Effect of the Increasing Use of Piperacillin/Tazobactam on the Incidence of Vancomycin-Resistant Enterococci in Four Academic Medical Centers

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Effect of the Increasing Use of Piperacillin/Tazobactam on the Incidence of Vancomycin-Resistant Enterococci in Four Academic Medical Centers

Usha Stiefel, MD; David L. Paterson, MD; Nicole J. Pultz, BS; Steven M. Gordon, MD; David C. Aron, MD, MS; Curtis J. Donskey, MD

ABSTRACT

BACKGROUND: The substitution of piperacillin/tazobactam, ampicillin/sulbactam, or both for third-generation cephalosporins has been associated with reduced vancomycin-resistant enterococci (VRE). However, piperacillin/tazobactam came into widespread use during a period in which the prevalence of VRE increased. We hypothesized that the increasing use of piperacillin/tazobactam and other agents with relatively enhanced anti-enterococcal activity (ie, piperacillin, ampicillin/sulbactam, and ampicillin) has been associated with increased or unchanged rates of VRE in some hospitals.

DESIGN: We retrospectively evaluated the correlation between hospital antibiotic use (defined daily doses per 10,000 patient-days of care) and incidence of stool or non-stool VRE isolation. We assessed whether a high or increasing proportion of use of beta-lactam agents with relatively enhanced anti-enterococcal activity (ie, third-generation cephalosporins and ticarcillin/clavulanate) anti-enterococcal activity would prevent increased VRE.

RESULTS: With the increasing use of piperacillin/tazobactam, the use of beta-lactam agents with enhanced activity against enterococci surpassed the combined use of third-generation cephalosporins and ticarcillin/clavulanate in each hospital. In one hospital, the incidence of VRE was positively correlated with the use of piperacillin/tazobactam or beta-lactam agents with enhanced anti-enterococcal activity ($P < .0001$). The incidence of VRE rose steadily in another hospital despite relatively high use of beta-lactam agents with enhanced versus minimal anti-enterococcal activity. A negative correlation between VRE and piperacillin/tazobactam or beta-lactam agents with enhanced anti-enterococcal activity was observed in one hospital, but this correlation was not statistically significant.

CONCLUSION: Increasing the hospital use of piperacillin/tazobactam and other beta-lactams with relatively enhanced anti-enterococcal activity may not be an effective control measure for VRE (Infect Control Hosp Epidemiol 2004;25:380-383).

In four published reports, formulary substitution of beta-lactam/beta-lactamase inhibitor combinations such as piperacillin/tazobactam and ampicillin/sulbactam for third-generation cephalosporins was associated with reductions in vancomycin-resistant enterococci (VRE). Although these data are intriguing, the premise that such formulary substitutions may be an effective control measure for VRE deserves further consideration for several reasons. First, some of the studies that demonstrated reductions in VRE had significant methodologic limitations such as concurrent implementation of other infection control measures. Second, the prevalence of VRE in the United States increased during the period in which piperacillin/tazobactam came into widespread use, suggesting that many hospitals have had increasing rates of VRE despite increasing use of piperacillin/tazobactam, but have not reported these findings. Third, although piperacillin/tazobactam has sufficient anti-enterococcal activity to inhibit the establishment of VRE colonization in mice, both piperacillin/tazobactam and ampicillin/sulbactam promote persistent overgrowth of VRE in the stool of mice or patients once colonization has been established. Finally, Paterson et al. demonstrated that individual patients receiving antibiotic regimens that include piperacillin/tazobactam frequently acquire VRE colonization. We hypothesized that increasing the proportion of use of beta-lactam antibiotics with relatively enhanced (ie, piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, and ampicillin) versus minimal (ie, third-generation cephalosporins and ticarcillin/clavulanate) anti-enterococcal activity has been associated with increasing or unchanged rates of VRE in some hospitals.

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METHODS

A retrospective study was conducted in four Cleveland teaching hospitals to examine the correlation between hospital antibiotic use and the incidence of VRE. The characteristics of the hospitals are listed in the table. Two of the hospitals (hospitals 2 and 4) perform active surveillance for VRE stool colonization by screening stool samples submitted for Clostridium difficile testing and isolate colonized patients, whereas the other two hospitals perform no active surveillance but do isolate patients with clinical VRE isolates.

Data regarding the yearly use of antibiotics from 1993 (or 1996) through 2002 were obtained from pharmacy records. Antibiotics included in the analysis were third-generation cephalosporins (cefotaxime, ceftriaxone, ceftizoxime, and ceftazidime), cefepime, ticarcillin/clavulanate, piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, ampicillin, quinolones, clindamycin, metronidazole, and vancomycin. Antibiotic use was calculated as defined daily doses per 10,000 patient-days of care. Data regarding patient-days of care were obtained from the Ohio Department of Health Annual Hospital Registration and Planning Report.

The number of patients from whom cultures of non-stool specimens (ie, clinical cultures including blood, sputum, urine, wounds, and catheter tips) and stool specimens yielded VRE (excluding Enterococcus gallinarum or E. casseliflavus) was obtained from the databases of the microbiology laboratory. Patients with multiple isolates were included only once in the entire cohort for each category of specimen. The incidences of VRE per 10,000 patient-days of care were calculated.

Data were analyzed using SPSS software (version 10.0; SPSS, Inc., Chicago, IL). To evaluate the correlation between antibiotic use and VRE, Pearson correlation coefficients were calculated. Piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, and ampicillin were grouped together because these agents have similar in vitro anti-enterococcal activity (minimal inhibitory concentrations [MICs] of 312.5 to 1,250 µg/mL for Cleveland VRE isolates).6 Ticarcillin/clavulanate was considered to be similar to third-generation cephalosporins because it has minimal anti-enterococcal activity (MICs > 10,000 µg/mL for Cleveland VRE isolates).6

RESULTS

The figure shows the incidences of VRE and selected antibiotic use data. After VRE was first isolated, the incidence increased for 2 to 5 years in each institution before leveling off or decreasing. The most rapid rise and highest peak in the incidence of VRE occurred in hospital 1, which did not perform active surveillance. After piperacillin/tazobactam became available on formulary, use of this agent increased rapidly in each hospital. Between 1997 and 1999, hospital 1 substituted piperacillin/tazobactam for ticarcillin/clavulanate as the most commonly used beta-lactam/beta-lactamase inhibitor combination.

With the increasing use of piperacillin/tazobactam, the total use of beta-lactam agents with relatively enhanced (ie, piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, and ampicillin) anti-enterococcal activity surpassed the combined total use of beta-lactam agents with minimal (ie, third-generation cephalosporins and ticarcillin/clavulanate) anti-enterococcal activity in each hospital (Figure). In hospital 2, the incidence of stool and non-stool VRE was positively correlated with the use of piperacillin/tazobactam and the total use of beta-lactam agents with relatively enhanced anti-enterococcal activity (P < .0001 for each correlation). In hospital 3, the incidence of non-stool VRE was positively correlated with the use of piperacillin/tazobactam (P = .04) but not the total use of beta-lactam agents with relatively enhanced anti-enterococcal activity (P = .07). In hospital 4, there was no significant correlation between non-stool or stool VRE and the use of piperacillin/tazobactam or total beta-lactam agents with relatively enhanced anti-enterococcal activity (P ≥ .08 for each comparison); however, the incidence of VRE rose steadily despite maintenance of a relatively high proportion of use of beta-lactam agents with enhanced versus minimal anti-enterococcal activity (ratio, 2.2 to 3.8). In hospital 1, a decrease in the incidence of non-stool VRE occurred after piperacillin/tazobactam was substituted for ticarcillin/clavulanate, resulting in negative correlations between non-stool VRE and piperacillin/tazobactam or beta-lactam agents with enhanced anti-enterococcal activity, but these correlations were not statistically significant (P = .54 and .47).

VRE was positively correlated with the use of clindamycin and vancomycin in hospitals 3 and 4 and with the use of quinolones in hospital 4. No other statistically significant correlations were found between VRE and specific classes of antibiotics.

DISCUSSION

We found that an increasing proportion of use of beta-lactam antibiotics with relatively enhanced (ie, piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, and ampicillin) versus minimal (ie, third-generation cephalosporins and ticarcillin/clavulanate) anti-enterococcal activity was not temporally associated with reductions in the incidence of VRE in 3 of the 4 hospitals.

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VRE = vancomycin-resistant enterococci.
In hospital 2, the increasing use of piperacillin/tazobactam and total beta-lactams with enhanced anti-enterococcal activity was temporally correlated with a statistically significant increase in stool and non-stool VRE (Fig. B). In hospital 4, a steady rise in VRE occurred despite maintenance of a high proportion of use of beta-lactams with enhanced versus minimal anti-enterococcal activity (Fig. D). Although retrospective ecologic studies have many limitations, our findings suggest that the increasing use of piperacillin/tazobactam and other agents with relatively enhanced anti-enterococcal activity may not always be associated with reductions in VRE.

Although the correlation was not statistically significant, the incidence of non-stool VRE decreased in hospital 1 after piperacillin/tazobactam was substituted for ticarcillin/clavulanate (Fig. A). Because there were no concurrent changes in infection control measures, it is possible that the reduction in VRE could have been attributable in part to the formulary change. Ticarcillin/clavulanate possesses potent anti-anaerobic activity and minimal anti-enterococcal activity, and thus promotes the establishment and persistence of VRE colonization in mice. Alternatively, the other epidemic curves demonstrate a similar rise in VRE followed by a plateau or reduction in incidence; the reduction of VRE in hospital 1 therefore could simply be representative of the typical epidemic curve for VRE in Cleveland, with the formulary change being coincidental.

Our study has several limitations. We studied only four academic medical centers in one geographic location. Additional data from other centers are needed. The retrospective, ecologic study design is subject to bias related to failure to control for non-antimicrobial confounding factors, fluctuations in the incidence of VRE that represent the natural history of outbreaks, and failure of group-level-effect estimates to reflect the biological effect at the individual-patient level. These types of bias also limit the conclusions that can be drawn from previous studies that examined the effect of formulary changes on VRE. Data were not available regarding compliance with infection control measures in the study hospitals. Some of the patients may have acquired VRE in outside hospitals or nursing homes and, therefore, may have been colonized on admission. However, of a subset of 51 VRE-colonized patients from one of the institutions (hospital 4), only 4 (8%) had been admitted to an outside hospital or nursing...

**FIGURE.** Comparison of antibiotic use (defined daily doses [DDD] per 10,000 patient-days of care) and incidence of isolation of vancomycin-resistant enterococci (VRE) from stool and non-stool sites in four academic medical centers in Cleveland, Ohio (A through D, respectively). Antibiotic use data were not available for hospital 3 in 1997 and 1998. Doc = patient-days of care; solid diamonds = combined use of piperacillin/tazobactam, ampicillin/sulbactam, piperacillin, and ampicillin; solid triangles = piperacillin/tazobactam; solid squares = total third-generation cephalosporins including ceftazidime, cefotaxime, ceftizoxime, and ceftriaxone; solid circles = ticarcillin/clavulanate; open circles = non-stool VRE; and open squares = stool VRE.
home within the previous 5 years. Although the ratio of use of beta-lactams with enhanced versus minimal anti-enterococcal activity rose in each of the hospitals, total third-generation cephalosporin use did not decrease significantly in any of the hospitals. May et al. previously found that the increasing use of piperacillin/tazobactam was associated with a decrease in the prevalence of VRE in an intensive care unit that also significantly reduced third-generation cephalosporin use, but not in 2 similar units that did not concurrently reduce cephalosporin use. Because non–beta-lactam classes of antibiotics may promote VRE, the frequent use of agents such as clindamycin or vancomycin may result in the maintenance of high rates of VRE even if beta-lactams with enhanced anti-enterococcal activity inhibit the establishment of colonization. Efforts to limit the unnecessary use of all classes of antibiotics are likely to be most effective in controlling VRE, and the combination of such efforts with contact precautions has been shown to be effective in reducing rates of VRE on an oncology unit.

REFERENCES