Outpatient vancomycin use and vancomycin-resistant enterococcal colonization in maintenance dialysis patients


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Background. Although outpatient vancomycin is widely used as empiric therapy for dialysis-associated infections, its relationship with vancomycin-resistant enterococcal (VRE) colonization is not established.

Methods. During a two-year prospective cohort study, rectal swabs obtained from patients at the start and finish of the study period and during interim hospitalizations were cultured for VRE.

Results. Ten of 124 patients initially grew VRE. Twenty-four of the remaining patients had no follow-up cultures because of patient death (62%), transfer to another dialysis facility (17%), patient’s refusal (7%), and transplantation (4%), and were thus excluded. The remaining patients (N = 90) had a median age of 54.3 years and were 92% African American and 50% male. Fifty-eight percent were treated by hemodialysis. They received 403 g of intravenous vancomycin over 157.2 patient-years of follow-up, 73% as outpatients. Sixteen of 90 patients (17.8%) became colonized with VRE, an incidence rate of one case per 9.8 patient-years of follow-up. None of the 29 patients who did not receive vancomycin developed VRE compared with 26% of those treated with vancomycin (P = 0.001). The odds ratio (95% CI) for the association of outpatient vancomycin (g per year) with VRE colonization was 1.23 (1.05, 1.44, P = 0.008). The association remained significant following adjustment in separate logistic regression analyses for relevant demographic, clinical, antimicrobial (inpatient vancomycin, oral or intravenous cephalosprins, aminoglycosides, quinolones, or anaerobics), and hospitalization exposures. The unadjusted relative risk of death in patients growing VRE was significantly higher than in those not colonized with VRE (P = 0.005).

Conclusions. VRE colonization is a relatively common and underrecognized problem among chronic dialysis patients. It is strongly and independently associated with the outpatient use of vancomycin, which should be avoided whenever possible.

METHODS

Study design

In December of 1996, we conducted a cross-sectional prevalence study of VRE colonization in our outpatient dialysis center, a freestanding unit located in East Baltimore (MD, USA). Using a standardized protocol, perirectal swabs (culturette; Becton Dickinson Microbiology system, Cockeysville, MD, USA) were obtained from all consenting patients and were cultured for VRE. Patients whose initial cultures did not grow VRE were entered into a cohort study and followed for up to a maximum of 25 months. During follow-up, patients hospitalized at the Johns Hopkins Hospital were also intermittently
cultured for VRE colonization, as part of routine hospital practice. Standard infection control measures in the dialysis unit included the use of universal precautions and the cleaning of all dialysis equipment and the dialysis chair between uses with 2% bleach solution. No specific procedures were in place for dialyzing patients with a history of VRE infection or colonization. In-hospital management included the use of gowns and gloves and the isolation or cohorting of known VRE colonized or infected patients. These infection control measures were unchanged over the period of the study. At the end of the study period (December 1998), we conducted a second cross-sectional prevalence study of VRE rectal colonization in all surviving cohort members.

Outcome ascertainment

Patients were defined as being colonized with VRE only if a cultured rectal swab grew VRE without clinical infection. Rectal swabs were cultured using an identical technique throughout the study period. In brief, specimens were plated on agar appropriate for each body site and on selective trypticase soy agar media containing 5% sheep’s blood, 10 μg/mL vancomycin, and 8 μg/mL gentamicin. Colonies consistent with enterococcus, which hydrolyze PYR and were gram positive, were speciated using motility, pigment production, and 10% lactose tests. Final speciation occurred according the scheme of Facklam and Collins [19]. Vancomycin susceptibility was tested using agar dilution technique and concentrations of vancomycin of 1, 2, 4, 16, and 64 μg/mL. If the organism had a minimal inhibitory concentration (MIC) of greater than 16 but less than 64, the E test was used to confirm according to the National Committee for Clinical Laboratory Standards [20].

Exposure assessment

Baseline demographic information and clinical characteristics of the participating subjects were abstracted from the patients’ medical records. The dose of vancomycin, as well as any additional antibiotics, administered or prescribed in the dialysis unit was obtained from dialysis unit records. These antibiotics were prescribed according to the discretion of the attending physician and without use of standing orders. In-patient antibiotic use was obtained from the hospital’s pharmacy record, and details regarding the in-patient hospital stay and intensive care unit admissions were obtained from the Johns Hopkins Hospital case-mix database, a database that records the duration and location of patients’ stay in the hospital. Information on orally prescribed antibiotics was checked by cross-referencing data from the hospital outpatient pharmacy. As this pharmacy delivers medicine directly to the dialysis unit, it is widely, although not exclusively, used by our dialysis patients.

Exposure data were obtained for all patients from the time of study entry (December 1996) until the time of their first positive VRE rectal culture or until the last recorded negative culture either at the end of the study or prior to the subject exiting the cohort. Patients exited the cohort prior to study’s termination due to transplantation, transfer to another dialysis unit, or patient death. Patients who had no repeat rectal culture during the course of the study and whose follow-up VRE status was thus unknown were, by necessity, excluded from the primary analysis. Patients who had a positive VRE rectal swab obtained within 48 hours of hospitalization were assumed to have had VRE colonization prior to hospitalization and did not have this last hospitalization counted among their exposure data. As the duration of follow-up was different for different subjects, exposure data were expressed in terms of a subject’s average exposure per year.

Primary analysis

In the primary analysis, the effects of vancomycin administered in the chronic dialysis unit were studied separately from that administered within the hospital. The influence of topical antimicrobial preparations and of prophylactic use of cotrimoxazole among HIV patients—on which we had incomplete data—was not examined. A subgroup analysis was, however, performed excluding HIV seropositive patients.

Statistical methods

Outlying values for the distribution of each variable were identified using boxplots, and their validity was checked against the original clinical record. The VRE-positive and -negative groups were compared using the Mann-Whitney U test for continuous and the Fisher’s exact test for categorical data. The association of outpatient vancomycin use with the development of VRE was examined using unconditional logistic regression. The influence of individual potential confounders was examined, one at a time, in separate logistic regression analyses. Because of the limited available sample size, more extensive regression modeling was not attempted. Patient survival was examined using the Kaplan–Meier method and compared using the log rank test. Patients were censored at the time of transplantation or at loss to follow-up. For all analyses, a type I error rate of 0.05 was used. Statistical analysis was performed using SPSS software, version 7.5 (Chicago, IL, USA).

RESULTS

One hundred twenty-four of the 147 patients (84.4%) attending our dialysis unit in December 1996 agreed to participate in the study. Seventy-four patients were treated with hemodialysis and the remaining 50 with peritoneal dialysis. Ten of the 124 (8%) patients were
colonized with VRE when initially cultured (1996) and are not entered into the follow-up cohort. This result was perceived as being similar to that reported by others [3, 15–18] and did not lead to any formal change in the use of vancomycin in our unit. Twenty-four of the remaining patients initially without VRE were not analyzable, as they had no subsequent VRE culture, and thus their follow-up VRE status was unknown. One patient underwent renal transplantation. Four transferred to another dialysis unit, and 15 died before the VRE screen at the end of the study. An additional four patients remained within the cohort but declined to undergo repeat VRE screening at the end of follow-up. In comparison to the analyzable group, these 24 patients were older (P = 0.03) and were more likely to be Caucasian (P = 0.003).

### VRE incidence rate

The 90 analyzable patients contributed a total of 157.2 years of follow-up, with a mean duration of follow-up per subject of 1.75 years. Sixteen incident cases of VRE rectal colonization were detected over the course of the study, an incidence rate of 1 case per 9.83 patient years of follow-up.

Of the 90 patients, only 70 patients underwent repeat VRE screening at the end of the study, of whom 6 patients (8.6%) grew VRE. Two of these patients had their VRE status established previously during prior hospitalizations; however, the VRE colonization status of the remaining four subjects had been unknown to the dialysis staff.

### Determinants of VRE colonization

The 90 patients received a total of 403 g of intravenous vancomycin, 73% of which was administered in the outpatient dialysis unit. There was no significant difference in the baseline demographic characteristics, the proportion of patients with HIV infection, or diabetes between patients who grew and did not grow VRE (Table 1). The two groups’ antibiotics and hospitalization exposure are compared in Table 2. Of the 29 patients who did not receive vancomycin, none became colonized with VRE, whereas 26% of patients who received at least one dose of vancomycin developed VRE during the course of the study (P = 0.001). The median outpatient vancomycin exposure was 3.3 g per year higher among the VRE-colonized group than among those not colonized with VRE (P = 0.002). The VRE-colonized group also had significantly greater exposures to inpatient vancomycin, aminoglycosides, anaerobic antimicrobial agents, hospital admissions, duration of in-hospital stay, and intensive care unit admissions.

Using logistic regression, outpatient vancomycin (g per year) was significantly associated with the development of VRE with an odds ratio (95% CI) of 1.23 (1.05, 1.44). This association remained significant following adjustment in separate analyses for the main potential confounders, as shown in Table 3. This odds ratio for the association between outpatient vancomycin use and VRE colonization was reduced in only three of these analyses, as compared with the unadjusted odds ratio (1.23). In each case, however, outpatient vancomycin continued to exert a significant and independent effect. Adjustment for the other potential confounders resulted in either no effect or a slight increase in this odds ratio. When outpatient vancomycin was simultaneously adjusted for average duration of hospital stay and either inpatient vancomycin dose or number of hospitalizations, the association between outpatient vancomycin (g per year) and VRE colonization continued to be significant, with an odds ratio of 1.29 (1.07, 1.57, P = 0.007) and 1.22 (1.03, 1.45, P = 0.02), respectively. More extensive regression modeling was not undertaken because of the small number of available cases (N = 16). Repeat analyses using combined inpatient and outpatient vancomycin dose and a subgroup analysis excluding HIV seropositive subjects revealed similar significant results as that of the primary analysis (data not shown).

### Clinical VRE infection

Over the course of follow-up, 6 out of 16 (37.5%) VRE colonized patients developed an overt infection related to VRE, including one surgical site infection, one urinary tract infection, one episode of peritonitis, and three cases of VRE bacteremia, confirmed in at least two blood culture bottles. Ten of the 90 patients (11.0%), whose follow-up VRE status was known died over the course of the study. Six deaths occurred among the 74 patients (8.0%) who did not grow VRE, 4 among the 16 patients (25%) who grew VRE, including 2 of the 3 bacteremic patients. Survival in the VRE colonized group was significantly worse than for the noncolonized group (P = 0.005; Fig. 1).
Table 2. Comparison of number of subjects (%) exposed and median (range) yearly level of exposure for VRE-colonized and VRE non-colonized groups

<table>
<thead>
<tr>
<th>Colonized with VRE (N = 16)</th>
<th>Non-colonized with VRE (N = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) exposed</td>
<td>Median (range) in those exposed</td>
</tr>
<tr>
<td>N (%) exposed</td>
<td>Median (range) in those exposed</td>
</tr>
<tr>
<td>P*</td>
<td></td>
</tr>
<tr>
<td>Average total vancomycin g/year</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Average inpatient vancomycin g/year</td>
<td>14 (88)</td>
</tr>
<tr>
<td>Average outpatient vancomycin g/year</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Average total aminoglycoside mg/year</td>
<td>15 (93.8)</td>
</tr>
<tr>
<td>Average 3rd generation cephalosporins g/year</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Average 1st &amp; 2nd generation cephalosporins g/year</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Average total ciprofloxacin g/year</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Average total anti-anaerobics g/year</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Average number of hospitalizations per year</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Average duration of hospital stay per year</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Average number of ICU admissions per year</td>
<td>16 (100)</td>
</tr>
</tbody>
</table>

NS is not significant.

*For comparison of median yearly exposure between all subjects in both groups

Table 3. Odds ratio (95% CI) for the association of outpatient vancomycin use with VRE-colonization, both unadjusted and adjusted in separate analyses for the major demographic, clinical, antimicrobial and hospitalization exposures

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>P value*</th>
<th>−2 Log likelihood for specified model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Demographic and clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.24 (1.05, 1.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted for gender</td>
<td>1.27 (1.07, 1.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted for race</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for dialysis modality</td>
<td>1.26 (1.07, 1.49)</td>
<td>0.006</td>
</tr>
<tr>
<td>Adjusted for duration of dialysis</td>
<td>1.23 (1.05, 1.43)</td>
<td>0.009</td>
</tr>
<tr>
<td>Adjusted for diabetes mellitus</td>
<td>1.27 (1.06, 1.50)</td>
<td>0.007</td>
</tr>
<tr>
<td>Adjusted for HIV seropositive</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.009</td>
</tr>
<tr>
<td>Antimicrobial data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for average in-patient vancomycin g/year</td>
<td>1.21 (1.04, 1.40)</td>
<td>0.013</td>
</tr>
<tr>
<td>Adjusted for average total aminoglycoside mg/year</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted for average 3rd generation cephalosporins g/year</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted for average 1st &amp; 2nd generation cephalosporins g/year</td>
<td>1.23 (1.05, 1.43)</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted for average ciprofloxacin g/year</td>
<td>1.23 (1.05, 1.44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospitalization data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for average duration of hospital stay days per year</td>
<td>1.21 (1.03, 1.41)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for average number of hospitalizations per year</td>
<td>1.19 (1.03, 1.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for average number of ICU admissions per year</td>
<td>1.26 (1.07, 1.48)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ICU is intensive care unit.

*P value for association of out-patient vancomycin use with VRE colonization post-adjustment for specified variable

DISCUSSION

Our study is the first, to our knowledge, to define the incidence of detectable VRE colonization in a cohort of outpatient dialysis subjects. In both our 1996 and 1998 prevalence studies, we found comparable prevalence ratios (8 and 8.5%) to that described in other cross-sectional studies. However, the calculated incidence ratio per year was higher than either of these two point prevalence estimates. In keeping with this observation, we detected a decreased survival in the VRE colonized as compared with the noncolonized subjects; however, in this data set we cannot determine whether this association is in any way causal in nature.

In the 11 years since it was first described, VRE has become a global health concern [21]. The excretion of VRE has been shown to dramatically increase following exposure to vancomycin [22]. The unrestricted and rapid increase in the use of vancomycin over the last two decades has been implicated in the rapid spread of VRE. In one center, the amount of vancomycin prescribed increased 20-fold in the period between 1981 and 1991 [23]. The Centers for Disease Control and Prevention has specifically advised that vancomycin should not be used for prophylactic or empiric therapy or for reasons of dosing convenience when alternative treatment options are available. In response, the Ad Hoc Committee on
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Fig. 1. Survival of vancomycin resistant enterococcal (VRE)-colonized (solid line) and noncolonized (dashed line) subjects from time of study entry ($P < 0.01$).

the Treatment of Peritonitis in 1996 changed its recommendations regarding the empiric treatment of peritonitis. Many nephrologists, however, have failed to adopt these recommendations. In part, this is because of limited alternatives in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections and in part because much of the literature to date regarding VRE colonization has been based on patients hospitalized in intensive care units or oncology centers [24], and the applicability of these studies to the outpatient dialysis setting is uncertain.

Several studies to date have examined the prevalence of VRE in dialysis populations [2, 3, 15, 17, 18] and have been perceived as offering reassurance that the continued widespread use of vancomycin in these patients has not been associated with increased rates of developing VRE. More recently, Roghmann et al studied 168 dialysis patients and found a VRE prevalence of 9.5% [15]. However, the cross-sectional nature of these studies leads them to be susceptible to incidence-prevalence bias [25]. That is, if VRE infection is associated with decreased survival, then a high incidence rate will not necessarily result in a high prevalence rate. Thus, cross-sectional study designs offer little actual reassurance regarding the effect of dialysis-associated antibiotic practices on the risk of developing VRE.

This high incidence rate for developing VRE raises the possibility that practices within dialysis units may be a major driving force in the development and spread of VRE, especially given the relatively better survival of dialysis patients as compared with many intensive care unit patients. Our study confirms the significant contribution of outpatient vancomycin use in the development of this high incidence rate. Other factors, including infec-

tion-control practices both within the dialysis unit and hospital and the degree of patient comorbidity, also undoubtedly influence the background incidence of VRE, although an analysis of these influences was beyond the scope of our study. The potential influence of dialysis practices on the development of VRE is consistent with the observations that one of the first reported outbreaks of VRE in 1988 occurred in a dialysis unit [16], that in one study in a single year, from 1995 to 1996, the percentage of American hemodialysis facilities reporting treatment of VRE colonized patients jumped from 17 to 21% [26], and that chronic dialysis patients represented 12 to 22% of cases of VRE in three large, separate hospital-based studies [26]. Finally, the observation that five of the seven recently described patients infected with S. aureus with intermediate susceptibility to vancomycin were supported on chronic dialysis [9-14] suggests that these patients are at a high risk of developing resistant organisms, including those more virulent than enterococci. In addition, considering that only two of the six patients in our cohort who were colonized with VRE in the follow-up 1998 prevalence study had their VRE status previously known to the dialysis staff suggests that the effective surveillance of VRE carriage may require formal regular screening programs, as are routinely conducted in other high-risk areas such as in intensive care units [4].

We demonstrate a clinically and statistically significant independent association between outpatient vancomycin use and the development of VRE, a finding in agreement with several studies examining the determinants of VRE infection in hospitalized patients [21, 24, 27-30]. These data clearly call into question the long-term safety of the ongoing widespread use of vancomycin in dialysis patients. They further underscore the need to reduce the incidence of dialysis-associated infections, such as by decreasing the use of hemodialysis catheters [31], and the development of alternative effective antimicrobials for the treatment of MRSA. In situations in which there is high background prevalence of MRSA, the initial use of empiric vancomycin therapy for suspected infections may be warranted. However, confirmation of a methicillin-susceptible organism should prompt the rapid conversion to an alternative antimicrobial regimen. In hemodialysis, cefazolin when administered postdialysis has been shown to maintain therapeutic levels for up to 72 hours and thus avoid the need for supplemental dosing between dialysis sessions [32]. The efficacy of cefazolin in peritoneal dialysis patients is, however, less clear [1, 2, 33].

Several important limitations exist regarding our current study. Twenty-one percent of our original study cohort was excluded because a follow-up VRE surveillance culture was not available. The ascertainment of VRE status during the study was not uniform, being dependent on screening performed during hospitaliza-
tions. This may have potentially introduced a bias associating VRE with hospitalization. However, it would not explain an association with the outpatient use of vancomycin, which in the majority of cases does not lead to hospitalization. While our ascertainment of outpatient vancomycin use is likely to be complete, as this was exclusively used in the dialysis unit, we are unlikely to have complete exposure information on several potential risk factors. In-hospital information was only available for patients hospitalized at Johns Hopkins Hospital; however, as our dialysis unit is situated adjacent to Johns Hopkins Hospital and serves a local and largely uninsured population, it is therefore the primary care facility for these patients. In a survey conducted in 1997, we found that over 90% of our dialysis patients were either hospitalized directly to Johns Hopkins Hospital or were subsequently transferred there following admission to another facility (Brigitte Sullivan, personal communication). We have, however, no reason to believe that incomplete ascertainment of the previously mentioned variables should have introduced a bias leading to a spurious association with the outpatient use of vancomycin. Although our study shows a strong independent association between outpatient vancomycin and VRE colonization, due to its observational nature, it is clearly unable to prove that the demonstrated association is causative in nature.

In conclusion, we demonstrate a high incidence of VRE among chronic dialysis subjects. There is a strong, statistically significant and independent effect of outpatient vancomycin use on the development of VRE. Pending further results from larger prospective studies, we believe that, in keeping with suggested recommendations [4, 5], the outpatient use of vancomycin in the chronic dialysis setting should be avoided whenever possible. Further research is urgently required in order to examine and develop alternative regimens for the empiric treatment of suspected dialysis-associated infections. The role and optimal method of screening for VRE in dialysis patients also needs to be examined. Finally, the frequency with which cross-infection of VRE occurs within the dialysis unit requires investigation. To date there are no specific guidelines on the management of VRE-colonized dialysis patients or formal recommendations regarding infection control management of such patients in the setting of a dialysis unit. Limiting the spread of VRE represents a major challenge facing the dialysis community; however, it is clearly essential in order to safeguard both the public health and the health of patients treated by long-term maintenance dialysis.

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