Treatment of *Clostridium difficile*-Associated Disease with Teicoplanin

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Forty-seven patients affected by *Clostridium difficile*-associated disease were treated orally with either vancomycin (patients hospitalized from February 1984 to February 1987) or teicoplanin (from March 1987 to December 1988). All patients given teicoplanin remained asymptomatic after discontinuation of treatment, and all but one were also cleared of *C. difficile*. In the vancomycin group, clinical symptoms recurred in 3 of 23 evaluable patients, and follow-up cultures were positive in another asymptomatic case.

Clostridium difficile causes a wide variety of clinical manifestations, ranging from an asymptomatic intestinal carrier state (15) to a sometimes fatal pseudomembranous colitis (PMC). Recent data indicate that this microorganism is almost invariably involved in PMC and accounts for about one-fourth to one-third of all cases of antibiotic-associated diarrhea in which endoscopic examination does not show any pseudomembrane or plaque (*C. difficile*-associated diarrhea) (16). Antimicrobial agents most commonly implicated as inciting factors of both *C. difficile* intestinal colonization and disease are clindamycin, cephalosporins, and ampicillin (1–3, 9, 14, 17, 26). *C. difficile*, however, has also been isolated from the inanimate hospital environment, especially in areas with patients known to harbor the microorganism and from individuals who are in contact with symptomatic patients. Moreover, nosocomial spread and cross infection have recently been extensively documented (1, 5, 10, 21), suggesting the possibility of enteric isolation for carriers and symptomatic cases. Prevention of outbreaks can, however, also successfully be achieved by using suitable antibiotics to eliminate gut colonization by toxigenic strains.

C. difficile isolates are highly susceptible in vitro to many antimicrobial agents, including vancomycin, metronidazole, bacitracin, rifampin (13), and amoxycillin-clavulanic acid (6), and several studies document the effectiveness of oral vancomycin (12, 16, 24, 28), metronidazole (8, 27), and bacitracin (29). Generally, vancomycin is considered the drug of choice for the treatment of PMC (11, 19, 24, 28), with metronidazole and bacitracin as useful alternatives (22). Recently, in clinical situations in which enteral therapy has not been possible, intravenous metronidazole has been advocated (20). The clinical response to vancomycin treatment is usually very good and prompt, with a reduction in severity of diarrhea within 48 to 72 h (12). Relapse after vancomycin therapy has, however, been reported in 14 to 20% of patients (4, 12, 24), and posttreatment asymptomatic carriage of *C. difficile* is even more common, occurring in as many as 28% of patients (12). Teicoplanin, a new glycopeptide antibiotic, is very active in vitro against *C. difficile* isolates (22, 23). However, teicoplanin treatment of some cases of PMC in humans has previously been reported only by us and as preliminary data (10a). Here we report our experience using vancomycin (patients hospitalized in the period from Febru-

ary 1984 to February 1987) and teicoplanin (given since March 1987, when this drug was first available in Italy) as therapy for PMC and *C. difficile*-associated diarrhea in a larger cohort of patients.

In this study, *C. difficile*-associated diarrhea and PMC were diagnosed by demonstrating both *C. difficile* and cytotoxin in the feces of symptomatic patients, i.e., in patients passing more than three loose stools per day and in the absence of other recognized intestinal pathogens. The diagnosis of PMC was based also on the colonoscopic demonstration of the typical endoscopic picture. For isolation of *C. difficile*, stool samples were cultured anaerobically by direct plating on CD Selective Blood Agar (Oxoid Ltd., Basingstoke, United Kingdom) supplemented with cycloserine (250 μg/ml) and cefoxitin (8 μg/ml) after heat shock (80°C for 10 min) and in enrichment broth (7). The broth was subcultured on CD Selective Agar after 24 h. The microorganism was identified by colony morphology, gas-liquid chromatography, and biochemical tests according to criteria given in the *Anaerobe Laboratory Manual* of Virginia Polytechnic Institute (18). The in vitro susceptibilities of *C. difficile* isolates were determined by the agar dilution method (25). Cytotoxin was identified by inoculating fixed dilutions of stool filtrates into 96-well microdilution plates seeded with Vero cells, incubated overnight, and read after 24 h. Positive samples were confirmed by neutralization with specific antitoxin. Results of rapid diagnostic tests, such as direct immunofluorescence (using a specific antiserum, the gift of M. Sebald, Pasteur Institute, Paris) and latex agglutination assay (Culturette Brand CD Latex Test; Marion Scientific Inc., Kansas City, Mo.), on stool suspension were considered only presumptive and were not taken into account unless confirmed by positive culture and toxin assay.

Patients were treated orally either with 500 mg of vancomycin four times a day for 10 days (in the period from February 1984 to February 1987) or with 200 mg of teicoplanin three times a day on day 1, followed by 200 mg twice a day for the subsequent 9 days (in the period from March 1987 to December 1988). The clinical follow-up of the patients lasted at least 1 month. During this period, no patient received any antibiotic treatment. All patients underwent a clinical control 10 days after discontinuation of the treatment and then 20 to 30 days later. On the occasion of clinical controls, stool samples were collected for *C. difficile* culture and cytotoxin assay. Moreover, after the last visit the

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TABLE 1. Treatment of *C. difficile*-associated disease with either vancomycin or teicoplanin

Characteristic[a]	No. of patients receiving:	
	Vancomycin	Teicoplanin
No. tested	25	22
Occurrence of PMC/CDAD[b]	15/4[c]	20/0[d]
Previous surgery	14	13
Previous antibiotic therapy	20	22
Evaluable	23	22
Response to treatment		
Clinically cured (%)	23 (100)	22 (100)
Clinical relapse (%)	3 (13.0)	0 (0)
Asymptomatic carriage (%)	1 (4.3)	1 (4.5)

[a] Mean ages (ranges) were 59.2 years (7 to 90 years) and 59.5 years (17 to 87 years) for vancomycin and teicoplanin groups, respectively.
[b] *C. difficile*-associated diarrhea.
[c] Six patients did not undergo colonoscopy.
[d] Two patients did not undergo colonoscopy.

TABLE 2. MICs for *C. difficile* isolates (47 strains)

Antibiotic	MIC (μg/ml)[a]		
	Range	50%	90%
Teicoplanin	<0.125–0.250	<0.125	0.250
Vancomycin	<0.125–1.00	0.50	1.00
Metronidazole	<0.125–2.00	1.00	1.00
Penicillin	<0.125–4.00	2.00	2.00
Piperacillin	<0.125–32.00	8.00	16.00
Clindamycin	<0.125–>128	>128	>128
Cefoxitin	8.00–>128	128	>128
Cefotetan	8.00–>128	64	64
Imipenem	1.00–>128	4.00	64
Ciprofloxacin	0.500–16	4.00	8.00

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.

patients were instructed to contact the infectious diseases consultant if diarrhea or any other intestinal disturbances occurred.

In the period of our study, *C. difficile* culture and cytotoxin assay were positive in 47 symptomatic patients. A total of 39 patients (19 in the vancomycin group and 20 in the teicoplanin group) underwent colonoscopy, and typical endoscopic appearances of PMC were seen in 15 and 20 patients, respectively. Endoscopy was not performed in six subjects receiving vancomycin and in two given teicoplanin. A total of 25 patients (13 males and 12 females) were treated with vancomycin, and 22 (12 males and 10 females) received teicoplanin. The main features of the two treatment groups, as well as the responses to therapy, are shown in Table 1. In the vancomycin group, two patients died (on days 2 and 3 of treatment) as a result of the underlying disease. Clinical symptoms recurred in 3 of 23 evaluable patients after discontinuation of therapy. Furthermore, follow-up cultures from another asymptomatic patient were positive. These patients underwent a second course of vancomycin, and all were cleared of *C. difficile* 10 days after discontinuation of therapy. All patients treated with teicoplanin remained asymptomatic, and all but one were also cleared of *C. difficile*. Clinical response to each drug was very good, with a decrease in diarrhea within 24 to 48 h. No side effects related to vancomycin or teicoplanin treatment were observed. The most favorable MICs for *C. difficile* among the assayed antibiotics were of teicoplanin (Table 2).

The results of our teicoplanin therapy (no clinical relapse and only one asymptomatic carriage after treatment in 22 symptomatic cases) seem very encouraging. However, prospective, comparative, randomized trials between vancomycin and teicoplanin are needed in order to define the role of teicoplanin in the treatment of *C. difficile*-associated disease.

LITERATURE CITED

1. **Aronsson, B., R. Möllby, and C. E. Nord.** 1984. Diagnosis and epidemiology of *Clostridium difficile* enterocolitis in Sweden. J. Antimicrob. Chemother. **14**(Suppl. D):85–95.

2. **Aronsson, B., R. Möllby, and C. E. Nord.** 1985. Antimicrobial agents and *Clostridium difficile* in acute enteric disease: epidemiological data from Sweden, 1980–1982. J. Infect. Dis. **151**: 476–481.

3. **Bartlett, J. G., N. S. Taylor, T. W. Chang, and J. Dzink.** 1980. Clinical and laboratory observations in *Clostridium difficile* colitis. Am. J. Clin. Nutr. **33**:2521–2526.

4. **Bartlett, J. G., F. J. Tedesco, S. Shull, B. Lowe, and T. W.**

4a. **Chang.** 1980. Symptomatic relapse after oral vancomycin therapy of antibiotic-associated pseudomembranous colitis. Gastroenterology **78**:431–434.

5. **Bender, B. S., B. E. Laughon, C. Gaydos, M. S. Forman, R. Bennet, W. B. Greenough, S. D. Sears, and J. G. Bartlett.** 1986. Is *Clostridium difficile* endemic in chronic-care facilities? Lancet **ii**:11–13.

6. **Brazier, J. S., P. N. Levett, K. D. Stannard, K. D. Phillips, and A. T. Willis.** 1985. Antibiotic susceptibility of clinical isolates of clostridia. J. Antimicrob. Chemother. **15**:181–185.

7. **Buchanan, A. G.** 1984. Selective enrichment broth culture for detection of *Clostridium difficile* and associated cytotoxin. J. Clin. Microbiol. **20**:74–76.

8. **Cherry, R. D., D. Portnoy, M. Jabbari, D. S. Daly, D. G. Kinnear, and C. A. Goresky.** 1982. Metronidazole: an alternative therapy for antibiotic-associated colitis. Gastroenterology **82**:849–851.

9. **Church, J. M., and V. M. Fazio.** 1986. A role for colonic stasis in the pathogenesis of disease related to *Clostridium difficile*. Dis. Colon Rectum **29**:804–809.

10. **Cumming, A. D., B. J. Thomson, J. Sharp, I. R. Poxton, and A. G. Fraser.** 1986. Diarrhoea due to *Clostridium difficile* associated with antibiotic treatment in patients receiving dialysis: the role of cross infection. Br. Med. J. **292**:238–239.

10a.**de Lalla, F., D. Santoro, E. Rinaldi, F. Suter, M. Cruciani, M. H. Guaglianone, G. Rizzardini, and G. Pellegata.** 1989. Teicoplanin in the treatment of infections by staphylococci, *Clostridium difficile* and other Gram-positive bacteria. J. Antimicrob. Chemother. **23**:131–142.

11. **Fekety, R.** 1983. Recent advances in management of bacterial diarrhoea. Rev. Infect. Dis. **5**:246–257.

12. **Fekety, R., J. Silva, B. Buggy, and H. G. Deery.** 1984. Treatment of antibiotic-associated colitis with vancomycin. J. Antimicrob. Chemother. **14**(Suppl. D):97–102.

13. **Fekety, R., J. Silva, R. Toshniwal, M. Allo, J. Armstrong, R. Browne, J. Ebright, and G. Rifkin.** 1979. Antibiotic associated colitis: effects of antibiotics on *Clostridium difficile* and the disease in hamsters. Rev. Infect. Dis. **1**:386–396.

14. **Finegold, S. M.** 1986. Clinical considerations in the diagnosis of antimicrobial agent-associated gastroenteritis. Diagn. Microbiol. Infect. Dis. **3**:S87–S91.

15. **George, R. H.** 1986. The carrier state: *Clostridium difficile*. J. Antimicrob. Chemother. **18**(Suppl. A):47–58.

16. **George, W. L.** 1984. Antimicrobial agent-associated colitis and diarrhoea: historical background and clinical aspects. Rev. Infect. Dis. **6**(Suppl. 1):S208–S213.

17. **George, W. L., R. D. Rolfe, and S. M. Finegold.** 1982. *Clostridium difficile* and its cytotoxin in feces of patients with antimicrobial agent-associated diarrhea and miscellaneous conditions. J. Clin. Microbiol. **15**:1049–1053.

18. **Holdeman, L. V., E. P. Cato, and W. E. C. Moore (ed.).** 1977. Anaerobe laboratory manual, 4th ed. Virginia Polytechnic Institute and State University, Blacksburg.

19. **Keighley, M. R. B., D. W. Burdon, Y. Arabi, J. Alexander-Williams, H. Thompson, D. Youngs, M. Johnson, S. Bentley,**

R. H. George, and G. A. A. Mogg. 1978. Randomized controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. Br. Med. J. 2:1667–1669.

20. Kleinfeld, D. I., R. J. Sharpe, and S. T. Donta. 1988. Parenteral therapy for antibiotic-associated pseudomembranous colitiis. J. Infect. Dis. 157:389.

21. Malamou-Ladas, H., S. O'Farrel, J. Q. Nash, and S. Tabaqchali. 1983. Isolation of Clostridium difficile from patients and the environment of hospital wards. J. Clin. Pathol. 36:88–92.

22. Newsom, S. W. B., J. Matthews, and A. M. Rampling. 1985. Susceptibility of Clostridium difficile strains to new antibiotics: quinolones, efrotomycin, teicoplanin and imipenem. J. Antimicrob. Chemother. 15:648–650.

23. Pantosti, A., I. Luzzi, R. Cardines, and P. Gianfrilli. 1985. Comparison of the in vitro activities of teicoplanin and vancomycin against Clostridium difficile and their interactions with cholestyramine. Antimicrob. Agents Chemother. 28:847–848.

24. Silva, J., D. H. Batts, R. Fekety, J. F. Plouffe, G. D. Rifkin, and I. Baird. 1981. Treatment of Clostridium difficile colitis and diarrhoea with vancomycin. Am. J. Med. 71:815–822.

25. Sutter, V. L., A. L. Barry, T. D. Wilkins, and R. J. Zabransky. 1979. Collaborative evaluation of a proposed reference dilution method of susceptibility testing of anaerobic bacteria. Antimicrob. Agents Chemother. 16:495–502.

26. Talbot, R. W., R. C. Walker, and R. W. Beart. 1986. Changing epidemiology, diagnosis and treatment of Clostridium difficile toxin-associated colitis. Br. J. Surg. 73:457–460.

27. Teasley, D. G., D. N. Gerding, M. M. Olson, L. R. Peterson, R. L. Gebhard, M. J. Schwartz, and J. T. Lee. 1983. Prospective randomised trial of metronidazole versus vancomycin for Clostridium difficile-associated diarrhoea and colitis. Lancet ii:1043–1046.

28. Tedesco, F., R. Markham, M. Gurwith, D. Christie, and J. G. Bartlett. 1978. Oral vancomycin for antibiotic-associated pseudomembranous colitis. Lancet ii:226–228.

29. Young, G. P., P. B. Ward, N. Bayley, D. Gordon, G. Higgins, J. A. Trapani, M. I. McDonald, J. Labrooi, and R. Hecker. 1985. Antibiotic associated colitis due to Clostridium difficile: double blind comparison of vancomycin with bacitracin. Gastroenterology 89:1038–1045.