bloody stools	Toxin EIA (day 6); culture positive for ribotype 087	Mtz (days 6–16); Vm (days 17–27)	24 days (days 28–51), then 2 courses of pulse therapy[b] (days 59–65 and 73–79)	Day 7	Day 4	No

NOTE. EIA, enzyme immunoassay; Mtz, metronidazole; Vm, vancomycin.

[a] The day (after hospital admission) on which the toxin EIA result was positive or the day (after hospital admission) on which therapy was started is given in parentheses.

[b] After 24 days, 2 additional weeks of treatment were interspersed with 1 treatment-free week.

Herpers BL, et al. CID 2009;48:1732-5.

Stool transplant

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

- **Systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis.**
- **In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases.**
- **Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion.**

- **Death and adverse events were uncommon.**

Gough E et al. CID 2011;53:994-1002

Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent *Clostridium difficile* Infection

- **77 patients (average age: 65 years).**
- **The mean long-term follow-up period was 17 months.**
- **The average symptom duration before FMT was 11 months and patients had failed an average of 5 conventional antimicrobial regimens.**
- **Diarrhea resolved in 82 % and improved in 17 % of patients within an average of 5 days after FMT. The primary cure rate was 91 % .**
- **The secondary cure rate was 98 % .**

Brandt LJ et al. Am J Gastroenterol 2012;107:1079-87

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

- **Vancomycin + bowel lavage followed by donor feces duodenal infusion**

vs

- **Standard vancomycin regimen**

vs

- **Standard vancomycin regimen + bowel lavage**

Van Nood MD et al. NEJM 2013

RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

Van Nood MD et al. NEJM 2013

Immunoglobulins

Journal of Antimicrobial Chemotherapy (2004) **53**, 882–884
DOI: 10.1093/jac/dkh176
Advance Access publication 8 April 2004

JAC

Descriptive study of intravenous immunoglobulin for the treatment of recurrent *Clostridium difficile* diarrhoea

Mark H. Wilcox*

Department of Microbiology, Leeds Teaching Hospitals and University of Leeds, Old Medical School, Leeds LS1 3EX, UK

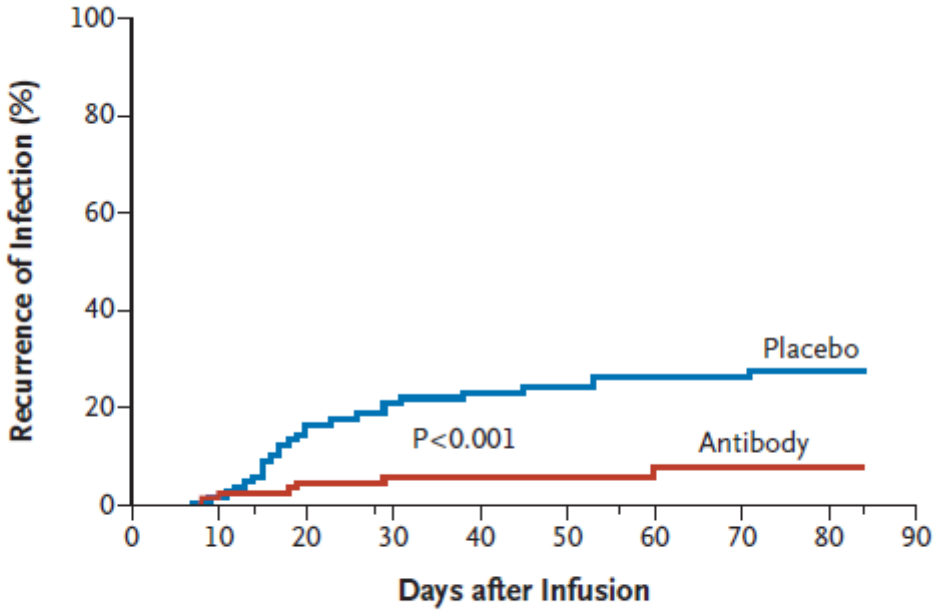
Received 4 December 2003; returned 2 February 2004; revised and accepted 10 February 2004

IgG Antibody Response to Toxins A and B in Patients with Clostridium difficile Infection

- **IgG antibodies against *Clostridium difficile* toxins A and B were followed in controls and in patients with an initial CDI.**
- **Of the 50 CDI patients, 38 were cured and 12 developed recurrence.**
- **Compared to controls, patients had significantly lower anti-toxin A and B IgGs at inclusion, but the subsequent levels rose slightly regardless of clinical outcome.**

Wullt M, et al. Clin Vaccine Immunol 2012;19:1552-4

Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins



No. at Risk

Antibody	101	93	89	85
Placebo	99	77	66	62

Figure 1. Time to Recurrence of *Clostridium difficile* Infection (CDI).

The cumulative percentages of 32 patients with laboratory-documented recurrent CDI during the 84-day study period are shown for the two study groups: 7% in the antibody group and 25% in the placebo group. Five patients had a second episode of CDI recurrence: two in the antibody group and three in the placebo group. The P value was calculated by means of the log-rank test.

Lowy I et al. NEJM 2010;362:197-205

Protection Against *Clostridium difficile* Infection With Broadly Neutralizing Antitoxin Monoclonal Antibodies

Andre J. Marozsan,[a] Dangshe Ma,[a,b] Kirsten A. Nagashima, Brian J. Kennedy,[b] Yun (Kenneth) Kang,[c] Robert R. Arrigale, Gerald P. Donovan, Wells W. Magargal, Paul J. Maddon, and William C. Olson

Progenics Pharmaceuticals, Inc, Tarrytown, New York

The spore-forming bacterium *Clostridium difficile* represents the principal cause of hospital-acquired diarrhea and pseudomembranous colitis worldwide. *C. difficile* infection (CDI) is mediated by 2 bacterial toxins, A and B; neutralizing these toxins with monoclonal antibodies (mAbs) provides a potential nonantibiotic strategy for combating the rising prevalence, severity, and recurrence of CDI. Novel antitoxin mAbs were generated in mice and were humanized. The humanized antitoxin A mAb PA-50 and antitoxin B mAb PA-41 have picomolar potencies in vitro and bind to novel regions of the respective toxins. In a hamster model for CDI, 95% of animals treated with a combination of humanized PA-50 and PA-41 showed long-term survival relative to 0% survival of animals treated with standard antibiotics or comparator mAbs. These humanized mAbs provide insight into *C. difficile* intoxication and hold promise as potential nonantibiotic agents for improving clinical management of CDI.

Marozsan AJ, et al. JID. 2012;206:706-13

Conclusions

- **Recurrence is common in CDI infection**
- **Several factors, including IgG antibodies against *Clostridium difficile* toxins play in role in the occurrence of resistance.**
- **Some virulent strains are more prone to recurrence.**
- **Management of recurrences include the same antimicrobials as in the first episode, or different approaches.**
- **Fidaxomicin is the most promising antimicrobial approach.**
- **Best results were obtained by fecal transplantand immunoglobulin use**