

COMPARISON OF VANCOMYCIN VERSUS CEFAZOLIN AS INITIAL THERAPY FOR PERITONITIS IN PERITONEAL DIALYSIS PATIENTS

Quresh Khairullah, Robert Provenzano, Jukaku Tayeb, Aijaz Ahmad, Radhakrishnan Balakrishnan, and Linda Morrison

Division of Nephrology, Department of Internal Medicine, St John Hospital & Medical Center, Detroit, Michigan, USA

The incidence of peritonitis ranges from 1 episode every 24 patient treatment months to 1 episode every 60 patient treatment months [Keane WF, *et al.* ISPD Guidelines/Recommendations. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit Dial Int* 2000; 20:396-411.]. Gram-positive organisms account for over 80% of continuous ambulatory peritoneal dialysis (PD)-associated peritonitis. Recent fear of vancomycin-resistant enterococci (VRE) has prompted suggestions of limiting vancomycin use.

Fifty-one episodes of peritonitis in 30 patients studied over 2 years were evaluated. Cloudiness of the PD fluid and/or abdominal pain were considered suggestive of peritonitis and were confirmed by cell count and culture. Baseline cell count, Gram stain, and cultures were obtained, with periodic follow-up. Patients were randomized to receive either vancomycin 1 g/L intraperitoneally (IP) as loading dose, repeated on day 5 or day 8, depending on residual renal function, for 2 weeks, or cefazolin 1 g in the first PD bag and continued with 125 mg/L every exchange for 2 or 3 weeks, depending on culture results. All patients also received gentamicin 40 mg IP every day until the culture results were available. A similar randomized trial comparing vancomycin and cefazolin in the past used a lower concentration of cefazolin 50 mg/L [Flanigan MJ, Lim VS. Initial treatment of dialysis associated peritonitis: a controlled trial of vancomycin versus cefazolin. *Perit Dial Int* 1991; 11:31-7.].

Peritoneal dialysate fluid cultures revealed 31 (60.7%) gram-positive organisms, 7 (13.7%) gram-negative organisms, and 2 (3.9%) cultured yeast; 11 (21.5%) cultures yielded no growth.

The incidence of peritonitis at our center was 1 episode every 42 patient treatment months. No case of VRE was noted. There was no statistical difference in clinical response or relapse rate for the two protocols. It was the authors' and nurses' observation that patient compliance and satisfaction was better with vancomycin, and the cost

per treatment was 23% less than cefazolin. Based on these data we believe vancomycin should still be considered for first-line treatment of PD-associated peritonitis.

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KEY WORDS: Peritonitis; vancomycin; cefazolin; vancomycin-resistant enterococci.

Peritonitis remains a common problem in patients with end-stage renal disease receiving peritoneal dialysis (PD) as renal replacement therapy (1-6). With the introduction of Y-set disconnect systems, the incidence of peritonitis in continuous ambulatory peritoneal dialysis (CAPD) patients has fallen significantly, particularly with respect to gram-positive organisms (7-10). The reported incidence of peritonitis differs from center to center, ranging from 1 episode every 24 patient treatment months to 1 episode every 60 patient treatment months (1).

Although one major advantage of CAPD is more freedom in personal lifestyle, peritonitis remains the most frequent reason for transfer to hemodialysis (11), at a rate of approximately 20% per year.

Controversy regarding the use of vancomycin with the emergence of vancomycin-resistant enterococci (VRE) (12-16) and case reports of vancomycin resistance in coagulase-negative staphylococci (17,18) have prompted altered protocols to avoid the use of vancomycin (1-3). At the same time, there are concerns about promoting methicillin resistance in staphylococcus species and VRE with the use of cephalosporins (19,20).

Despite recommendations made by the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis (1,3), the route of antibiotic administration, duration of treatment, and initial choice of antibiotics still differ from center to center (19,21-24).

In our study, we compared the efficacy of vancomycin versus cefazolin (vancomycin 1 g/L dialysate;

Correspondence to: Q. Khairullah, Division of Nephrology, Department of Internal Medicine, St. John Hospital and Medical Center, 22201 Moross Road, Suite 150, Detroit, Michigan 48236 USA.

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cefazolin 125 mg/L; the higher concentration was used in hopes of overcoming methicillin-resistant coagulase-negative *Staphylococcus epidermidis* as initial therapy for peritonitis in PD patients. Secondary end points included evaluation of cost, patient compliance, and patient satisfaction.

SUBJECTS AND METHOD

Our study was conducted at a tertiary-care teaching hospital-based PD program. Ninety patients trained to perform PD and followed at the St. John Hospital & Medical Center, Home Dialysis Treatment Center, were included. Fifty-one cases of peritonitis in 30 patients were identified over 2 years (1 October 1997 to 20 September 1999). The average patient age was 48 years (range 26 - 74 years); there were 17 males and 13 females. Fourteen (47%) patients had diabetes mellitus; the remainder had either hypertension or glomerulonephritis listed as cause of end-stage renal disease. Patients participating in the study were given detailed study information and gave informed consent. Institutional Review Board approval was granted.

Study patients maintained a log/diary, recording symptoms of peritonitis: abdominal pain, fever, and cloudiness of PD fluid. A record of severity of symptoms was also maintained throughout the treatment period. Baseline PD fluid cell count, Gram stain, and cultures were done and followed at periodic intervals of 0, 2, 4, and 7 days and at the end of treatment. Diagnosis of peritonitis was established if the effluent cell count exceeded 100 WBC/mL, with more than 50% polymorphonuclear cells, and the PD fluid was sent for Gram stain and culture.

Patients were excluded if they had sensitivities to penicillin or vancomycin, were already receiving antibiotics, were known to be noncompliant, could not follow instructions, were younger than 18 years old, or were pregnant. Additionally, patients were excluded from analysis if their cultures grew gram-negative or fungal organisms.

All enrolled patients were given two kits, each marked A or B. They were instructed to call the dialysis nurse if they developed symptoms suggestive of peritonitis as described above. Patients were then randomized by the nurse to initiate treatment with either kit A (vancomycin) or kit B (cefazolin). Intra-peritoneal (IP) gentamicin was included in both protocols. Dosage of the above antibiotics is shown in Table 1.

All patients (kit A or B) were treated for 3 weeks for methicillin-sensitive *S. aureus* (MSSA) and for 2 weeks for all other gram-positive organisms. Gentamicin was discontinued if the culture did not grow gram-negative organisms. All patients whose cultures

revealed no growth were considered to have gram-positive peritonitis and were treated for 2 weeks.

Dialysis nurses kept in touch with the patients by telephone and updated infection report sheets on a daily basis. Therapy was considered curative if all signs and symptoms of peritonitis were eliminated by the prescribed duration of treatment and the patient remained infection free for 2 weeks following cessation of treatment. If the infection recurred within 2 weeks of antibiotic treatment, the episode was considered either a relapse of the original or if no organism was recovered, or superinfection when a new organism was identified. Catheters were removed when infections were not responsive to treatment, when peritonitis was life threatening, or if the effluent grew persistent gram-negative or fungal organisms. Mean abdominal pain scores (scale of 1 to 10) in both groups were noted on days 0, 2, 4, and 7 and at the end of the treatment. The PD fluid WBC counts were measured at the time of diagnosis and on days 2, 4, and 7 and at the end of treatment. Effectiveness of both drugs was determined based on each patient's pain score, PD fluid cell count, and relapse rates.

STATISTICAL ANALYSIS

Statistical analysis was made using Pearson chi-square test; probability values of less than 0.05 were considered significant.

RESULTS

A total of 51 cases of peritonitis occurred in 30 patients: 18 patients had only 1 episode of peritonitis, 4 had 2 episodes, and 6 had more than 2 episodes. Thirty-one (60.7%) grew gram-positive organisms, 7 (13.7%) grew gram-negative organisms, and 2 (3.9%) grew yeast; 11 cases (21.5%) had no growth. Of the gram-positive organisms, the dominant isolate was *S. epidermidis* (18 cases; 58%) followed by *S. aureus* (MSSA) (9 cases, 29%). No dominant gram-negative organism was identified. The organisms isolated from PD fluids are shown in (Table 2).

Of the 31 episodes of gram-positive peritonitis, 16 were treated with kit A and 15 with kit B. In the 11 episodes of peritonitis that were culture negative, 6 were treated with kit A and 5 with kit B (Table 3).

Mean abdominal pain scores fell for both groups, from an average of 3.5 (kit A) and 2.7 (kit B) to less than 1 for both groups, at 96 hours (Figure 1). No statistical differences were noted for either group at any time.

The WBC counts were 1431 ± 432 /mL in patients treated with vancomycin (kit A) and 1915 ± 676 /mL in the cefazolin (kit B) group. White blood cell counts decreased rapidly and were less than 100/mL at

TABLE 1
Intraperitoneal (IP) Antibiotic Kits

	Loading dose	Maintenance
Vancomycin (kit A)	2 g IP	2 g IP on day 8 (if urine output > 500 cc/day, repeat on day 5)
Cefazolin (kit B)	500 mg/L 1 g in 2-L bag	125 mg/L 250 mg in 2-L every exchange
Gentamicin	40 mg/day in one bag	—

TABLE 2
Organisms Isolated from Peritoneal Dialysis Fluid and Number of Cases

Organism	Cases (n)
Gram-positive	31 (60.7%)
<i>Staphylococcus epidermidis</i>	18 (58%)
<i>S. aureus</i> (MSSA)	9 (29%)
<i>S. aureus</i> (MRSA)	1 (3%)
Enterococcus	2 (6%)
Strep D non enterococcus	1 (3%)
Gram-negative	7 (15.6%)
Pseudomonas	1 (14%)
<i>Klebsiella pneumoniae</i>	2 (28.5%)
<i>Escherichia coli</i>	2 (28.5%)
<i>Stenotrophomonas maltophilia</i>	2 (28.5%)
Yeast	2 (3.9%)
No growth	11 (21.5%)
Total	51

MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*.

TABLE 3
Gram-Positive Organisms and Cases of No Growth Randomized to Two Treatment Groups

Organism	Vancomycin (kit A)	Cefazolin (kit B)
<i>Staphylococcus epidermidis</i>	8 (44%)	10 (56%)
<i>S. aureus</i> (MSSA)	6 (67%)	3 (33%)
<i>S. aureus</i> (MRSA)	1	0
Enterococcus	0	2
Strep D non enterococcus	1	0
No growth (culture-negative)	6	5

MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*.

96 hours in patients treated with either kit. No statistical differences were noted between either group at any time (Table 4). Three cases of relapse in 2 patients in the vancomycin group (all *S. aureus*) and 2 relapses in the cefazolin group (both *S. epidermidis*) were noted and were treated successfully with vancomycin. No relapses were noted in the culture-negative group. Two patients in the cefazolin group had

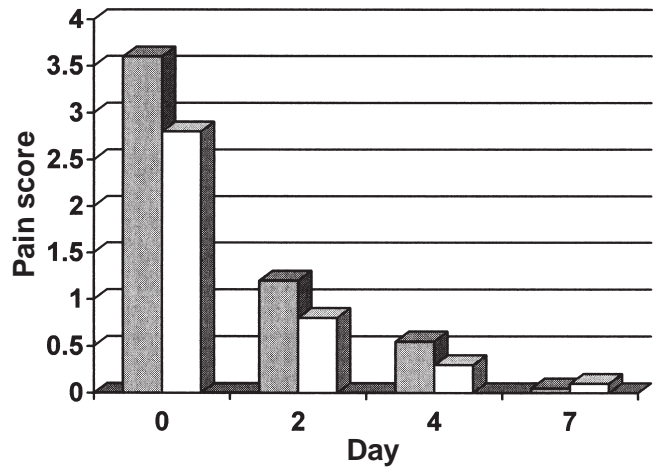


Figure 1 - Average abdominal pain scale for administration of vancomycin (dark bars) and cefazolin (white bars).

TABLE 4
White Blood Cell Count in Peritoneal Dialysis Fluid (WBCs/mL)

	Vancomycin (kit A)	Cefazolin (kit B)
Day 0	1431±432	1915±676
Day 2	239±110	117±57
Day 4	58±24	58±36
Day 7	18±6	10±3
End of treatment	8.2±3.2	7.6±2.8

Mean ± SE; no significant differences between vancomycin and cefazolin.

evidence of exit-site infection at the time of presentation, and no patient in either group showed any sign of tunnel infection. Two cases of enterococcus in the cefazolin group responded to treatment with vancomycin.

There were no cases of vancomycin-resistant organisms isolated during the study period. Catheters were removed from 12 patients, 8 in the vancomycin group and 4 in the cefazolin group. Reasons for catheter removal in the vancomycin group included gram-negative infection in 2 patients, fungi in 1, recurrent peritonitis with gram-positive organisms in 3, "failure to thrive" in 1, and poor compliance in 1 (trans-

ferred to hemodialysis). In the cefazolin group, reasons for catheter removal included gram-negative peritonitis in 2 patients, fungal peritonitis in 1, and recurrent gram-positive infection unresponsive to vancomycin in 1 (Table 5).

The relapse rate in patients with gram-positive peritonitis was 16.7% (3 patients) in the vancomycin group and 15.3% (2 patients) in the cefazolin group (values not significant).

Cost analysis revealed drug cost per episode of peritonitis was US\$30.21 versus \$39.32 in the vancomycin and cefazolin groups, respectively (Table 6).

DISCUSSION

Patient self-administration of empiric antibiotic therapy is an accepted practice in treating PD-associated peritonitis (2,3). The majority of episodes of peritonitis resolve with this outpatient treatment. Our study was prompted by a growing concern of possible promotion of vancomycin resistance in enterococci and, more ominously, resistance in *S. epidermidis* by empiric use of vancomycin. There are suggestions in the literature that vancomycin use should be reserved for methicillin-resistant *S. aureus* (MRSA) and ampicillin-resistant enterococci (ARE) only (1,3).

The prevalence of VRE in hospitalized patients is reported to be 0.4% to 14%, but higher in larger hos-

pitals that are university affiliated (14). Weinstein et al. suggest that enteral tube feedings, the presence of diarrhea, and prior use of multiple antibiotics, including third-generation cephalosporins, are risk factors for inducing vancomycin resistance in enterococci in hospitalized patients (25). A patient with vancomycin-resistant coagulase-negative staphylococci described by Schwalbe et al. (26) received multiple courses of vancomycin prior to isolation of VRE. Troidle et al. described cases of VRE that occurred either in hospitalized patients or after recent hospitalization (16). Therefore, the use of many antibiotics other than or in addition to vancomycin is associated with the development of not only VRE but of multiple-antibiotic-resistant enterococci (27,28).

The choice of empiric outpatient treatment is dictated by convenience of self-administration by the patient and by the drug's pharmacokinetics, its cost, and its effectiveness. The pharmacokinetics of vancomycin allows IP dosing at weekly intervals (29). We did not monitor plasma levels of vancomycin, which may be necessary in patients with significant residual renal function and which may potentially result in undertreatment, but we did allow for more frequent dosing in patients with significant renal function (Table 1).

The use of cefazolin in treating peritonitis requires multiple doses for the 2 - 3 weeks of therapy. This affects patient compliance and could potentially lead to inadequate or partial treatment. The increased dosing frequency of cefazolin requires more equipment and offsets the cost savings of the less expensive drugs, resulting in overall increased cost for treatment of each episode of peritonitis (Table 6). It was noted that 2 patients in our study refused to be randomized to cefazolin because of prior inconvenience with its use.

The incidence of peritonitis at our center was 42 episodes/patient/month. No case of VRE was noted. There was no statistical difference in clinical response or relapse rate for the two protocols (Table 7). Although there was no statistical difference in the compliance rate for either group (Table 7), it was the authors' and nurses' observation that patients found it more convenient to administer vancomycin than to administer multiple doses of cefazolin.

TABLE 5
Reasons for Catheter Removal

	Vancomycin (kit A)	Cefazolin (kit B)
Gram-negative infections	2	2
Fungal infection	1	1
Recurrent peritonitis with gram-positive organisms	3	1
Other	2	0
Total	8	4

TABLE 6
Cost Comparison (US\$) for Treating 1 Episode
of Peritonitis for 3 Weeks

Vancomycin (kit A)		Cefazolin (kit B)	
Vancomycin	\$28.02	Cefazolin	\$21.78
Saline	6 \$1.14	Saline	11 \$2.09
Syringes	6 \$0.48	Syringes	84 \$4.20
Needles	6 \$0.18	Needles	11 \$0.33
Betadine	3 \$0.15	Betadine	84 \$4.20
Mask	3 \$0.24	Mask	84 \$6.72
Total	\$30.21	Total	\$39.32

TABLE 7
Relapse and Catheter Removal Rates

	Vancomycin	Cefazolin	p Value ^a
Relapse	3 (16.7%)	2 (15.3%)	1.0
Catheter removal	8 (44%)	4 (30%)	0.63
Noncompliance	0	2 (16.7%)	0.15

^a Fisher exact scale.

CONCLUSION

Vancomycin should still be considered first-line treatment for PD-associated peritonitis. No VRE was isolated over the 2 years of our study despite empiric IP vancomycin use. Our data do not support the premise that empiric use of vancomycin induces resistance in either enterococcus or staphylococcus species when used judiciously in an outpatient setting. Prompt catheter removal for recurrent episodes of peritonitis rather than multiple antibiotic courses may help in preventing antibiotic resistance. Additionally, when additional supply costs are considered, the cost per treatment using vancomycin is substantially less than when using cefazolin.

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REFERENCES

- Keane WF, Ballie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, et al. ISPD Guidelines/Recommendations. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update (Published erratum appears in *Perit Dial Int* 2000; 20:828-9). *Perit Dial Int* 2000; 20:396-411.
- Flanigan MJ, Lim VS. Initial treatment of dialysis associated peritonitis: a controlled trial of vancomycin versus cefazolin. *Perit Dial Int* 1991; 11:31-7.
- Keane WF, Alexander SR, Bailie GR, Boeschoten E, Gokal R, Golper TA, et al. Peritoneal dialysis related peritonitis treatment recommendations: 1996 update. *Perit Dial Int* 1996; 16:557-73.
- Boeschoten EW. Long-term consequences of peritonitis. *Perit Dial Int* 1996; 16(Suppl 1):S349-54.
- Fried L, Bernardini J, Johnston JR, Piraino B. Peritonitis influences mortality in PD patients (Abstract). *J Am Soc Nephrol* 1995; 6:530.
- Lupo A, Tarchini R, Cancarini G, Catizone L, Cocchi R, De Vecchi A, et al. Long-term outcome in continuous ambulatory peritoneal dialysis: a 10 year survey by the Italian Cooperative Peritoneal Dialysis Study Group. *Am J Kidney Dis* 1994; 24:826-37.
- Maiorca R, Cantaluppi A, Cancarini GC, Scalapogna A, Broccoli R, Graziani G, et al. Prospective controlled trial of a Y-connector and disinfectant to prevent peritonitis in continuous ambulatory peritoneal dialysis. *Lancet* 1983; 2:644-52.
- Maiorca R, Cancarini GC, Brasa S, Colombrita D, Manili L, Camerini C. Y-system with disinfectant in the prevention of peritonitis in CAPD. *Contrib Nephrol* 1987; 17:178-84.
- Canadian CAPD Clinical Trials Group. Peritonitis in continuous ambulatory peritoneal dialysis (CAPD): a multicenter randomized clinical trial comparing the Y-connector disinfectant system to standard systems. *Perit Dial Int* 1989; 9:159-63.
- Port FK, Held PJ, Nolph KD, Turenne MN, Wolfe RA. Risk of peritonitis and technique failure by CAPD connection technique: a national study. *Kidney Int* 1992; 42:967-74.
- Burkart J, Schreiber M, Tabor T, Korbet S, Stallard R, and PD Collaborative Group. Prospective multicenter evaluation of patient transfer from PD to HD in 1995 (Abstract). *Perit Dial Int* 1996; 16(Suppl 2):S66.
- Low DE, Willey BM, Betschel S, Kreiswirth B. Enterococci: pathogens of the 90s. *Euro J Surg Suppl* 1994; 573:19-24.
- Wood AJJ. Vancomycin-resistant enterococcal infections. *N Engl J Med* 2000; 342:710-21.
- Hospital Infection Control Practices Advisory Committee. Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 1995; 16:105-13.
- Barlett JG, Bradley SF, Herwaldt LA, Jacobs MR, Perl TM, Poole MD, et al. A roundtable discussion of antibiotic resistance: putting the lesson to work. *Am J Med* 1999; 106(Suppl 5A):48-52.
- Troidle L, Kliger AS, Gorban-Brennan N, Fikrig M, Golden M, Finkelstein FO. Nine episodes of CPD-associated peritonitis with vancomycin resistant enterococci. *Kidney Int* 1996; 50:1368-72.
- Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. *N Engl J Med* 1999; 340:493-501.
- Luzar MA, Coles GA, Faller B, Slingeneyer A, Dah Dah G, Briat C, et al. *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. *N Engl J Med* 1990; 322:505-9.
- Onzato ML, Caramori JCT, Barretti P. Initial treatment of CAPD peritonitis: poor response with association of cefazolin and amikacin. *Perit Dial Int* 1999; 19:88-9.
- Mason NA, Zhang T, Messana J. Methicillin resistance patterns associated with peritonitis in a university-based peritoneal dialysis center. *Perit Dial Int* 1999; 19:483-6.
- Kent JR, Almond MK. A survey of CAPD peritonitis management and outcomes in North and South Thames NHS Regions (U.K.): support for the ISPD guidelines. *Perit Dial Int* 2000; 20:301-5.
- Sandoe JAT, Gokal R, Struthers JK. Vancomycin-resistant enterococci and empirical vancomycin for CAPD peritonitis. *Perit Dial Int* 1997; 17:617-18.
- Churchill DN. CAPD peritonitis: a critical appraisal of prophylactic strategies. *Semin Dial* 1991; 4:94-100.
- Teitelbaum I. Vancomycin for the initial therapy of peritonitis: don't throw out the baby with the bathwater. *Perit Dial Int* 2001; 21:235-8.
- Weinstein JW, Roe M, Towns M, Sanders L, Thorpe JJ, Corey GR, et al. Resistant enterococci: a prospective study of prevalence, incidence, and factors associated with colonization in a university hospital. *Infect Con-*

- trol and Hosp Epidemiol* 1996; 17:36-41.
26. Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococci. *N Engl J Med* 1987; 316:927-31.
 27. Pearl TA. The threat of vancomycin resistance. *Am J Med* 1999; 106 (Suppl 5A) :26S-37D.
 28. Morris JG, Shay DK, Hebden JN, McCarter JN, Perdue BE, Jarvis W, *et al.* Enterococci resistant to multiple antimicrobial agents, including vancomycin: establishment of endemicity in a university medical center. *Ann Intern Med* 1995; 123:250-9.
 29. Johnson CA, Zimmerman SW, Rogge M. The pharmacokinetics of antibiotics used to treat peritoneal dialysis associated peritonitis. *Am J Kidney Dis* 1984; 4:3-17.
 30. Hockensmith ML, Madinger NE, Teitelbaum I. Concerns regarding recommendations for the treatment of CAPD peritonitis. *Perit Dial Int* 2001; 21:317-19.

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Professor Carol Pollock
Chair of the ISPD Future Meeting Site Committee
Department of Medicine
University of Sydney
Royal North Shore Hospital
St Leonards 2065
Australia

Telephone: +61 2 9926 7126
Fax: +61 2 9436 3719
Email: carpol@med.usyd.edu.au