Running title: VRE acquisition during antibiotic therapy

Title: Acquisition of vancomycin-resistant Enterococcus rectal colonization among intensive care unit patients treated with piperacillin/tazobactam versus cefepime-containing antibiotic regimens

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ABSTRACT

In contrast to third-generation cephalosporins, beta-lactam/beta-lactamase inhibitors such as piperacillin/tazobactam have rarely been associated with vancomycin-resistant Enterococcus (VRE) colonization and infection. In mice, piperacillin/tazobactam has sufficient antienterococcal activity to inhibit establishment of colonization during treatment, but this effect has not been confirmed in patients. We prospectively evaluated acquisition of VRE rectal colonization among intensive care unit patients receiving antibiotic regimens containing piperacillin/tazobactam versus cefepime, a fourth-generation cephalosporin with minimal antienterococcal activity. Rectal swabs were obtained weekly and cultured for VRE. For 146 patients with a negative rectal swab for VRE prior to therapy, there was no significant difference in the frequency of VRE acquisition between patients receiving piperacillin/tazobactam and cefepime-containing regimens (19/72, 26.4% versus 23/74, 31.1%, respectively; \( P = 0.28 \)). Of the 19 patients who acquired VRE in association with piperacillin/tazobactam, 10 (53%) developed new detection of VRE during therapy. Patients initiating cefepime-containing regimens were significantly more likely than those initiating piperacillin/tazobactam-containing regimens to have received antibiotic therapy in the prior 30 days (55/74, 74.3% versus 22/72, 30.6%; \( P < 0.001 \)). These finding suggest that piperacillin/tazobactam and cefepime-containing antibiotic regimens may be associated with frequent acquisition of VRE in “real-world” intensive care unit settings. Although piperacillin/tazobactam inhibits the establishment of VRE colonization in mice when exposure occurs during treatment, our data suggest that this agent may not prevent acquisition of VRE in patients.
INTRODUCTION

Antibiotics play a crucial role in the pathogenesis of vancomycin-resistant Enterococcus (VRE) intestinal colonization (6-7). Studies using mouse models suggest that the effect of antibiotics on colonization represents a balance between promotion due to suppression of anaerobes that compete with VRE and inhibition due to antimicrobial activity against VRE strains (7, 15). Antibiotics that do not disrupt the anaerobic microflora (e.g., cefepime, aztreonam) do not promote VRE colonization in mouse models (7). Antibiotics that disrupt the anaerobic microflora and possess minimal antienterococcal activity (e.g., ceftriaxone, with an MIC of >10,000 µg/mL for the VRE test strain used in mouse models) promote colonization (7). Antianaerobic antibiotics with relatively enhanced antienterococcal activity that are excreted in high concentrations in bile (e.g., piperacillin/tazobactam, with an MIC of 625 µg/mL for the VRE test strain) may inhibit establishment of VRE colonization during treatment (7, 15). However, piperacillin/tazobactam may also promote establishment of colonization when exposure to VRE occurs after treatment and prior to recovery of the anaerobic microflora (7, 15). In addition, once VRE colonization is established, piperacillin/tazobactam and ampicillin/sulbactam promote persistent overgrowth in mice and in colonized patients (6-7, 15).

Because third-generation cephalosporins have frequently been associated with VRE, formulary modifications that involve restriction of these agents have been suggested as a control measure. However, the optimal agents that might be substituted for third-generation cephalosporins as a means to limit VRE colonization are unknown. Beta-lactam/beta-lactamase inhibitor combinations such as piperacillin/tazobactam have
often been chosen as substitutes for third-generation cephalosporins because they have rarely been associated with VRE in clinical studies and because they inhibit establishment of colonization in mice (2, 6-7, 8-9, 13-15). Such formulary substitutions have been associated with reductions in VRE in some but not all published studies (2, 8-9, 11, 13-14). As noted above, however, beta-lactam/beta-lactamase inhibitor combinations may promote VRE in some circumstances (7, 15). In addition, it has not been confirmed that agents such as piperacillin/tazobactam inhibit establishment of VRE colonization during treatment in humans. Agents that do not disrupt intestinal anaerobes (e.g., cefepime, aztreonam) offer another alternative to third-generation cephalosporins; however, the potential advantage of these agents may not be realized in clinical settings in which they are frequently administered in combination or in sequence with other agents that may promote VRE.

In this study, we compared the frequency of acquisition of VRE rectal colonization among intensive care unit patients receiving cefepime versus piperacillin/tazobactam-containing antibiotic regimens. Third-generation cephalosporins were not included as a comparison group because these agents are rarely used in the study units. Our goal was to evaluate VRE acquisition in a “real-world” setting in which the antibiotics of interest might often be given in sequence or in combination with other antimicrobials. We hypothesized that piperacillin/tazobactam-containing regimens might be associated with lower rates of VRE acquisition in such settings because the inhibitory activity of piperacillin against VRE would be maintained despite disruption of the indigenous microflora by other agents. Because piperacillin/tazobactam inhibits establishment of colonization by VRE during treatment in mice, we hypothesized that
acquisition of VRE would be particularly uncommon during the course of therapy with this agent. Finally, we also examined the frequency of persistence of VRE colonization among patients with positive rectal swab cultures for VRE prior to initiation of therapy.

METHODS

Setting and study design. The University of Pittsburgh Medical Center is an 800-bed tertiary care referral center and Level 1 trauma center. VRE has been endemic in the medical center since the early 1990s. There are approximately 120 ICU beds spread between several ICUs. Consecutive patients commenced on either piperacillin/tazobactam or cefepime in these ICUs were assessed for new detection of VRE stool colonization as a quality assurance project of the hospital’s antibiotic management program. Piperacillin/tazobactam and cefepime were the two most widely used beta-lactam antibiotics, with antipseudomonal activity, in these ICUs. Rectal swabs were obtained on a weekly basis from patients in each ICU and cultured for VRE as part of routine infection control surveillance.

Prior use of any antibiotic in the 30 days before the piperacillin/tazobactam or cefepime course was assessed. Patients who had received either piperacillin/tazobactam or cefepime in this 30 day period were excluded from further analysis. Prior therapy was defined as including antibiotics with anti-anaerobic activity if it comprised therapy with metronidazole, clindamycin, ticarcillin/clavulanate, imipenem, meropenem, ertapenem, amoxicillin/clavulanate or ampicillin/sulbactam (6).

Demographic details collected on all patients included age, gender, length of hospital stay and length of ICU stay prior to receiving the course of
piperacillin/tazobactam or cefepime, and the particular ICU in which the patient was accommodated. Infection types were defined as pneumonia, urinary tract infections, wound infections, intra-abdominal infections and bloodstream infections according to Centers for Disease Control and Prevention definitions. Information regarding isolation of VRE from clinical cultures was obtained by review of Microbiology Laboratory records.

Patients were defined as acquiring VRE rectal carriage if they were negative by rectal swab for VRE prior to receiving piperacillin/tazobactam or cefepime-containing antibiotic regimens but became positive on rectal swabs during or in the 30 days after initiation of this antibiotic therapy. For patients treated with piperacillin/tazobactam, we assessed whether acquisition of VRE occurred during or after therapy because this agent inhibits establishment of colonization during treatment in mice. For patients with positive cultures for VRE prior to receiving piperacillin/tazobactam or cefepime, we assessed whether colonization persisted during and after completion of treatment. Patients were only excluded from the assessment of VRE acquisition or persistence if they died or were discharged from the hospital.

**Microbiologic analysis.** In order to screen for VRE, rectal swabs were plated onto Enterococcus agar containing vancomycin (6 µg/mL). Identification and susceptibility testing was performed in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines (10). Isolates of *E. gallinarum* and *E. casseliflavus*, species that are intrinsically resistant to low concentrations of vancomycin, were not included. Additional speciation to distinguish *E. faecium* from *E. faecalis* or other species was not routinely performed by the Microbiology Laboratory.
**Statistical analysis.** Data were analyzed using SPSS, version 10.0 (SPSS). Bivariate analyses were performed to compare baseline characteristics of the cefepime and piperacillin/tazobactam-treated patients who were evaluated for new detection of VRE rectal colonization. Continuous data were analyzed using Student’s unpaired \(t\)-tests. Categorical data were analyzed using the Pearson chi-square test or Fisher’s exact test. Based on previous Infection Control data, we estimated that ~20% of patients with negative initial cultures would acquire VRE colonization during their ICU admission. A power calculation indicated that including 70 patients per group would provide 77% power to detect a clinically significant reduction in the rate of acquisition of VRE, which was defined as a reduction from 20% to 5%.

**RESULTS**

**Patient characteristics.** Four-hundred seventy patients commenced on piperacillin/tazobactam or cefepime were assessed (235 patients received piperacillin/tazobactam and 235 patients received cefepime). Of these, 29 patients who received piperacillin/tazobactam and 44 patients who received cefepime had received either piperacillin/tazobactam or cefepime in the 30 days prior to the initiation of the antibiotic in the ICU, and so were excluded from further analysis. Of the remaining 397 patients, 52 (13%) were colonized with VRE prior to beginning therapy with cefepime or piperacillin/tazobactam. Of the 397 patients, 146 were eligible for the analysis of VRE acquisition because they had a negative rectal swab for VRE prior to commencing piperacillin/tazobactam (72 patients) or cefepime (74 patients) therapy, and had a follow-up rectal swab performed in the 30 days after antibiotic therapy commenced.
Table 1 shows a comparison of the baseline characteristics of the 146 cefepime and piperacillin/tazobactam-treated patients who were evaluated for VRE acquisition. Cefepime-treated patients had significantly longer prior hospital and ICU stays and were more likely to be cared for in the Cardiothoracic ICU and to receive therapy with the study antibiotics for pneumonia. Antibiotic therapy was administered frequently in the 30 days prior to commencement of the piperacillin/tazobactam and cefepime-containing regimens, and patients in the cefepime group were significantly more likely to have received prior antibiotic therapy (59/74, 79.7% versus 35/72, 48.6%; \( P < 0.001 \)).

**VRE acquisition.** Of the 146 patients assessed for VRE acquisition, 42 (28.8%) had new detection of VRE rectal colonization. There were no significant differences in acquisition of VRE between patients receiving piperacillin/tazobactam (19/72 patients, 26.4%) or cefepime (23/74 patients, 31.1%) (\( p=0.28 \)) (Table 2). Of the 19 patients who acquired VRE in association with piperacillin/tazobactam therapy, 10 (53%) developed new detection of VRE during the course of piperacillin/tazobactam treatment. Of the 23 patients who acquired VRE in association with cefepime therapy, 11 (48%) developed new detection during the course of cefepime therapy. The number of swabs collected to assess acquisition of VRE did not differ in the piperacillin/tazobactam and cefepime groups (2.3 ± 0.4 and 2.5 ± 0.7, respectively; \( P = 0.52 \)).

**Persistence of established VRE colonization.** Eighteen additional patients were eligible for analysis of the effect of antibiotic therapy on persistence of established colonization because they had a positive rectal swab culture for VRE prior to commencing piperacillin/tazobactam (8 patients) or cefepime (10 patients) therapy, and had a follow-up rectal swab performed in the 30 days after antibiotic therapy.
commenced. One-hundred percent of the cefepime-treated patients continued to have positive cultures for VRE during or after completion of the course of treatment, whereas 88% (7/8) of the piperacillin/tazobactam-treated patients continued to have positive cultures for VRE ($P > 0.20$).

**Isolation of VRE from clinical cultures.** Of 397 patients who had not received therapy with piperacillin/tazobactam or cefepime in the 30 days prior to initiation of therapy in the ICU, 25 (6.3%) had VRE isolated from clinical cultures. There was no significant difference between the frequency of isolation of VRE from clinical cultures in patients treated with piperacillin/tazobactam (4.9%; 10 of 206) or cefepime (7.9%; 15 of 191) ($P = 0.20$).

**DISCUSSION**

Our findings do not provide support for our hypothesis that piperacillin/tazobactam-containing antibiotic regimens may be associated with lower rates of VRE acquisition in ICU settings than cefepime-containing regimens. There was a non-significant increase in the frequency of VRE acquisition in the cefepime group; however, patients receiving cefepime had significantly longer prior hospital and ICU stays and were more likely to have received antibiotics in the preceding 30 days. Cefepime-treated patients were more likely than piperacillin/tazobactam-treated patients to be cared for in the Cardiothoracic ICU; however, it is unlikely that this biased the results in favor of cefepime because the frequency of VRE acquisition was high for both agents in the unit (12 of 23 {52%} cefepime-treated patients and 2 of 5 {40%} piperacillin/tazobactam-treated patients on the unit acquired VRE colonization). In fact,
we re-analyzed the data after exclusion of the Cardiothoracic ICU patients and found that 11/51 (22%) cefepime-treated patients versus 17/67 (25%) piperacillin/tazobactam-treated patients acquired VRE colonization ($P = 0.23$). Of patients with known VRE colonization prior to beginning therapy, piperacillin/tazobactam and cefepime-containing regimens were associated with persistent positive stool cultures in 88% and 100% of patients, respectively. These findings demonstrate that both piperacillin/tazobactam and cefepime therapy may be associated with frequent acquisition and persistence of VRE in “real-world” intensive care unit settings.

Although piperacillin/tazobactam may inhibit the establishment of VRE colonization in mice when exposure occurs during treatment (7, 15), we are aware of only one previous study that prospectively examined acquisition of VRE rectal colonization during therapy with this agent in patients. DiNubile et al (4) found that only 1.6% of piperacillin/tazobactam-treated patients with intraabdominal infections acquired VRE during therapy versus 6.4% of ertapenem recipients. However, because end-of-therapy stool specimens could be collected up to 3 days after discontinuation of therapy in that study, it is not possible to assess whether VRE was acquired during or shortly after completion of therapy (4).

Of the 19 patients who acquired VRE in association with piperacillin/tazobactam therapy in our study, 10 (53%) developed new detection of VRE during the course of therapy. One possible explanation for the discrepancy between our current findings and previous mouse model studies is that some patients may have had low levels of VRE in the intestinal tract prior to beginning piperacillin/tazobactam therapy (i.e., the finding of new positive rectal swab cultures could represent new detection of colonization due to
expansion of pre-existing VRE populations rather than exogenous acquisition of VRE).

In fact, we have found that modification of the previous mouse model (15) to include orogastric inoculation of 10,000 colony-forming units of VRE 1 day prior to beginning piperacillin/tazobactam results in reduced efficacy in preventing establishment of colonization (50% versus 0% colonization rate for controls receiving VRE concurrently with initiation of piperacillin/tazobactam treatment) (authors’ unpublished data). Because rectal swab cultures may have poor sensitivity for detection of low-density VRE colonization (lower limit of detection, ~4 \log_{10} \text{cfu/g of stool}) (3), our current study may have not detected low levels of VRE present prior to initiation of therapy. Also, it is plausible that patients may repeatedly ingest small numbers of VRE while receiving antibiotic regimens, whereas a single oral inoculum of VRE has typically been administered in mouse model studies. Repeated ingestion of VRE during therapy could potentially increase the risk of acquiring colonization during piperacillin/tazobactam therapy in mice or in patients (12). In addition, some clinical VRE isolates could be more resistant to inhibition by piperacillin/tazobactam than the VRE test strain used in the mouse model studies (piperacillin MIC, 625 µg/mL) (7), or relatively low concentrations of piperacillin could be excreted into the intestinal tracts of patients in comparison to mice. In fact, both Nord et al. (11) and Wilcox et al. (17) have demonstrated significant inter-patient variability in the levels of piperacillin and tazobactam detected in stool of patients. Finally, concurrent use of other antibiotics in combination with piperacillin/tazobactam may have reduced the protective effect of this agent in patients.

Although our current and previous findings (6) suggest that piperacillin/tazobactam therapy may promote VRE colonization in patients, this agent has
not been associated with VRE in case-control studies. However, it is notable that many clinical studies have either failed to look for an association between piperacillin/tazobactam and VRE, or have grouped penicillins together for purposes of analysis. For example, of 14 such studies included in a review of antimicrobial risk factors for VRE, 5 (36%) included “penicillins” in the analysis and 9 (65%) either definitely did not include penicillins in the analysis or provided insufficient details to determine whether penicillins were included (5). Grouping of penicillins together is problematic because these agents differ significantly in biliary excretion and antienterococcal and antianaerobic activity. In addition, many studies that evaluated antimicrobial risk factors for VRE were conducted prior to the emergence of piperacillin/tazobactam as a “workhorse” antibiotic in the United States.

Cefepime is excreted in minimal concentrations into bile and does not cause significant disruption of the anaerobic stool microflora of healthy humans (1). Because most cefepime-treated patients that developed new detection of VRE had received therapy with other antibiotics in the prior 30 days, it is not possible to determine if VRE colonization was promoted by cefepime or by the other antibiotics. In theory, choosing antibiotics that have relatively little effect on the anaerobic microflora of the colon could be a useful strategy to limit the spread of VRE (6-7). Additional studies are needed to examine the effect of cefepime (and of other agents that cause minimal disruption of the anaerobic microflora) on VRE colonization in settings in which this agent is used as monotherapy in patients who have not received recent antibiotic therapy.

Our study has several limitations. First, we did not precisely measure the level of adherence to the culture protocol and we did not perform a time-dependent analysis of the
rate and timing of VRE acquisition. However, the overall rate of compliance with weekly rectal surveillance cultures in the ICUs during the year of the study was greater than 80% (authors’ unpublished data) and the number of swabs collected to assess acquisition of VRE did not differ in the 2 groups. Second, because the treatment groups were not randomized, it is possible that there were differences among the groups in addition to those previously discussed that might have affected risk of acquiring VRE. Finally, the VRE isolates from the study patients were not subjected to speciation or molecular typing, so we cannot exclude the possibility that clonal outbreaks were occurring in some of the ICUs. However, a hospital-wide culture survey in 2000 demonstrated that 95% of VRE isolates were *E. faecium* and 6 distinct pulsed-field gel electrophoresis (PFGE) clones were identified. Based on infection control records, no significant increases in the rate of VRE colonization or infection were noted in the ICUs during the study period. In addition, PFGE of 18 VRE isolates from the Cardiothoracic intensive care unit at the time of the study demonstrated presence of 5 distinct PFGE clones.

In summary, the rate of new detection of VRE rectal colonization did not differ significantly among intensive care unit patients receiving piperacillin/tazobactam versus cefepime-containing antibiotic regimens. New detection of VRE in association with piperacillin/tazobactam frequently occurred during the course of therapy, suggesting that this agent may not inhibit exogenous acquisition of VRE in patients. However, additional studies utilizing broth-enrichment cultures or polymerase-chain reaction are needed to exclude the possibility that piperacillin/tazobactam therapy caused expansion of pre-existing VRE populations that were not detected using rectal swabs. Although
formulary substitutions of piperacillin/tazobactam or cefepime for third-generation cephalosporins offer a potential strategy for controlling VRE, our data suggest that neither of these agents is likely to provide a panacea for control of this important nosocomial pathogen.

ACKNOWLEDGMENT

Supported in part by an Advanced Research Career Development Award from the Department of Veterans Affairs to C.J.D.
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TABLE 1. Comparison of baseline characteristics of 146 intensive care unit patients treated with cefepime versus piperacillin/tazobactam-containing antibiotic regimens and evaluated for new detection of vancomycin-resistant Enterococcus rectal colonization.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cefepime</th>
<th>Piperacillin/Tazobactam</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 74)</td>
<td>(n = 72)</td>
<td></td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>43 (58.1)</td>
<td>37 (51.4)</td>
<td>0.20</td>
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<td>Age, mean ± SD</td>
<td>58.9 ± 18.1</td>
<td>61.4 ± 17.5</td>
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<td>Days in hospital prior, mean ± SD</td>
<td>10.2 ± 9.1</td>
<td>5.4 ± 7.1</td>
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<td>Days in ICU prior, mean ± SD</td>
<td>8.0 ± 7.2</td>
<td>3.3 ± 4.5</td>
<td>0.001</td>
</tr>
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<td>Any antibiotic treatment in prior 30 days, no. (%)</td>
<td>59 (79.7)</td>
<td>35 (48.6)</td>
<td>&lt;0.001</td>
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<td>Vancomycin</td>
<td>38 (51.4)</td>
<td>11 (15.3)</td>
<td>&lt;0.001</td>
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<td>Third-generation Cephalosporin</td>
<td>4 (5.4)</td>
<td>3 (4.2)</td>
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<td>Fluoroquinolone</td>
<td>30 (40.5)</td>
<td>14 (19.4)</td>
<td>0.005</td>
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<td>Agent with anti-anaerobic activity</td>
<td>42 (56.8)</td>
<td>8 (11.1)</td>
<td>&lt;0.001</td>
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<td>Clindamycin*</td>
<td>3 (4.1)</td>
<td>1 (1.4)</td>
<td>0.32</td>
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<td>Infection type, no. (%)</td>
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<td>Pneumonia</td>
<td>31 (41.9)</td>
<td>15 (20.8)</td>
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<td>UTI</td>
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<td>Category</td>
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<td>Medical</td>
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<td>Cardiothoracic</td>
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<td>Neonatal</td>
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<td>Surgical</td>
<td>4 (5.4)</td>
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<td>Other</td>
<td>12 (16.2)</td>
<td>15 (20.8)</td>
<td>0.36</td>
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*Clindamycin was a subset of agents with antianaerobic activity. Vancomycin included only patients receiving intravenous therapy.
TABLE 2. Comparison of rates of new detection of vancomycin-resistant *Enterococcus* (VRE) colonization and of VRE infection among 146 intensive care unit patients treated with cefepime versus piperacillin/tazobactam-containing antibiotic regimens.

<table>
<thead>
<tr>
<th></th>
<th>Cefepime (n = 74)</th>
<th>Piperacillin/tazobactam (n = 72)</th>
<th>P</th>
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<tr>
<td>VRE colonization, no. (%)</td>
<td>23 (31.1)</td>
<td>19 (26.4)</td>
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<tr>
<td>VRE infection, no. (%)</td>
<td>5 (6.8)</td>
<td>4 (5.6)</td>
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