MAJOR ARTICLE

Changes in the Prevalence of Vancomycin-Resistant Enterococci in Response to Antimicrobial Formulary Interventions: Impact of Progressive Restrictions on Use of Vancomycin and Third-Generation Cephalosporins

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This study sought to assess the impact of restricting use of vancomycin and third-generation cephalosporins on vancomycin-resistant enterococci (VRE) prevalence. All clinical enterococcal isolates identified at a large academic medical center during a 10-year period were analyzed. Changes in VRE prevalence after sequential restrictions on use of vancomycin and third-generation cephalosporins were evaluated. The correlation between antibiotic use and VRE prevalence was also investigated. Vancomycin use initially decreased by 23.9% but returned to preintervention levels by the end of the study. Third-generation cephalosporin use decreased by 85.8%. However, VRE prevalence increased steadily from 17.4% to 29.6% during the 10-year period ($P < .001$). Clindamycin use was significantly correlated with VRE prevalence. Restricting the use of vancomycin and third-generations cephalosporins had little impact on VRE prevalence. The association between clindamycin use and the prevalence of VRE suggests that restriction of this and perhaps other antianaerobic agents might be an important component of future antimicrobial interventions.

The incidence of nosocomial enterococcal infections has increased markedly in the past 20 years [1], with enterococcal infections currently accounting for >10% of nosocomial bloodstream infections [2]. Furthermore, enterococcal bacteremia has been associated with an attributable mortality of >30% and an additional length of hospital stay of 39 days [2, 3]. The impact of these multidrug-resistant pathogens has been intensified by the emergence of vancomycin-resistant enterococci (VRE). First described in 1988 [4], VRE currently account for 20%–25% of all nosocomial enterococcal isolates [5] and are associated with increased mortality rates, length of hospital stay, and hospital cost compared with their vancomycin-susceptible counterparts [6, 7].

The most commonly identified modifiable risk factor for VRE infection is prior antibiotic use, particularly the use of vancomycin and third-generation cephalosporins [8–12]. However, the few studies that have eval-

Received 1 July 2002; accepted 6 November 2002; electronically published 24 January 2003.

Presented in part: 39th Annual Meeting of the Infectious Diseases Society of America, San Francisco, CA, 27 October 2001.

Financial support: Public Health Service (grant DK-02987-01) of the National Institutes of Health (to E.L.). This study was also supported in part by an Agency for Healthcare Research and Quality Centers for Education and Research on Therapeutics cooperative agreement (U18-HS10399).

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Clinical Infectious Diseases 2003; 36:440–6

1058-4838/2003/3604-0008$15.00

uated the impact of restricting use of these antibiotics on VRE prevalence have reported conflicting results [13–16]. Limitations of these studies have included short follow-up periods, concurrent implementation of both antimicrobial restriction interventions and enhanced infection control initiatives, and a focus only on certain patient populations or specific hospital units.

We undertook the current study to evaluate the specific impact of sequential and progressive restrictions of the use of vancomycin and third-generation cephalosporins, without concomitant aggressive infection-control interventions, on the prevalence of VRE among inpatient clinical enterococcal isolates over a 10-year period. In addition, we conducted an ecological study to identify correlations between annual hospitalwide use of specific antibiotics or antibiotic classes and the yearly VRE prevalence.

PATIENTS AND METHODS

This study was conducted at the Hospital of the University of Pennsylvania (HUP), a 725-bed academic quaternary care medical center in Philadelphia. In response to the increasing prevalence of VRE at our institution, sequential alterations in the hospital antimicrobial formulary were instituted. These interventions were implemented under the auspices of the hospital's antimicrobial management program (AMP), a program described elsewhere [17].

Beginning in 1994, a series of antimicrobial interventions were implemented to limit the emergence of VRE (table 1). On the basis of the demonstrated association between vancomycin use and the development of VRE [8], use of vancomycin for >72 h required approval of the AMP beginning on 7 February 1994. A subsequent study conducted at our institution demonstrated a continued strong relationship between vancomycin use and development of VRE even after the initial 72-h restriction for vancomycin [9]. Thus, vancomycin use was fully restricted, with all use requiring AMP approval, beginning on 15 February 1996.

Two years later, we restricted the use of third-generation cephalosporins. These changes were made in response to reports demonstrating an association between use of such agents and emergence of VRE [10, 18], as well as the recent emergence at our institution of organisms demonstrating extended-spectrum β-lactamase resistance [19]. On 1 October 1997, we restricted the use of ceftriaxone with few exceptions (e.g., empirical treatment of suspected bacterial meningitis). In place of ceftriaxone, the use of ampicillin-sulbactam, with or without gentamicin, was recommended. Finally, on 16 February 1998, ceftazidime was replaced with cefepime. No other specific antimicrobial class restrictions or substitutions occurred during the study period.

Table 1. Antimicrobial formulary restrictions at the Hospital of the University of Pennsylvania, 1991–2001.

		Antimicrobial formulary interventions	
Period	Inclusive dates	Vancomycin	Third-generation cephalosporins
1	1991–1993	No restriction	No restriction
2	1994–1995	Use for >72 h requires approval	No restriction
3	1996–1997	All use requires approval	No restriction
4	1998–2000	All use requires approval	Full restriction

To permit comparison with antimicrobial susceptibility data, which are calculated on an annual basis, the precise dates of implementation of antimicrobial interventions were approximated to the nearest year. Interventions that occurred in February were considered to have occurred on the preceding 1 January of the same year. Interventions that occurred in October were considered to have taken place on the following 1 January. Antimicrobial use was calculated as defined daily doses (DDD) per 1000 patient-days.

All clinical enterococcal isolates recovered during the study period (1991–2000) were included in this study. Isolates were categorized according to the year of collection and the anatomic site of infection (i.e., blood, nonurine, and urine). It is of note that the categories for anatomic site of infection were mutually exclusive. Enterococcal isolates were further divided into 4 distinct time periods, on the basis of which agent was restricted (i.e., vancomycin or third-generation cephalosporins), as well as on the level of antimicrobial restriction (i.e., no restriction, 72-h restriction, or full restriction; table 1).

The prevalence of VRE was calculated as the percentage of all enterococcal isolates identified in the clinical microbiology laboratory that demonstrated resistance to vancomycin. This percentage was calculated as an annual percentage and as a composite percentage for each of the 4 time periods of the study, to reflect the mean prevalence of VRE during a given study period. If multiple isolates from the same anatomic site were recovered during a single patient admission, only the first isolate was included.

We investigated whether there was a correlation between the annual hospitalwide use of certain antibiotics (described in DDD per 1000 patient-days) and the yearly prevalence of VRE. The specific antimicrobial agents investigated were vancomycin, third-generation cephalosporins (i.e., ceftazidime and ceftriaxone), cefepime, fluoroquinolones (i.e., ciprofloxacin, ofloxacin, and levofloxacin), β-lactam/β-lactamase inhibitors (i.e., ampicillin-sulbactam, amoxicillin-clavulanate, and ticarcillin-clavulanate), nafcillin, carbapenems (i.e., imipenem and meropenem), clindamycin, and metronidazole. We did not include chloramphenicol because this agent is commonly used at our institution to treat VRE infection [20].

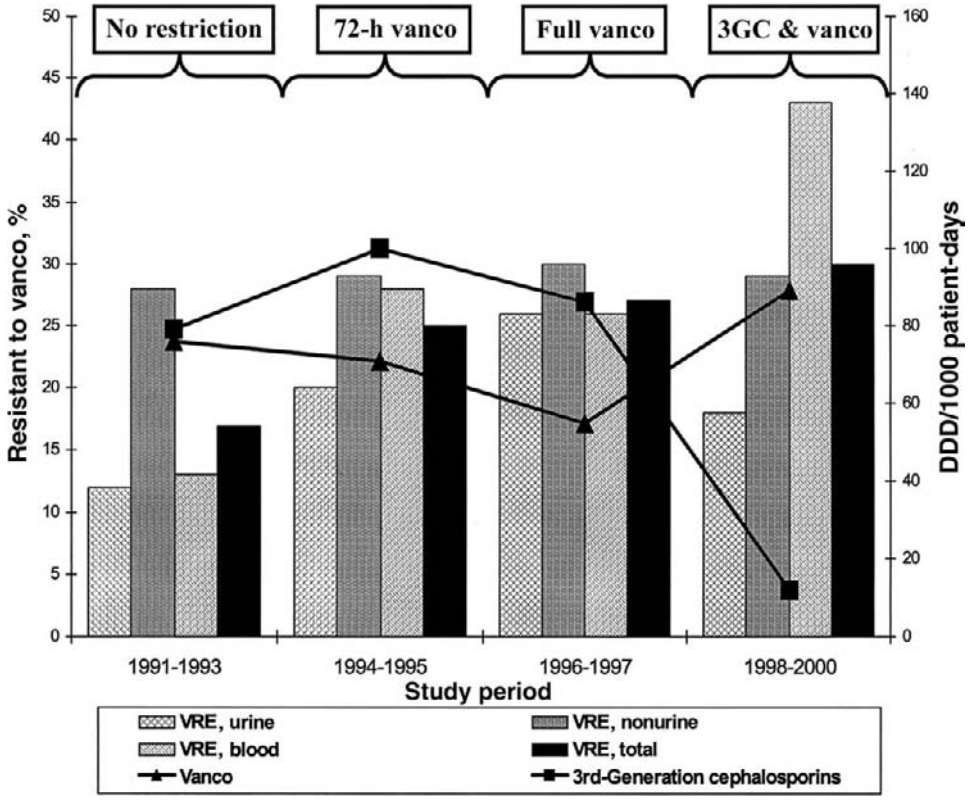

Figure 1. Changes in vancomycin-resistant enterococci (VRE) prevalence associated with antimicrobial formulary interventions. 3GC, third-generation cephalosporin; vanco, vancomycin.

All clinical specimens at the HUP are processed and cultured in a central clinical microbiology laboratory. Enterococci were identified to genus level by use of conventional methods [21]. Antimicrobial susceptibilities were determined according to established criteria [22]. Before May 1995, the VITEK system (bioMérieux) was the primary method of susceptibility testing. After this time, the laboratory changed to Microscan conventional panels that were read with use of the MicroScan Walkaway (Dade Behring). In addition to the semiautomated susceptibility systems, vancomycin resistance was detected with use of BBL vancomycin screen agar (6 μg/mL), and high-level aminoglycoside susceptibility was determined with use of the BBL enterococcus screen agar quad plates (Becton Dickinson Microbiology Systems). Enterococci are not routinely identified to the species level at our institution. However, in a 1993 survey of 101 enterococcal isolates, 91 were *Enterococcus faecium,* 7 were *Enterococcus faecalis,* and 3 were *Enterococcus gallinarum* (Irving Nachamkin, personal communication).

Proportions were compared with use of a χ^2 test of binomial proportions. To evaluate the trend in the proportion of positive tests over time, the Cochran-Armitage trend test (χ^2 test for trend) was performed [23]. A Spearman rank correlation coefficient was calculated to evaluate the relationship between antimicrobial use and VRE prevalence. A significance level of .05 (2-sided) was used for all tests. Statistical analyses were performed with use of standard programs in STATA, version 6.0 (Stata), and StatXact, version 4.0 (Cytel Software).

RESULTS

Vancomycin resistance in an enterococcal isolate was first noted at HUP in September 1991. At that time, a policy was instituted mandating full contact precautions for all patients for whom VRE was isolated from a clinical specimen. Patients noted to be colonized or infected with VRE were treated under contact precautions throughout their hospitalization, and if they were readmitted to the hospital within the next year, they were again placed under contact precautions. No changes in this policy have occurred since that time. It is of note that there is no active surveillance program to identify patients who were colonized with VRE. Furthermore, no changes in the guidelines pertaining to the practice of obtaining clinical cultures were implemented during the study period. Finally, there were no significant differences in the mean monthly patient census across all years of the study ($P = .44$; determined with the Kruskal-Wallis test)

During the 10-year study period, 8241 enterococcal isolates were identified by the clinical microbiology laboratory. These

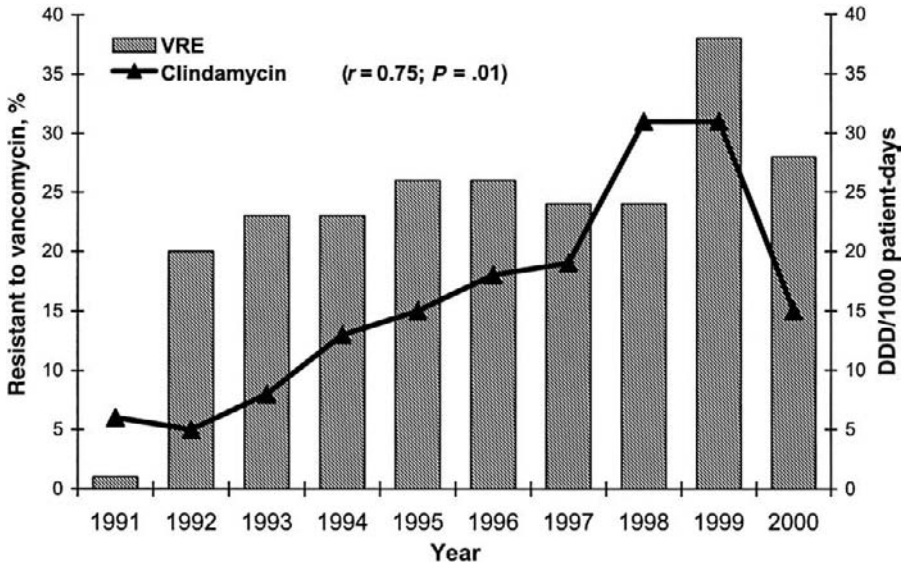

Figure 2. Correlation of antibiotic use with vancomycin-resistant enterococci (VRE) prevalence

included 3585 urinary isolates (43.5%), 3257 nonurinary isolates (39.5%), and 1399 blood isolates (17.0%). The mean annual number of enterococcal isolates tested increased steadily during the first 3 time periods but decreased in the final study period (596 isolates per year in 1991–1993, 959 isolates per year in 1994–1995, 1095 isolates per year in 1996–1997, and 886 isolates per year in 1998–2000). During the entire study period, 2074 (25.2%) of 8241 enterococcal isolates demonstrated vancomycin resistance.

Compared with the first study period (1991–1993), vancomycin use in the second study period (1994–1995) decreased by 8.1% (figure 1). In the third study period (1996–1997), vancomycin use decreased by 26.3% compared with study period 1 and by 23.9% compared with study periods 1 and 2 combined. During the final study period (1998–2000), vancomycin use again increased, exceeding the rate of use in study period 1 by 15.5%. In study period 4, use of third-generation cephalosporins decreased by 85.7% compared with study period 3, and it decreased by 85.8% compared with study periods 1–3 combined.

Despite restrictions on the use of vancomycin and third-generation cephalosporins, the overall prevalence of VRE increased steadily throughout the decade ($P < .001$; detected with the χ^2 test for trend; figure 1). The temporal changes in VRE prevalence differed somewhat by anatomic site of isolation (figure 1). Significant increases in VRE prevalence were noted for enterococcal bloodstream and urine isolates, but not for nonurine isolates ($P < .001$, $P < .001$, and $P = .754$, respectively; detected with the χ^2 test for trend; figure 1). The percentage of enterococci that demonstrated resistance to vancomycin increased from 17.4% to 25.0% from period 1 to period 2 ($P < .001$), from 25.0% to 26.9% from period 2 to period 3 ($P = .163$), and from 26.9% to 29.6% from period 3 to period 4 ($P = .051$; figure 1).

We subsequently investigated whether there was a correlation between the annual rate of hospital use (described in DDD per 1000 patient-days) of specific antibiotics or antibiotic classes and yearly VRE prevalence during the 10-year period (figure 2). Of 12 agents evaluated, only the use of clindamycin ($r = 0.75$; $P = .01$) was significantly correlated with VRE prevalence. We then examined the correlation between annual antibiotic use and VRE prevalence for specific anatomic sites. For urine enterococcal isolates, clindamycin was again associated with VRE prevalence ($r = 0.88$; $P = .001$). Similarly, for blood enterococcal isolates, use of clindamycin was associated with VRE prevalence ($r = 0.86$; $P = .002$). There was also a borderline significant association between VRE prevalence and fluoroquinolone use ($r = 0.61$; $P = .07$) in enterococcal blood isolates. Finally, there was no significant correlation between use of any of the evaluated agents and VRE prevalence in nonurine enterococcal isolates.

DISCUSSION

In this 10-year study, we examined the impact of sequential and progressive restrictions of the use of vancomycin and third-generation cephalosporins on VRE prevalence in inpatient clinical enterococcal isolates. Although vancomycin use initially decreased by >25%, use of this agent again increased to pre-intervention levels by the conclusion of the study. Use of third-generation cephalosporins decreased by >85% in response to the interventions. Despite these interventions, the prevalence of VRE increased steadily throughout the study. The only an-

tibiotic with an annual use rate that significantly correlated with VRE prevalence was clindamycin.

Antimicrobial interventions designed to address the emergence of VRE must be based on data regarding the epidemiology of this pathogen. Most studies examining the epidemiology of VRE, including one conducted at our institution, have noted vancomycin and cephalosporin use to be risk factors for development of VRE [8–11]. Furthermore, a recent ecologic study conducted at 126 intensive care units noted that vancomycin and third-generation cephalosporin use were the only independent risk factors for development of VRE [12].

Although these data suggest that decreasing use of these agents could reduce VRE prevalence, the results of such interventions have been mixed. Morris noted that, despite a 59% and 85% decrease in parenteral and oral vancomycin use, respectively, the point prevalence of fecal colonization with VRE 6 months after the intervention was unchanged [14]. Another study assessed fecal colonization with VRE in patients in "high-risk" wards who were receiving antibiotics after an intervention, including enhanced infection control and a reduction in vancomycin use of 47% [15]. The monthly number of VRE isolates recovered in the 5 months after the initiative decreased from 30 to 4.

In a study conducted at a Veterans Affairs Medical Center, use of vancomycin, ceftazidime, cefotaxime, and clindamycin decreased by 34%, 55%, 84%, and 80%, respectively, although use of gowns for VRE-colonized patients was also implemented [13]. Six months after implementation of these interventions, the point prevalence of fecal colonization with VRE decreased from 47% to 15%. Finally, a study of VRE prevalence from an 11-room oncology unit evaluated a multifaceted intervention, including performance of surveillance cultures, patient and nursing staff cohorting, use of gowns and gloves, and review of antibiotic use by an infectious diseases physician [16]. Use of vancomycin, ceftazidime, ciprofloxacin, imipenem, aztreonam, and gentamicin decreased significantly, and clindamycin use significantly increased. After the intervention, bloodstream infections with VRE and VRE colonization among patients in the unit decreased significantly.

Although some studies have demonstrated a decrease in VRE prevalence, others (including ours) have not. Several reasons for these discrepant results may exist. First, several reports that have demonstrated successful reductions in VRE prevalence involved only a small subset of the hospitalized population [15, 16], for whom stricter control of antimicrobial use may be possible. Second, the duration of follow-up after interventions has been limited in most previous studies, ranging from $\leq$6 months [13–15] to 1 year [16]. Long-term effectiveness in reducing VRE prevalence must be demonstrated for an approach to be considered successful.

Third, restriction of >1 antimicrobial agent may be necessary. Although vancomycin has most often been associated with the development of VRE, other agents, such as cephalosporins and antianaerobic drugs, have also been linked to the emergence of these pathogens [10, 11, 24, 25]. Indeed, although current guidelines appropriately emphasize the prudent use of vancomycin in addressing the spread of VRE, the evaluation of use of other antibiotics is not emphasized [26].

A final possible explanation for the discrepant results of these studies is that many interventions included an aggressive infection-control component (e.g., ongoing fecal surveillance and cohorting) [13, 15, 16]. Whether the reductions in VRE prevalence were due to enhanced infection-control interventions or to antibiotic use interventions are thus unclear. Although some studies have demonstrated success in limiting VRE prevalence simply with use of infection-control precautions [27, 28], these successes have generally been limited to small outbreaks of infection that were identified early, with early intervention. It is of note that a recent study reported significantly decreased VRE colonization rates in multiple health care facilities in a specific region after the implementation of an active infection-control intervention shortly after initial recognition of the emergence of VRE infection in these settings [29]. However, other reports have failed to demonstrate any success associated with infection-control precautions alone [18, 30]. One possible implication of our results and of the compiled results of others is that, although the respective contributions of infection-control interventions and antibiotic use interventions may be difficult to quantify, optimal response in VRE prevalence may require a comprehensive component of both types of interventions.

In exploring whether consideration should be given to restricting the use of additional agents, we found a significant association between the development of VRE and use of clindamycin. This association is supported by past studies that have also demonstrated an association between antianaerobic agents and the development of VRE [24, 25]. In evaluating whether restricting the use of clindamycin might be effective in limiting emergence of VRE, it should be noted that, of 2 studies that demonstrated decreases in VRE prevalence, one noted a significant reduction in clindamycin use [13] and the other noted a significant increase in use of this agent [16].

Despite a comprehensive antimicrobial-management program, we were only able to transiently reduce vancomycin use by ~25%. It may be that vancomycin use needs to be reduced further to significantly reduce VRE prevalence. Indeed, an evaluation of vancomycin use performed at our institution in the year after the 72-h restriction of vancomycin noted that approximately one-third of vancomycin courses did not meet current guidelines [31].

One obstacle to reducing vancomycin use dramatically is that this agent remains the drug of choice in many clinical settings.

The breadth of antibiotics available to treat gram-negative infections (e.g., third-generation cephalosporins, fluoroquinolones, and carbapenems) more easily allows class substitution in response to emerging resistance patterns. However, given the few alternative agents with broad gram-positive activity, it is likely that there is a threshold level of vancomycin use below which it would be difficult to descend. This is evidenced both in our results as well as those of others who noted much more substantial reductions in the use of third-generation cephalosporins than in vancomycin use [13].

Further reductions in vancomycin use might be possible if one were to consider expanded use of newer agents with gram-positive activity (i.e., quinupristin-dalfopristin, and linezolid). Expanded use of these agents, however, would be limited by increased cost [32, 33], increased exposure to possible adverse events [34, 35], and the potential for increased emergence of resistance to these agents [36, 37].

There were several potential limitations to our study. First, although all enterococci identified were recovered from inpatients, we did not distinguish between nosocomial and community-acquired isolates. Such a distinction might be important, because any changes in antimicrobial use patterns would only affect nosocomially acquired VRE. It is of note that a previous study at our institution revealed that 81.9% of vancomycin-susceptible enterococci and 94.4% of VRE isolates were nosocomially acquired [9]. Second, we calculated the prevalence of VRE only on the basis of clinical isolates. Because the rate of VRE colonization may greatly exceed the rate of VRE infection [38], our estimates of VRE prevalence are likely a substantial underestimate of the rate of VRE carriage in our hospitalized population. Third, because we did not routinely identify enterococci to the species level, it is possible that our results may reflect the particular distribution of enterococcal species at our institution. Furthermore, because of the unavailability of isolates to permit molecular epidemiologic analysis, we were unable to determine whether our results were due to the presence of multiple unrelated strains or the clonal dissemination of a few strains. Fourth, our study of the correlation between antibiotic use and VRE prevalence was of an ecological nature. The lack of individual-level data limits the extent to which causal inferences can be drawn and makes control of confounding more challenging [39]. Finally, our study was conducted at a large academic medical center, and results may not reflect those at other dissimilar institutions.

In summary, antimicrobial formulary interventions restricting use of vancomycin and third-generation cephalosporins had little impact on VRE prevalence. The correlation between clindamycin use and the development of VRE suggests that restriction of this and possibly other antianaerobic agents might be an important consideration in future antimicrobial interventions. Finally, randomized studies should evaluate the respective impact of both antimicrobial and enhanced infection-control interventions to determine their relative importance and to assess whether optimal control of VRE infection may rely on significant components of both types of interventions.

Acknowledgment

We thank Brian L. Strom for his thoughtful review of the manuscript.

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