Manipulation of a Hospital Antimicrobial Formulary to Control an Outbreak of Vancomycin-Resistant Enterococci

John Quale, David Landman, Guillermo Saurina, Elaine Atwood, Virginia DiTore, and Keval Patel

From the Departments of Medicine and Infection Control, Department of Veterans Affairs Medical Center, and the Department of Medicine, State University of New York Health Science Center, Brooklyn, New York

Infection control practices are not uniformly successful in limiting outbreaks of vancomycin-resistant enterococci (VRE). Despite the implementation of barrier precautions for VRE-infected patients, nearly one-half of the inpatients at our center were found to have gastrointestinal colonization by VRE. In an attempt to control the outbreak, we altered the antibiotic formulary by restricting the use of cefotaxime and vancomycin and adding β-lactamase inhibitors to replace third-generation cephalosporins. The use of clindamycin was also restricted because of a concomitant outbreak of Clostridium difficile colitis. After 6 months, the average monthly use of cefotaxime, ceftazidime, vancomycin, and clindamycin had decreased by 84%, 55%, 34%, and 80%, respectively (P < .02). The point prevalence of fecal colonization with VRE decreased from 47% to 15% (P < .001), and the number of patients whose clinical specimens were culture positive also gradually decreased. A change in antibiotic use appears to have significantly affected our VRE outbreak when previous measures failed.

Nosocomial outbreaks of vancomycin-resistant enterococci (VRE) are being increasingly recognized. Many of these outbreaks have been localized to a single area within a hospital [1–6] and have involved genetically related strains of enterococci [1, 3, 4–6]. Infection control measures based on recent recommendations [7] have successfully contained some of these outbreaks [1–3, 5].

However, outbreaks of VRE may be hospitalwide [8], and there have been recent reports of diverse strains of resistant enterococci within institutions [9–12]. Initiation of infection control measures that emphasize barrier precautions and surveillance cultures has not been uniformly successful in reducing the transmission of VRE [8]. A reduction in the use of vancomycin, in addition to the institution of traditional infection control measures, was also ineffective in containing one hospitalwide outbreak [11]. Additional measures need to be considered to control these outbreaks.

Since 1991, our hospital has been the site of an outbreak of VRE that affects all medical and surgical units [13]. Multiple distinct strains of Enterococcus faecium, as well as other species of VRE, have been recovered from patients at our hospital [13, 14]. Traditional infection control measures have not been effective in interrupting the transmission of VRE [13]. In this report we describe a significant decline in widespread colonization with VRE and a decrease in the number of patients whose clinical cultures were positive for VRE. We attribute these decreases to a change in the hospital antibiotic formulary and in the prescribing habits of the physicians.

Methods

The setting. The Brooklyn Veterans Affairs Medical Center (VAMC; Brooklyn, NY) is a tertiary care facility that is affiliated with SUNY–Health Science Center at Brooklyn. This facility has 310 inpatient medical and surgical beds, including distinct medical, surgical, and cardiac intensive-care areas. Cultures of specimens from patients (including all blood specimens and body fluids, urine, and wound and respiratory tract specimens) that yielded VRE were identified by review of microbiology laboratory records. Enterococci were identified using standard microbiological methods. The clinical microbiology laboratory performs vancomycin susceptibility testing with a disk diffusion assay according to the procedures of the National Committee for Clinical Laboratory Standards [15].

Initial infection control measures. In April 1993, several initial infection control measures were instituted at the Brooklyn VAMC in response to an increase in the number of patients whose cultures were positive for VRE. These measures were as follows: (1) infected patients were placed in single rooms with signs outside the entrance signifying the presence of a resistant pathogen; (2) the inguinal and perineal areas of infected patients were washed with chlorhexidine; (3) gloves were required when caring for infected patients; (4) chlorhexidine soap was used for handwashing by hospital staff; (5) electronic thermometers were removed; and (6) an infection control clinician made frequent rounds to reinforce adherence to these measures.
In addition, areas where infected patients were receiving care were cleaned with a 1:128 dilution of sodium hypochlorite (5.25%). In vitro studies with five VRE isolates revealed that the sodium hypochlorite solution at dilutions between 1:80 and 1:160 was bactericidal for these resistant enterococci (data not shown).

Finally, the hospital staff was encouraged to voluntarily reduce the use of vancomycin. These measures, whose failure has been previously noted [13], were emphasized during mandatory infection control courses for all health care workers. The courses were required by the State of New York to maintain a professional license.

Additional measures. When the results of a point-prevalence survey performed on 17 January 1995 revealed widespread gastrointestinal colonization with VRE [13], a second intervention, which forms the basis of this report, was initiated. This second intervention against VRE included the following measures.

Because the number of patients whose cultures yielded VRE at our hospital correlated with increased use of cefotaxime (the major cephalosporin used at our hospital [13]), beginning in May 1995 the approval of an infectious diseases physician was required before cefotaxime could be administered. Because of recent recommendations to decrease the use of vancomycin [7], administration of vancomycin also required the approval of an infectious diseases physician for patients located outside the intensive-care areas. Ampicillin/sulbactam and piperacillin/tazobactam were added to the hospital formulary, and their use in place of third-generation cephalosporins was encouraged. Finally, gowns were required when entering the rooms of patients whose cultures yielded VRE or when entering the rooms of patients with Clostridium difficile colitis or diarrhea of unknown etiology.

In addition to these measures, an attempt was made to limit a concomitant outbreak of C. difficile colitis. Since diminished use of clindamycin was associated with the termination of one outbreak of C. difficile [16], we stipulated that use of this drug also required the approval of an infectious diseases physician. The incidence of C. difficile infection was reported to be considerably lower when the β-lactam/β-lactamase inhibitor combination antibiotics were used [17]. Therefore, we hoped that by substituting these antibiotics for cephalosporins and clindamycin we would be able to limit the spread of C. difficile.

Point-prevalence survey. To determine the effectiveness of these measures, a second point-prevalence survey of all inpatients in the medical and surgical areas of the hospital was conducted on 24 October 1995, 6 months after institution of the intervention. The results of this survey were compared with the results of the first survey conducted in January 1995. For both surveys, cultures of perianal specimens obtained with rayon-tipped swabs were placed in Stuart’s transport medium. The swabs were placed in Enterococcusel broth (Becton Dickinson, Cockeysville, MD) containing vancomycin (64 μg/mL) and aztreonam (60 μg/mL). We found that use of this medium previously resulted in detection of colonization in 88% of colonized patients; VRE with low-level resistance to vancomycin are unusual at our hospital [14]. Demographic data and antibiotics administered within the preceding 30 days were recorded for each patient screened in the point-prevalence surveys.

All of the VRE isolated during the point-prevalence surveys were identified to the species level according to standard methods [18], and the MICs of vancomycin (Eli Lilly Co., Indianapolis, IN), ampicillin (Bristol-Myers Squibb, Princeton, NJ), and gentamicin (Schering-Plough Corp., Bloomfield, NJ), were determined by the agar dilution method [19].

Statistical analysis. Categorical variables were compared with use of the χ² test. Continuous variables were compared with use of Student’s t test, and results are expressed as the mean (±SD). Significance was defined as a two-tailed P value of <.05.

Results

VRE were first detected at our institution in August 1991. Sporadic cases occurred throughout 1992; however, by early 1993, the number of new patients per month whose cultures were positive for VRE was rising (figure 1A). There was no correlation between the hospital census or number of admissions and the number of patients with VRE [13]. As noted elsewhere [13], the intervention emphasizing barrier precautions and a voluntary reduction in the use of vancomycin was unsuccessful in reducing the number of new patients with cultures positive for VRE (figure 1A, arrowhead). The mean (±SD) number of new patients with positive cultures was 3.2 ± 3.9 patients per month for the 18 months preceding the intervention and 4.9 ± 3.1 patients per month for the 12 months following the intervention (P = .2). Furthermore, in January 1995 we conducted a surveillance study of all patients receiving care in the medical and surgical areas and found that 47% of inpatients were colonized with VRE [13].

Because of the extent of the outbreak, no attempt was made to isolate patients with positive surveillance cultures. Multiple regression analysis of antibiotic use from January 1991 through December 1994 revealed that increased use of cefotaxime (P < .001) in the preceding month was associated with an increased number of patients infected with VRE the following month [13]. None of the other antibiotics analyzed, including nearly all of the parenteral antibiotics used at our hospital, were associated with isolation of VRE.

After we recognized the association between cefotaxime use and isolation of VRE and the obvious failure of the infection control measures described above, we initiated the second intervention in May 1995. This intervention resulted in a rapid decline in the use of cefotaxime, clindamycin, and vancomycin and a marked increase in the use of the new formulary items ampicillin/sulbactam and piperacillin/tazobactam (figure 2).
Figure 1. A, number of new patients per month with cultures positive for vancomycin-resistant enterococci at Brooklyn Veterans Affairs Medical Center. Two interventions for the outbreak were undertaken; the first emphasized barrier precautions (arrowhead), and the second emphasized changing antibiotic use practices (arrow). B, number of new patients per month with proven Clostridium difficile colitis.

The mean (±SD) number of units of cefotaxime used for the 12 months preceding the intervention was 1,597 ± 191 units per month, whereas the mean (±SD) number of units used for the 8 months after the intervention was 252 ± 91 units per month, representing a statistically significant decrease in the use of cefotaxime (P < .00000001). The use of clindamycin also decreased from a baseline mean (±SD) of 876 ± 204 units per month to a mean (±SD) of 172 ± 103 units per month following the intervention (P = .00000005).

There was a modest decline in the use of intravenous vancomycin from a mean (±SD) of 540 ± 181 units per month preceding the intervention to a mean (±SD) of 358 ± 94 units per month for the 8 months after the intervention (P = .02). Oral vancomycin use decreased from a mean (±SD) of 293 ± 302 units per month preceding the intervention to a mean (±SD) of 108 ± 48 units per month after the intervention (P = .06). As a result of the change in the prescribing patterns, there was also a reduction in ceftazidime use from a mean (±SD) of 627 ± 127 units per month to a mean (±SD) of 279 ± 119 units per month (P < .00001). The mean (±SD) number of units of metronidazole used was 738 ± 259 units per month and 932 ± 253 units per month before and after the intervention, respectively (P = .12).

During the first point-prevalence survey, specimens from 75% of all inpatients were cultured; specimens from 80% of all inpatients were cultured during the second survey (P = not significant). Comparison of the patients who were included in the pre- and postintervention surveillance studies revealed similar demographic and clinical characteristics (table 1).

A comparison of the antibiotics administered to the patients in the two surveillance studies reflects the change in the antibiotic formulary (table 1). Only 1.5% of patients received cefotaxime following the intervention, which was a significantly lower percentage than that determined in the preintervention survey (P < .0001). Significantly fewer patients in the postintervention group had received clindamycin (P < .0001). As anticipated, there was a significant increase in use of β-lactam/β-lactamase inhibitors, which were added to the hospital formulary as part of the intervention. There was no statistically significant difference in the numbers of patients who received vancomycin in the two groups (table 1).

Following the intervention, there was a gradual decline in the number of clinical cases with VRE (figure 1A, arrow). The mean (±SD) number of new patients with positive cultures fell from 5.4 ± 2.7 patients per month (for the 18 months preceding the second intervention) to 3.3 ± 2.3 patients per month (for the 12 months after the intervention; P = .03). In the second surveillance study, only 15% of inpatients were colonized with VRE, whereas 47% of inpatients were colonized with VRE before the intervention was instituted (P < .001; table 1).
Table 1. Clinical data on patients for whom surveillance cultures were performed before and after intervention for an outbreak of vancomycin-resistant enterococci at Brooklyn Veterans Affairs Medical Center.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients with indicated characteristic</th>
<th>Preintervention (n = 192)</th>
<th>Postintervention (n = 192)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Mean ± SD age (y)</td>
<td></td>
<td>67 ± 13</td>
<td>66 ± 12</td>
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<tr>
<td>Mean ± SD length of hospital stay (d)</td>
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<td></td>
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<td>NS</td>
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<tr>
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<td>29 (15)</td>
<td>&lt;.001</td>
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</table>

NOTE. NS = not significant; VRE = vancomycin-resistant enterococci.

* Placed on formulary as part of the intervention.
† Use restricted as part of the intervention.
‡ Numbers in parentheses are percent.

**E. faecium** was the predominant species of VRE recovered during the point-prevalence surveys. Before the intervention, 95% of isolates were **E. faecium**; following the intervention, 72% of isolates were **E. faecium**. Before the intervention, the MIC_{50} and MIC_{90} of vancomycin were 512 μg/mL and 1,024 μg/mL, respectively; the MIC_{50} and MIC_{90} of ampicillin were 256 μg/mL and 256 μg/mL, respectively; and the MIC_{50} and MIC_{90} of gentamicin were >2,000 μg/mL and >2,000 μg/mL, respectively. The MIC_{50} and MIC_{90} data following the intervention were as follows: vancomycin, 512 μg/mL and 512 μg/mL, respectively; ampicillin, 128 μg/mL and 256 μg/mL, respectively; and gentamicin, 1,000 μg/mL and >2,000 μg/mL, respectively.

A decline in the mean number of patients with proven **C. difficile** diarrhea occurred concomitantly with the decline in the number of patients with cultures positive for VRE (figure 1B). The mean (±SD) number of new patients with **C. difficile** diarrhea fell from 5.7 ± 3.7 patients per month (for the 18 months before the intervention) to 2.2 ± 2.2 patients per month following the intervention; P = .006. The total number of samples submitted to the laboratory for detection of **C. difficile** toxin was 418 in 1994 and 545 in 1995. Therefore, the decline in the number of cases of **C. difficile** diarrhea could not be attributed to a decrease in the number of samples submitted for culture.

**Discussion**

Vancomycin-resistant enterococci have rapidly evolved into serious nosocomial pathogens [20]. Recent guidelines from the Hospital Infection Control Practices Advisory Committee (HICPAC) recommend strict barrier precautions, education of health care workers, performance of surveillance cultures for patients in high-risk areas, and diminished use of vancomycin as measures to control the spread of vancomycin resistance [7]. Recommended barrier precautions include isolation of infected patients, use of gowns and gloves, and disinfection of environmental surfaces and equipment.

Indeed, several outbreaks have been controlled with use of barrier techniques and surveillance cultures for patients in high-risk areas. The outbreaks that have been successfully eradicated have generally involved a small number of patients and have been confined to a single area of a hospital such as the intensive care unit(s) [1–3, 5] or oncology unit(s) [4]. Genetic analysis of VRE recovered during these contained outbreaks has usually demonstrated that the strains are identical or highly related [1, 3–5].

Unfortunately, there is growing evidence that the HICPAC recommendations may not be effective in all settings. Recent reports have noted dissemination of VRE throughout multiple areas of hospitals [8–12]. The rate of colonization for hospitalized patients has generally ranged from 5% to 18% [8, 10, 11], although rates of 54%–70% have been reported in hematology units and renal units [21]. When such high prevalence rates exist, it is impractical to follow the recommendations regarding isolation of all colonized patients.

In two reports, aggressive contact precautions (e.g., gowns, gloves, and dedicated use of noncritical items) did not reduce the percentage of patients colonized or infected over a 6-month period [8, 11]. Several genetically unrelated strains of VRE have been isolated in some outbreaks [9–11]. Therefore, multiple point sources may exist within a hospital, and methods that have been successful in reducing nosocomial transmission of a single strain may not be as effective.

A consistently recognized risk factor for acquisition of VRE is the prior administration of antimicrobials [1–3, 12, 13, 22]. In case-control studies, administration of vancomycin [2, 3, 11, 12], cephalosporins [1, 3], and antibiotics effective against
anaerobes [6] have been noted to increase the risk of infection or colonization with VRE. Clindamycin therapy has also been associated with infection or colonization with ampicillin-resistant enterococci [23]. We did not find a significant association between infection with VRE and vancomycin use [13].

In two studies, the combination of restricted use of vancomycin and use of barrier precautions failed to diminish rates of colonization with VRE [8, 11]. Reduction in the use of vancomycin is certainly a desirable goal. However, restricted vancomycin use by itself is unlikely to control outbreaks of VRE in hospitals where the organisms are highly endemic. We have previously documented an association between the number of patients with cultures positive for VRE and hospitalwide use of cefotaxime [13].

Cephalosporins lack activity against enterococci, and overgrowth of enterococci is common when patients receive antibiotics in this class. We believe that reducing the use of certain broad-spectrum antibiotics, not just vancomycin, may be necessary to control hospitalwide outbreaks that involve multiple strains of VRE.

At our institution, barrier precautions were the initial measure emphasized to reduce the transmission of VRE. After a 20-month trial of these precautions, an overwhelming percentage (47%) of our inpatients were colonized with VRE. Given the fact that these measures had failed and that the outbreak was associated with cefotaxime use, we altered the hospital antibiotic formulary in an attempt to control the outbreak. As a result of our intervention, there was a marked decrease in the use of third-generation cephalosporins and clindamycin and a 34% decline in the use of intravenous vancomycin. These decreases were accompanied by an increase in the use of ampicillin/sulbactam and piperacillin/tazobactam.

After 6 months of this intervention, the number of cases of infection due to VRE and C. difficile decreased, and the colonization rate with VRE significantly decreased. However, 15% of our inpatients still were colonized with VRE; therefore, our hospital continues to be affected by this pathogen.

It is difficult to ascertain specifically which measures in our intervention contributed to the decline in the number of patients with VRE. Restricting the use of selected antibiotics has successfully contained other outbreaks of nosocomial infections, including those due to C. difficile and ceftazidime-resistant Klebsiella pneumoniae [16, 24]. The decrease in cefotaxime use certainly may have played an important role in reducing the prevalence of VRE in our study. Although cefotaxime was the sole antibiotic correlated with our VRE outbreak, it is possible that diminished use of the other antibiotics may also have contributed to the outcome.

Contamination of the environment [2, 11] and patient care equipment with VRE [1, 2, 6, 11] has been reported, particularly when patients have diarrhea [5]. Since many patients with C. difficile colitis are colonized with VRE [25], reducing the incidence of antibiotic-associated diarrhea may decrease environmental contamination with VRE. Therefore, controlling our outbreak of C. difficile colitis may also have contributed to the decrease in colonization and infection due to VRE.

Finally, the use of gowns by health care workers has been considered important when caring for patients colonized with VRE [5]. Although part of the intervention at our hospital included the use of gowns in the care of patients with cultures positive for VRE, we believe this component played a minor role in containing the outbreak. Since the majority of colonized patients did not have cultures that were positive for VRE, barrier precautions were used for very few of the colonized patients. Further experience will determine if the changes we instituted will lead to a continued decline in the number of patients infected or colonized with VRE at our hospital.

References


