Lack of Efficacy of Oral Bacitracin Plus Doxycycline for the Eradication of Stool Colonization with Vancomycin-Resistant *Enterococcus faecium*

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In a prospective observational cohort study designed to assess the role of oral bacitracin solution plus doxycycline in the eradication of intestinal carriage of vancomycin-resistant *Enterococcus faecium* (VREF) in patients on a renal ward, rectal swab specimens were obtained from 15 treated and 24 control patients. Cultures of the rectal swabs were negative for 15 (100%) of the antibiotic-treated vs. eight (33.3%) of the untreated patients ($P < .001$) on day 14. However, follow-up for a mean of 127 and 130 days revealed 9 of 15 (60%) and 15 of 24 (62.5%) in the treated and untreated cohorts ($P = .86$), respectively, carried VREF intermittently or persistently. Quantitative VREF stool cultures in the treated cohort revealed an initial 3.1-$\log_{10}$/g decrease, but there was an increase to pretreatment levels at 2–4 and 5–7 weeks post-treatment (7.8 and 7.4 $\log_{10}$/g). Oral bacitracin and doxycycline were not efficacious in reducing the carriage of VREF beyond the 2-week interval during which they were given.

Vancomycin-resistant enterococcus (VRE) has become a nosocomial pathogen of increasing importance. First identified in Europe in 1988 [1], it has since been identified in multiple sites in the United States and Canada [2–4]. A 20-fold increase in the percentage of enterococci associated with nosocomial infections that were resistant to vancomycin, from 0.4% in 1989 to 7.9% in 1993, has been reported by the Centers for Disease Control and Prevention [5]. Recent recommendations to limit the emergence and transmission of vancomycin resistance have focused on prudent use of vancomycin, education of hospital staff, rapid identification and reporting by microbiology laboratories, and the implementation of contact-isolation precautions to prevent patient-to-patient transmission [6]. The effectiveness of the specific components of these recommendations remains controversial [7–9].

Intestinal colonization with VRE may be prolonged [10–14] and appears to be the major reservoir from which spread of the organism occurs in health care settings. Eradication of stool carriage as an adjunctive control measure has great appeal in limiting the spread of VRE. Few studies have formally examined this strategy; most are small case series with short follow-up periods and no adequate control groups [15–18]. Oral antibiotic regimens that achieve high fecal levels with adequate activity against enterococci include vancomycin, bac-

itracin, novobiocin, rifampin, and tetracycline. Efficacy [15–18] has varied widely (from zero to 100%) and the impact has not been determined.

Given this background, we sought to determine the longitudinal impact of a 2-week course of oral bacitracin plus doxycycline on stool colonization with VRE, as part of a control program during a nosocomial outbreak of VRE infection and colonization on a renal unit of a tertiary care hospital.

Methods

Setting. The Toronto Hospital is a 1,200-bed two-site tertiary care medical school–affiliated acute care institution that has one of the largest dialysis programs in North America. There are 2 hemodialysis units, one with 27 and the other with 29 stations, and services are provided 6 days of the week, in 3 shifts per day, for 336 patients. In addition, services are provided for >300 peritoneal dialysis patients, and there is a 38-bed inpatient unit. During the latter part of September and October 1995, an outbreak of VRE on the inpatient renal ward of our hospital was documented [19]. This represented the first time VRE had been identified in our institution, where an active surveillance system had been in place for the preceding 2 years.

Screening of the entire populations of the dialysis unit, renal ward, transplantation ward, and intensive care unit identified 45 patients colonized with VRE, of whom all but three were renal patients. The outbreak strain has been well characterized [19] in our laboratory and was a sorbitol-positive, VanB-containing *Enterococcus faecium* that was a single clonotype, as shown by pulsed-field gel electrophoresis.

Study design and selection of patients. The study was of a prospective observational-cohort design. From the screening of rectal swab or stool surveillance cultures during the first month

of the outbreak investigation, a cohort of 15 consecutively identified VRE-positive ward patients was selected to be treated with oral bacitracin plus doxycycline. All 15 patients had vancomycin-resistant *E. faecium* (VREF) isolated from rectal swabs on at least two occasions at least 2 days apart, prior to their enrollment in the study.

Patients were excluded according to the following criteria: survival for >3 weeks not expected; history of allergy to bacitracin or doxycycline; or adequate follow-up not expected to be feasible (for any reason). The control group consisted of a cohort of 24 patients (identified at the same time and selected from the same renal ward population) whose rectal swab or stool surveillance cultures were positive for VREF and for whom adequate follow-up could be expected.

All patients and their attending physicians were approached about the use of oral antibiotics as part of a strategy to limit VRE transmission. All the patients voluntarily agreed to receive oral doses of a bacitracin solution (75,000 U/15 mL; Apothekernes Laboratories, Oslo) four times daily and doxycycline (100 mg) once daily for 14 days. The control cohort received neither doxycycline nor bacitracin. No other antimicrobials with VRE activity were administered to either the treated cohort or the control cohort during the 14-day period. At the time of the outbreak, vancomycin restriction policies [6], as recommended by the Hospital Infection Control Practices Advisory Committee (HICPAC), were instituted and contact precautions (gloves and gowns) were used with all colonized patients.

Surveillance cultures and definitions. Rectal swabs were collected serially for qualitative culture at days 0, 7, and 14 and then biweekly for 6 weeks and monthly for 4 months. Stool samples were collected at the same time intervals whenever possible, or within a 2-day range. Stool samples were frozen at $-70°C$, and quantitative cultures were performed in a batched manner at later intervals.

The primary endpoint for this study was the classification of colonization status on the basis of follow-up rectal swab culture. The starting date was considered the first day of administration of the bacitracin plus doxycycline for the treated cohort and the first day on which a culture was positive for the control cohort. Patients were considered eligible for evaluation if more than three cultures were performed and follow-up was for >3 weeks.

Definitions were applied as follows. Noncarriage was defined by two or more positive cultures for VREF, followed by consistently negative cultures (a minimum of three, each separated by 3 weeks). Persistent carriage was that in which all cultures remained positive or, in the bacitracin plus doxycycline–treated cohort, all subsequent cultures (a minimum of three) following the 2-week treatment course remained positive. Carriage was considered intermittent when cultures were intermittently positive and negative and did not meet the

definition of another response, and carriage was indeterminate if inadequate follow-up was performed.

Microbiological methods. For selective isolation of VREF, rectal swabs were streaked onto M-enterococcal agar with vancomycin (6 μg/mL). Enterococci were identified by standard methods [20, 21]. Susceptibility testing was done with the MicroScan Walkaway System (Baxter Laboratories, Sacramento, CA), supplemented with the microbroth dilution [22] and/or agar dilution methods, implemented according to guidelines of the National Committee for Clinical Laboratory Standards for vancomycin, teicoplanin, doxycycline, and bacitracin.

For quantitative cultures a 0.1-g sample of feces was homogenized in 0.9 mL of sterile saline. Serial 10-fold dilutions were made, and 10 μl of each dilution was plated onto M-enterococcal agar, incubated at 35°C in O_2, and read at 48 and 72 hours. Colony types were identified and enumerated with use of standard techniques. The sensitivity of the quantitation was $\sim 10^3$ cfu/g (wet weight) of stool.

Statistical analysis. Baseline demographic characteristics were compared between the treated and the untreated cohorts by means of the χ^2 or Fisher's exact test for categorical variables and the two-tailed Student's *t* or Kruskal-Wallis test for continuous variables. Data were analyzed with use of Epi Info, version 6.02 [23]. Distributions of the time to enteric clearance of VREF for the two cohorts were estimated by the Kaplan-Meier method, and comparisons were made with the log-rank test [24]. The time to enteric clearance was estimated according to the date of the first culture-negative rectal swab, after which the patient was classified as a noncarrier if the definitions as noted previously were met. A one-tailed *P* value of <.05 was considered statistically significant.

Results

Characteristics of patients. All patients in the treated and untreated cohorts were hospitalized at the time of initial screening and during the 2-week "treatment" period. Baseline characteristics of patients in the two cohorts are summarized in table 1. Patients often had received broad-spectrum antibiotics, had significant associated medical illnesses, and had had prolonged hospitalizations. Median follow-up was 98 days in the treated cohort and 101 days in the control cohort. There was no statistically significant difference in any characteristic analyzed between the treated and untreated cohorts.

Measurement of compliance with the oral bacitracin and doxycycline (by personal interview) and assessment of the patient's medication record revealed that 98% of all prescribed doses were administered and taken. Adverse events were self-reported by patients, and mild unpalatability of the bacitracin was reported by 53.3% of patients.

Surveillance cultures. At 14 days, the qualitative rectal or stool cultures were negative for all 15 of the antibiotic-treated patients and 8 (33.3%) of the 24 controls ($P < .001$). However, with follow-up to the end of the study, there was no significant

Table 1. Baseline characteristics of antibiotic-treated patients and controls.

	No. (%) of patients and other data, per group		
Characteristic	Antibiotic-treated ($n = 15$)	Control ($n = 24$)	P value
Age (y; mean ± SD)	61.2 (±15.2)	65.2 (±13.6)	.43
Male:female ratio	6:9	12:12	.78
Days in hospital, mean (median)	72.7 (34)	63.1 (48)	.97
Follow-up days, mean (median)	127 (98)	130.4 (101)	.75
Broad-spectrum antibiotic use	14 (93.3)	18 (75)	.22
Vancomycin use	5 (33.3)	11 (45.8)	.66
Hemodialysis	6 (40)	10 (41.7)	.86
Peritoneal dialysis	9 (60)	8 (33)	.19
Diarrhea	7 (46.7)	10 (41.7)	.98
Clostridium difficile–positive	4 (26.7)	9 (37.5)	.73
Fecal incontinence	6 (40)	3 (12.5)	.06
No. of previous hospitalizations			.14
0	0	5 (20.8)	.07
1–2	5 (33.3)	10 (40)	.85
≥3	10 (66.7)	9 (37.5)	.14
Open wound(s)	11 (73.3)	13 (54.2)	.39
No. of associated medical conditions			
0	2 (13.3)	2 (8.3)	.63
1–2	8 (53.3)	15 (62.5)	.81
≥3	5 (33.3)	7 (29.2)	.93
Mobility			
None (bedridden)	5 (33.3)	7 (29)	.96
Limited	7 (46.7)	12 (50)	

difference in colonization status between groups (table 2). In the treated group, 6 of 15 (40%) were classified as noncarriers, compared with 9 of 24 (37.5%) in the control group (OR, 1.11; 95% CI, 0.24–5.09; $P = .86$). Similarly, by life-table analysis the estimated probability of not clearing VREF by day 15 was 70.8% in the treated group and 91.8% in the control group ($P = .03$).

By 30 days, however, there was no statistically significant difference with respect to colonization status between groups (probability of not clearing VREF was 70.8% for treated patients and 77.3% for controls; $P = .32$) (figure 1); at 120 days the actuarial estimates for not clearing VRE were 70.8% and 70.0%, respectively ($P = .5$).

Susceptibility testing with use of the MicroScan system revealed MICs of vancomycin of 8–128 μg/mL against the VREF isolates in each of the two groups. The MICs determined by the broth microdilution and agar dilution methods, respectively, were 4–64 and 2–64 μg/mL for vancomycin, <0.5 and <0.5 μg/mL for teicoplanin, 0.5–16 and <0.5–16 μg/mL for doxycycline, and 32 and 8–16 μg/mL for bacitracin. All of the strains in the treatment cohort were susceptible to the doxycycline, with an MIC range of 0.5–2 mg/mL.

Because of the potentially confounding factor of previously received courses of antimicrobials on the presence or absence of VREF in the surveillance rectal swab or stool cultures during the follow-up period, we reviewed the charts of all the patients in both the treated and untreated cohorts to determine if any differences existed that might explain the observed findings. This review revealed no significant differences (data not shown) in either the number or types of antimicrobials received in either of the cohorts.

Quantitative stool cultures.   Quantitative stool cultures revealed a baseline mean of 7.6 (median, 6.7) $\log_{10}$ cfu of VREF per gram (wet weight) of stool. At the time of the first follow-up stool sampling in the treated cohort (days 4–14), there was a 3.1-$\log_{10}$ cfu decrease in VREF, with a mean of 4.5 $\log_{10}$ cfu/g ($P < .001$ in comparison with baseline). In addition, in this cohort 82.6% of all specimens obtained at the first follow-up had no detectable VREF. However, by days 15–30 (1–15 days following completion of the antibiotic treatment), despite the 2 weeks of administration of bacitracin plus doxycycline, the quantitative counts of VREF had returned to baseline value, with a mean 7.8 $\log_{10}$ cfu/g (P value NS in comparison with baseline). A similar degree of colonization was also seen at the time of the follow-up cultures performed on days 31–49 (table 3).

Discussion

The use of antibiotics as an adjunctive measure to control transmission of VRE by reducing and eliminating its carriage has significant theoretical appeal. Eradication of colonization would obviate the need for prolonged, costly infection control interventions, especially isolation of patients, and could limit secondary spread. Similar strategies involving the use of topical mupirocin with or without oral agents have been well studied for the eradication of nasal colonization by methicillin-resistant *Staphylococcus aureus* [25, 26].

Several small case series that have examined the efficacy of attempts to eradicate enteric VREF colonization have been reported [15–18]. O'Donovan and colleagues reported that oral vancomycin eradicated colonization in eight of 19 patients (42%). Eight nonresponders received bacitracin (25,000 U every 6 hours) for 10 days; initially, all eight had microbio-

Table 2. Carrier status (per qualitative assessment based on rectal swab or stool culture) at the end of the follow-up period.

	No. (%) of patients, per group	
Carrier status	Treated ($n = 15$)	Control ($n = 24$)
Noncarrier	6 (40)	9 (37.5)
Persistent carrier	3 (20)	5 (20.8)
Intermittent carrier	6 (40)	10 (41.7)

NOTE.   See text for definitions of carrier status. In comparison of noncarrier vs. persistent or intermittent carrier status between the treated and control cohorts, $P = .86$ (Fisher's exact test).
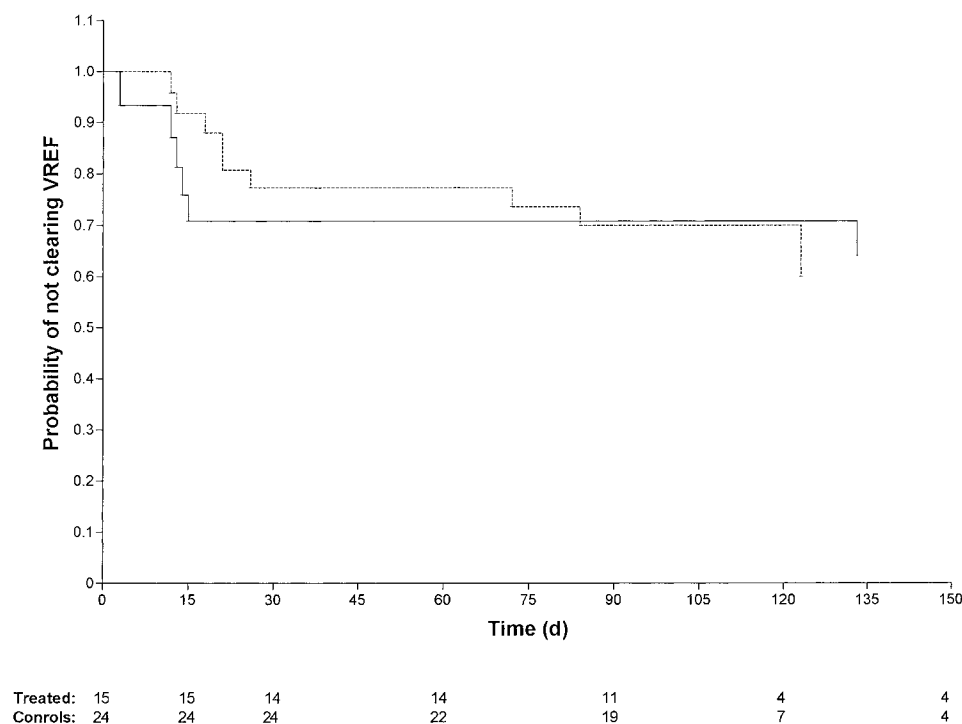
Figure 1. Kaplan-Meier analysis of probability of not clearing vancomycin-resistant *Enterococcus faecium* (VREF) in the cohort of patients treated for 2 weeks with oral bacitracin (75,000 U/15 mL four times daily) plus doxycycline (100 mg once daily) (*n* = 15; *solid line*) and in the cohort of nontreated control patients (*n* = 24; *dotted line*).

Treated:	15	15	14	14	11	4	4
Conrols:	24	24	24	22	19	7	4

logical responses, but two subsequently relapsed [15]. Chia et al. treated eight VRE-colonized patients with bacitracin (25,000 U twice daily) for 10 days [18]. Six patients (75%) responded to therapy (one after a second course of bacitracin), and one subsequently relapsed.

Montecalvo et al. reported that short courses of novobiocin and tetracycline or doxycycline were ineffective in eradicating gastrointestinal colonization [16]. Dembry et al. described two patients in whom doxycycline and rifampin successfully eliminated carriage [17]. None of these studies had any reference control group and most of the reports did not include data on long-term follow-up, circumstances that make the assessment of relapse problematic since carriage of VRE may persist for an extended time, often weeks to months [10–14].

In our study we employed a regimen of oral bacitracin plus doxycycline in an attempt to eradicate VREF colonization. Bacitracin has limited oral absorption, has excellent in vitro activity against VRE [27], and has been shown to suppress bowel flora when >100,000 U daily is administered [28]. Doxycycline has in vitro activity [29, 30], achieves adequate fecal levels [31] to have activity against VRE, and has shown clinical efficacy against VRE [17, 30]. Nord and Heimdahl showed that administration of oral doxycycline for 7 days decreased the number of enterococci in the feces by 2–3 logs [31] but also led to a significant increase in doxycycline-resistant strains.

Doxycycline is also safe for use by patients with impaired renal function [32]. In our study the VREF strains from patients in the treated cohort were considered susceptible to both

agents, and with biliary levels of doxycycline of 10–20 times the serum levels and use of an oral bacitracin preparation at a concentration of 67,500 mg/mL, MICs for the VREF in the gut would have been greatly exceeded.

Our findings have demonstrated that oral bacitracin plus doxycycline reduced intestinal carriage of VREF, as demonstrated by the absence of detectable VREF in rectal swab specimens from all 15 patients at the end of a 2-week course of treatment. A corresponding decrease in quantitative enterococcal counts in stool of ~3 log/g was also observed at 2 weeks, and most patients had levels below the threshold of detection.

These findings taken into consideration alone would corroborate many of the findings previously described in reports of case series. However, when findings for patients were com-

Table 3. Results of quantitative stool cultures (cfu/g [wet weight] of stool) for vancomycin-resistant *Enterococcus faecium* (VREF) in the bacitracin-plus-doxycycline-treated cohort (*n* = 15)

Sampling day	No. of specimens	Mean ($\log_{10}$)	Median ($\log_{10}$)	Range ($\log_{10}$)
0	15	7.6	6.7	3–8.5
4–14	23	4.5*	ND	ND–5.6
15–30	13	7.8	ND	ND–8.6
31–49	9	7.5	7.5	ND–8.5

NOTE. ND = not detected. VREF was not detected in 19 (82.6%) of 23 samples from days 4–14; 8 (61.5%) of 13 samples from days 15–30; and 4 (44.4%) of 9 samples from days 31–49.

* $P < .001$ for comparison of day 4–14 mean colony counts, compared with baseline (day 0) counts, per Kruskal-Wallis test.

pared with those for a control group identified as VREF-positive at the same time and with similar underlying medical illnesses, at a follow-up of 4 months there was no difference, with 60% and 62.5%, respectively, still carrying VREF intermittently or persistently. Similarly, by actuarial analysis, the probability at 120 days of remaining a persistent or intermittent carrier was almost identical between the two groups (70.8% and 70.0%). In addition, after the therapy with bacitracin plus doxycycline was stopped, several patients demonstrated a dramatic relapse of VREF colonization in their stools, at levels equivalent to or higher than those noted before therapy. These observations suggest that significant numbers of VREF persist in the gastrointestinal tract, and when conditions become more favorable for growth, a return to pretreatment levels or higher occurs.

Whitman and colleagues [33], using a mouse model of VRE intestinal colonization, recently studied the effects of various antibiotics on the quantitative burden of VRE, and their observations were remarkably similar to our own. In animals who received streptomycin and vancomycin and were inoculated with 5×10^8 cfu of VRE, the fecal concentrations were significantly higher and the duration of carriage of VRE was significantly longer than in control animals. High fecal concentrations of VRE at 8–9 $\log_{10}$ cfu/g persisted up to day 22, which was the end of follow-up in this study.

Administration of ramoplanin in an attempt to eradicate carriage appeared successful during treatment and VREF was undetectable upon the completion of therapy, but relapse occurred in 100% (all eight) of the animals 7 days following the completion of that therapy. In our population of heavily antibiotic-treated patients with a relatively high burden of illness, antibiotic pressure and/or underlying medical illness likely allowed for the continued presence of VREF in the colon.

It is unclear whether the transient suppression of VREF during therapy with bacitracin and doxycycline is clinically useful. Treated patients who became noncarriers did so more rapidly than the controls ($P = .03$ at 15 days), but whether this translates to a significant improvement in control of patient-to-patient transmission by lowering the overall population burden of VREF is not known. Prospective randomized controlled trials would be necessary to provide a definitive assessment of the effect of oral eradication therapy on the duration of suppression and to determine whether there is any significant difference in the magnitude of ward-based transmission.

Several limitations must be considered in interpreting our results. While the patients were not randomized to treatment groups, the controls consisted of similar patients that were well matched for baseline demographic characteristics. Although specimen collection for quantitative stool cultures was not complete for six patients, follow-up with qualitative assessments was complete and prolonged, allowing the natural history of enteric VREF colonization in this population to be fully described.

It may be argued that the use of rectal swabs is not a sensitive means of detecting colonization [34, 35]. Patients who are considered to no longer be colonized may still harbor low levels of VREF not detected in rectal swabs. These patients could remain sources of further transmission, but what precautions are needed, if any, are unknown. At the time of the study the use of rectal swabs to identify carriers of VREF was recommended in the guidelines published by the HICPAC [6]. New acquisition of other VRE was considered very unlikely since strain typing [19] revealed that only a single clone was identified. Whether the use of these agents would have a greater chance of eradicating VREF at lower quantitative burdens of colonization is unknown, but this is considered unlikely on the basis of our findings. Finally, this population was characterized by significant associated medical illnesses and heavy antibiotic use; the results may not be generalizable to other populations.

In conclusion, oral bacitracin plus doxycycline was effective in suppressing the quantitative burden of VREF in the stool during treatment, but the effect was transitory. Use of this drug combination ultimately affected neither the burden nor the frequency of carriage of VREF. Other factors, including broad-spectrum antibiotic use and the frequency and duration of hospitalizations, may be more important determinants of VRE carriage.

An additional concern with the use of bacitracin plus doxycycline is the possible selection of further resistant strains from the enteric flora. It remains to be seen if this or similar protocols will have an overall impact on transmission rates of VRE during a nosocomial outbreak. For the individual patient with underlying renal disease, bacitracin and doxycycline do not seem to offer a benefit. Prospective randomized controlled trials will be necessary to provide a more definitive assessment of the impact of oral eradication regimens on gastrointestinal carriage in this and other patient populations. Our data, which are the first derived from a study employing a similar control group and prolonged follow-up, suggest a minimal benefit.

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