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Association of Vancomycin-Resistant *Enterococcus* Bacteremia and Ceftriaxone Usage

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Abstract

Objective—Vancomycin-resistant *Enterococci* (VRE) have become a public health concern with implications for patient mortality and costs. Hospital antibiotic usage may impact VRE incidence, but the relationship is poorly understood. Animal investigations suggest ceftriaxone may be associated with VRE proliferation. We measured antimicrobial usage and VRE bloodstream infection (BSI) incidence to test our hypothesis that increased ceftriaxone use would be associated with a higher incidence of VRE-BSI.

Setting—The University of Alabama at Birmingham Medical Center is a 900-bed urban tertiary-care hospital

Methods—Retrospective analysis of antimicrobial usage and VRE-BSI from 2005 to 2008 (43 months). Antimicrobial usage quantified as days of therapy/1,000 patient-days (DOT). VRE-BSI incidence calculated as cases/1,000 patient-days. Negative binomial regression with adjustment for correlation between consecutive observations measured the association between antimicrobial usage and VRE-BSI incidence at the hospital- and care-unit levels.

Results—VRE-BSI incidence increased from 0.06 to 0.17 infections/1,000 patient-days. Hospital VRE-BSI incidence was associated with prior-month ceftriaxone DOT (Incidence Rate Ratio 1.38 per 10 DOT; $p=0.005$). After controlling for ceftriaxone, prior-month cephalosporin use (class) was not predictive of VRE-BSI ($p=0.70$). Similarly, prior-month use of piperacillin-tazobactam, ceftazidime, cefepime, ceftazolin, or vancomycin was not predictive of VRE-BSI when considered individually ($p > 0.4$ for all comparisons). The final model suggests that type of intensive care unit was related to VRE-BSI incidence.

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Conclusions—Ceftriaxone use in the prior month, but not cephalosporin (class) or vancomycin use, was related to VRE-BSI incidence. These findings suggest that an antimicrobial stewardship program that limits ceftriaxone may reduce nosocomial VRE-BSI incidence.

Introduction

Vancomycin-resistant enterococcal bloodstream infections (VRE-BSI) are a major cause of morbidity and mortality for hospitalized patients. *Enterococcus* spp. are now the second most common nosocomial bloodstream isolate in the United States and high-level vancomycin resistance is common among these isolates.¹ National surveys of intensive care units indicate that VRE represented <1% of enterococcal isolates in 1990, but currently exceed 30%¹⁻⁴. Using conservative incidence estimates, VRE-BSI leads to \$2 billion in annual U.S. healthcare costs and may be related to 10,000 to 25,000 deaths per year.⁵⁻¹⁵ The Infectious Disease Society of America has identified VRE as a major health concern, but effective and feasible prevention methods are lacking.^{16,17} As a complement to infection control measures, antimicrobial stewardship may have the potential to reduce the infections due to vancomycin-resistant *Enterococcus* spp.¹⁸⁻²⁶

Antimicrobial stewardship programs that provide guidance on appropriate selection, dosing, route and duration of antimicrobial usage, have been successful in reducing the incidence of multi-drug resistant gram-negative rods and methicillin-resistant *Staphylococcus aureus*.²⁷⁻²⁹ Multiple investigations report successful reductions in VRE incidence in hospitals that use antimicrobial stewardship to restrict all cephalosporins.¹⁸⁻²⁶ However, based on the clinical utility of the cephalosporin class, many hospitals such as ours determined that removing all cephalosporins from the hospital formulary class would not be feasible.

Using previously published human and animal investigations, we hypothesized that specific antibiotic agents may have different effects on the incidence of VRE. Moreover, we specifically hypothesized that ceftriaxone's high biliary excretion and resultant derangement of intestinal microflora would encourage propagation of VRE.³⁰⁻³⁶ The aim of this investigation was to determine if specific antimicrobial agents were associated with VRE-BSI incidence and thus may be good candidates for selective antimicrobial restriction.

Methods

Study Design and Setting

We conducted a retrospective investigation of antimicrobial usage and incidence of VRE-BSI at the University of Alabama at Birmingham Medical Center (UAB). UAB is an urban tertiary care hospital with over 900 beds. The investigation utilized data from January 1, 2005 to August 1, 2008.

The analysis was designed to determine the association between utilization of antimicrobials and VRE-BSI incidence across the entire hospital and within individual care areas. The care areas chosen for individual analysis included two medical intensive care units (ICUs), the medical ICU (MICU) and cardiac ICU (CICU), one surgical ICU (SICU), and two medical floor units (general medicine ward and general medicine/hematology ward). Standard infection control policies including requirements for the room assignments of patients, the use of dedicated instruments and equipment, and the cleaning and disinfecting of contaminated items were in place during the course of the study.¹⁶

Monitoring for VRE-BSI and Nosocomial Infections

Providers obtained blood cultures in all patients with suspected BSI as a matter of routine clinical care. All blood cultures were analyzed with an automated culture system (BacT/ALERT, bioMerieux Industries, Hazelwood, Missouri) and automated susceptibility testing (Microscan Walkaway 96 SI, Siemens Healthcare Diagnostics, Deerfield, IL). All patients who met CDC criteria for BSI with vancomycin-resistant *Enterococcus spp* were included in the study.³⁷ For the hospital level analysis, VRE-BSI incidence was calculated as number of patients with VRE-BSI per 1,000 patient days of care.

For the analysis of individual care areas, patients who met CDC criteria for VRE-BSI and whose index cultures were drawn in the care area or within 12 hours of transfer to another unit were included as cases.³⁷ VRE-BSI incidence was calculated per 1,000 patient days of care within the care area.

Antimicrobial Utilization

Antimicrobial usage is evaluated on a monthly basis by the institution's antimicrobial stewardship committee. The method utilized is based on individual patient charge data in which a day of therapy is represented by a patient receiving at least one dose of the selected antibiotic. Medication usage was quantified as days of therapy/1,000 patient days (DOT). Charge data were collected for all antibacterial and antifungal agents used in the hospital during the study period. Data on antiviral and antiretroviral medications were not collected.

Availability of antimicrobial agents on the formulary was dependent on pharmaceutical acquisition as negotiated by the hospital. In 2005, a national shortage of the ADD-Vantage® system for piperacillin tazobactam occurred impacting the institution's ability to acquire this product. Antimicrobial stewardship programs limiting fluorquinolone use were in place during the entire study period. Specifically, fluoroquinolones could only be prescribed with the oral assent of an infectious disease specialist.

Statistical Analysis

Guided by the results of exploratory graphical analyses, we used regression models for count data and 4-knot restricted cubic splines to evaluate the shape of potential temporal relations between antimicrobial usage and incidence of VRE-BSI in the entire hospital and within individual care areas. At the hospital level we performed time-trend regression analyses with monthly VRE-BSI incidence as the dependent variable and hospital DOT (prior and concurrent month) for each antibiotic on the hospital formulary as the predictor variable. Specifically, and based on the results of preliminary analyses, we used negative binomial regression with adjustment for correlation between consecutive observations to relate monthly VRE-BSI incidence to usage of individual antibiotics (predictor variable) on a log-linear scale (i.e, using log VRE incidence as the outcome variable). In multivariable analysis, the association between monthly VRE-BSI incidence and DOT for a given antibiotic was further adjusted for monthly usage of other antibiotics. We also conducted graphical analysis of residuals to detect time-trends in VRE-BSI incidence unaccounted for by the predictor variables included in the regression model.

At the care-unit level, we performed simple linear regression of relative incidence of VRE and antimicrobial DOT within individual care areas over the entire study period. We also investigated trends in relative incidence of VRE-BSI (Incidence Rate Ratio, SICU reference group) in each care unit as a function of relative usage of each individual antibiotic (DOT, SICU reference group) during the study period. We built a multivariable regression model to assess time-trend in VRE-BSI incidence as a function of usage of each antibiotic, controlling for individual care units. Residual analyses were performed as described above.

Results

There were 1,018,601 patient-days of care at UAB from January 1, 2005 to August 1, 2008. Incidence of VRE-BSI increased from a baseline of 0.06 infections/thousand patient days in January 2005 to 0.17 infections/thousand patient days in July 2008. Mean age of patients with VRE-BSI was 54 years and 42% were male. *E. faecium* caused 227 cases (97%) of VRE-BSI, with the remaining events due to *E. faecalis*. Trends in antibiotic utilization during the study period can be seen in Figure 1. There was a decline in piperacillin tazobactam DOT and an increase in cefepime DOT during 2005 and 2006. There was also a trend toward less use of fluoroquinolones.

Hospital Analysis

Hospital VRE-BSI incidence was log-linearly associated with ceftriaxone DOT during the prior month (IRR of 1.38 per 10 DOT, $p=0.005$; Figure 2). There was no association between VRE-BSI incidence and prior-month usage of cephalexin, cefepime, ceftazidime, vancomycin, piperacillin/tazobactam, or cephalosporins as a class ($p>0.05$ for all comparisons; Figure 3). After controlling for ceftriaxone use, no other antimicrobial agent was predictive of VRE-BSI incidence ($p=0.4$). Residual analysis confirmed that there was no time trend in VRE-BSI incidence left unexplained after accounting for the association with ceftriaxone DOT in the prior month. Unexplained VRE incidence was generally less than ± 1 case per month.

Analysis of Individual Care Areas

Analysis at the care-area (e.g., ICU) level suggested a relationship between local ceftriaxone DOT and local VRE-BSI incidence. A large proportion of the variance in VRE-BSI incidence across care units was explained by a linear relation with relative ceftriaxone use across units ($R^2 = 0.8637$, $p=0.05$). Correlations between relative VRE-BSI incidence and relative usage of ceftazidime, cefepime, cefazolin, vancomycin, and cephalosporins (class) across units were small and not statistically significant ($p>0.12$ for all comparisons).

Multivariable time-trend analysis of the relation between monthly VRE-BSI incidence within a care area and prior-month antibiotic DOT within the same care area found that prior ceftriaxone DOT was directly and log-linearly associated with local VRE-BSI incidence (IRR of 3.34 per 10 DOT, 95% Confidence Interval 1.2–8.9, $p=0.016$; Table 1). Concurrent cefepime DOT was associated with an increased incidence of VRE in some models, but after backward elimination of non-significant antimicrobial covariates, the only variable that remained statistically significant in the final model was prior-month ceftriaxone DOT.

The final model also suggests that type of care unit was related to VRE-BSI incidence. Among ICUs, the Surgical ICU (IRR 0.4, 95% Confidence Interval 0.2–0.8, $p=0.2$) and the Cardiac ICU (IRR 0.4, 95% Confidence Interval 0.2–0.9, $p=0.03$) had less VRE-BSI than the medical ICU. There was no difference between the general medicine and general medicine/hematology wards.

Discussion

In our analysis of antibiotic usage data on more than 100,000 admissions spanning 1 million patient-days of care, prior month utilization of ceftriaxone was a consistent predictor of VRE-BSI over time both in the hospital and within individual care areas. No other antibiotic was so consistently related with VRE-BSI. Notably, utilization of cephalosporins (overall as a class), vancomycin, and piperacillin tazobactam did not correlate with VRE-BSI incidence. Data from this investigation, supported by previous animal models showing a

relationship between ceftriaxone and VRE, may have identified an opportunity to reduce nosocomial VRE infection through targeted antimicrobial stewardship.

Intravenous vancomycin use did not correlate with VRE-BSI incidence at our institution. Although some older literature has suggested a relationship between vancomycin utilization and VRE, several large investigations and reviews of the literature have failed to detect such a strong relationship.³⁸⁻⁴³ A recent analysis of the literature concluded that some of the association between vancomycin utilization and VRE may be due to inappropriate control group selection and confounding by time at risk.⁴⁴ An analysis limited to studies adjusting for length of stay found only a small and non-significant association between vancomycin exposure and acquisition of VRE (pooled O.R.=1.4; 95% C.I.=0.7-2.6).⁴¹ Importantly, previously published antimicrobial stewardship programs designed to limit the use of vancomycin have little impact on VRE incidence without simultaneously improving infection control measures or limiting other antibiotics.⁴⁵

In contrast, published reports of programs that restrict use of the cephalosporin class of antibiotics have documented a reduction in VRE colonization or infection.¹⁸⁻²⁶ Data from these reports provide proof-of-principle that cephalosporin restriction can reduce VRE colonization and infection rates. Despite the available evidence, antimicrobial stewardship committees have not widely adopted restriction protocols that prevent prescribing of the entire cephalosporin class. Restricting the entire cephalosporin class would severely limit provider's options for therapy and could lead to poor patient outcomes and/or overuse of other classes of antimicrobials that could lead to the emergence of other resistant pathogens. Although protocols for restriction of select cephalosporins could be a pragmatic alternative, investigations on the impact of select antibiotic restriction on VRE-BSI incidence have, to our knowledge, not been performed.

Our observation of a consistent association over time between ceftriaxone DOT and VRE-BSI incidence in hospitalized patients is a novel and important finding of this study. Previous investigations with animal models and selected patient populations have implicated ceftriaxone in the propagation and dissemination of VRE.^{30,31,33-36} Ceftriaxone achieves high concentrations in bile and has no activity against *Enterococcus* spp.³⁶ As a result, ceftriaxone is thought to significantly change intestinal flora, reducing microecologic competition and allowing for VRE overgrowth and heavy rectal colonization.^{46,47} Data with other antimicrobial agents suggest that high biliary excretion and minimal activity against enterococci are likely to promote VRE colonization.⁴⁸ VRE "colonization pressure", defined as the percentage of patients with asymptomatic VRE in stool or urine, is known to play an important role in VRE transmission.⁴⁹

Our data associating ceftriaxone use with VRE-BSI incidence on a local and hospital level may represent an important opportunity to curb healthcare expenditure and patient mortality from VRE infections through feasible and rational restriction of ceftriaxone. We are also aware of data suggesting that restriction of ceftriaxone may also impact incidence of *Clostridium difficile* infections, lending further support to the idea that selective restriction of cephalosporins may have beneficial impact on infection control and healthcare related infections.^{50,51} However, there are limitations to our investigation. As an ecologic study, we do not have data on individual patients and cannot adjust for important clinical co-factors, such as severity of illness or history of antibiotic exposure. The hospital formulary at the University of Alabama is limited and some antibiotics that may promote VRE, such as ticarcillin/clavulanate, were not used and could not be analyzed.⁴⁸ In addition, some patients may have been transferred into our institution with ongoing VRE bacteremia and would have been included in our analysis. We were also unable to obtain reliable data on the impact of antibiotics on the incidence of VRE colonization. In an attempt to quantify the

relative risk of colonization and antibiotic DOT, we performed a post-hoc, pilot analysis of VRE colonization in the medical ICU. After adjusting for days in the ICU and previous hospitalization, ceftriaxone DOT was independently associated with increased risk of incident VRE colonization (Odds Ratio 1.2, 95% Confidence Interval 1.01–1.3; $p=0.046$).⁵² Further study of the association between ceftriaxone and VRE-BSI should be conducted, including adjustments for individual patient characteristics and comorbidities, systematic and routine measures of VRE colonization, and detailed collection of antibiotic exposure history.

Finally, antibiotic stewardship is not the only way to prevent VRE-BSI. Infection control interventions (e.g. improved hand hygiene, barrier precautions) are a critical series of actions that aim to interrupt person-to-person transmission.¹⁶ Despite these precautions, VRE is increasing in US hospitals.⁵³ Maintaining high rates of hand hygiene and diligent isolation is challenging and expanded testing for persons asymptomatically colonized with VRE is not routine.⁵⁴ Thus, in conjunction with infection control efforts, improved methods of VRE prevention are needed. We believe that data from our investigation should prompt aggressive investigation of the impact of individual antimicrobials on the incidence of VRE colonization and infection. Results from such investigations could identify pragmatic, effective, and selective antibiotic stewardship protocols aimed to prevent the unacceptably high human and financial costs associated with VRE-BSI infection.

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References

1. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol.* 2008; 29(11):996–1011. [PubMed: 18947320]
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004; 39(3):309–317. [PubMed: 15306996]
3. Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis.* 2007; 58(2):163–170. [PubMed: 17368801]
4. System NNIS. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control.* 2004; 32(8):470–485. [PubMed: 15573054]
5. Scott, RD. Division of Healthcare Quality Promotion National Center for Preparedness D, and Control of Infectious Diseases Coordinating Center for Infectious Diseases Centers for Disease Control and Prevention, editor. The Direct Medical Costs of Healthcare-Associated Infections in US Hospitals and the Benefits of Prevention. Vol http://www.cdc.gov/ncidod/dhqp/pdf/Scott_CostPaper.pdf2009
6. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep.* 2007; 122(2):160–166. [PubMed: 17357358]
7. Carmeli Y, Eliopoulos G, Mozaffari E, Samore M. Health and economic outcomes of vancomycin-resistant enterococci. *Arch Intern Med.* 2002; 162(19):2223–2228. [PubMed: 12390066]

8. Song X, Srinivasan A, Plaut D, Perl TM. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. *Infect Control Hosp Epidemiol.* 2003; 24(4):251–256. [PubMed: 12725353]
9. Reik R, Tenover FC, Klein E, McDonald LC. The burden of vancomycin-resistant enterococcal infections in US hospitals, 2003 to 2004. *Diagn Microbiol Infect Dis.* 2008; 62(1):81–85. [PubMed: 18508225]
10. Song JH, Ko KS, Suh JY, et al. Clinical implications of vancomycin-resistant *Enterococcus faecium* (VRE) with VanD phenotype and vanA genotype. *J Antimicrob Chemother.* 2008; 61(4): 838–844. [PubMed: 18230690]
11. DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clin Infect Dis.* 2005; 41(3):327–333. [PubMed: 16007529]
12. Garbutt JM, Ventrapragada M, Littenberg B, Mundy LM. Association between resistance to vancomycin and death in cases of *Enterococcus faecium* bacteremia. *Clin Infect Dis.* 2000; 30(3): 466–472. [PubMed: 10722429]
13. Lucas GM, Lechtzin N, Puryear DW, Yau LL, Flexner CW, Moore RD. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. *Clin Infect Dis.* 1998; 26(5):1127–1133. [PubMed: 9597241]
14. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. *Ann Intern Med.* 2001; 135(7): 484–492. [PubMed: 11578151]
15. Bhavnani SM, Drake JA, Forrest A, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. *Diagn Microbiol Infect Dis.* 2000; 36(3):145–158. [PubMed: 10729656]
16. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control.* 2007; 35(10 Suppl 2):S165–193. [PubMed: 18068814]
17. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2009; 48(1):1–12. [PubMed: 19035777]
18. Quale J, Landman D, Saurina G, Atwood E, DiTore V, Patel K. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin Infect Dis.* 1996; 23(5):1020–1025. [PubMed: 8922796]
19. Bradley SJ, Wilson AL, Allen MC, Sher HA, Goldstone AH, Scott GM. The control of hyperendemic glycopeptide-resistant *Enterococcus* spp. on a haematology unit by changing antibiotic usage. *J Antimicrob Chemother.* 1999; 43(2):261–266. [PubMed: 11252332]
20. Montecalvo MA, Jarvis WR, Uman J, et al. Infection-control measures reduce transmission of vancomycin-resistant enterococci in an endemic setting. *Ann Intern Med.* 1999; 131(4):269–272. [PubMed: 10454948]
21. Smith DW. Decreased antimicrobial resistance after changes in antibiotic use. *Pharmacotherapy.* 1999; 19(8 Pt 2):129S–132S. discussion 133S–137S. [PubMed: 10456610]
22. Manzella J, Benenson R, Pellerin G, et al. Choice of antibiotic and risk of colonization with vancomycin-resistant *Enterococcus* among patients admitted for treatment of community-acquired pneumonia. *Infect Control Hosp Epidemiol.* 2000; 21(12):789–791. [PubMed: 11140916]
23. May AK, Melton SM, McGwin G, Cross JM, Moser SA, Rue LW. Reduction of vancomycin-resistant enterococcal infections by limitation of broad-spectrum cephalosporin use in a trauma and burn intensive care unit. *Shock.* 2000; 14(3):259–264. [PubMed: 11028540]
24. Nourse C, Byrne C, Murphy H, Kaufmann ME, Clarke A, Butler K. Eradication of vancomycin resistant *Enterococcus faecium* from a paediatric oncology unit and prevalence of colonization in hospitalized and community-based children. *Epidemiol Infect.* 2000; 124(1):53–59. [PubMed: 10722130]
25. Puzniak LA, Mayfield J, Leet T, Kollef M, Mundy LM. Acquisition of vancomycin-resistant enterococci during scheduled antimicrobial rotation in an intensive care unit. *Clin Infect Dis.* 2001; 33(2):151–157. [PubMed: 11418873]

26. Lautenbach E, LaRosa LA, Marr AM, Nachamkin I, Bilker WB, Fishman NO. 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. *Clin Infect Dis.* 2003; 36(4):440–446. [PubMed: 12567301]
27. Loeffler JM, Garbino J, Lew D, Harbarth S, Rohner P. Antibiotic consumption, bacterial resistance and their correlation in a Swiss university hospital and its adult intensive care units. *Scand J Infect Dis.* 2003; 35(11–12):843–850. [PubMed: 14723360]
28. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis.* 2004; 38 (Suppl 4):S341–345. [PubMed: 15127367]
29. Empey KM, Rapp RP, Evans ME. The effect of an antimicrobial formulary change on hospital resistance patterns. *Pharmacotherapy.* 2002; 22(1):81–87. [PubMed: 11794434]
30. Donskey CJ, Chowdhry TK, Hecker MT, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med.* 2000; 343(26):1925–1932. [PubMed: 11136263]
31. Donskey CJ, Hoyen CK, Das SM, Helfand MS, Hecker MT. Recurrence of vancomycin-resistant *Enterococcus* stool colonization during antibiotic therapy. *Infect Control Hosp Epidemiol.* 2002; 23(8):436–440. [PubMed: 12186208]
32. Paterson DL, Muto CA, Ndirangu M, et al. Acquisition of rectal colonization by vancomycin-resistant *Enterococcus* among intensive care unit patients treated with piperacillin-tazobactam versus those receiving cefepime-containing antibiotic regimens. *Antimicrob Agents Chemother.* 2008; 52(2):465–469. [PubMed: 18025111]
33. Donskey CJ, Hanrahan JA, Hutton RA, Rice LB. Effect of parenteral antibiotic administration on persistence of vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J Infect Dis.* 1999; 180(2):384–390. [PubMed: 10395853]
34. Lakticova V, Hutton-Thomas R, Meyer M, Gurkan E, Rice LB. Antibiotic-induced enterococcal expansion in the mouse intestine occurs throughout the small bowel and correlates poorly with suppression of competing flora. *Antimicrob Agents Chemother.* 2006; 50(9):3117–3123. [PubMed: 16940110]
35. Rice LB, Lakticova V, Helfand MS, Hutton-Thomas R. In vitro antienterococcal activity explains associations between exposures to antimicrobial agents and risk of colonization by multiresistant enterococci. *J Infect Dis.* 2004; 190(12):2162–2166. [PubMed: 15551215]
36. Rice LB, Hutton-Thomas R, Lakticova V, Helfand MS, Donskey CJ. Beta-lactam antibiotics and gastrointestinal colonization with vancomycin-resistant enterococci. *J Infect Dis.* 2004; 189(6):1113–1118. [PubMed: 14999616]
37. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control.* 2008; 36(5):309–332. [PubMed: 18538699]
38. Fridkin SK, Edwards JR, Courval JM, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. *Annals of internal medicine.* 2001; 135(3):175–183. [PubMed: 11487484]
39. Kritsotakis EI, Christidou A, Roubelaki M, Tselentis Y, Gikas A. The dynamic relationship between antibiotic use and the incidence of vancomycin-resistant *Enterococcus*: time-series modelling of 7-year surveillance data in a tertiary-care hospital. *Clin Microbiol Infect.* 2008; 14(8):747–754. [PubMed: 18727798]
40. Harbarth S, Cosgrove S, Carmeli Y. Effects of antibiotics on nosocomial epidemiology of vancomycin-resistant enterococci. *Antimicrob Agents Chemother.* 2002; 46(6):1619–1628. [PubMed: 12019066]
41. Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis.* 2001; 32(7):1055–1061. [PubMed: 11264034]
42. Carmeli Y, Eliopoulos GM, Samore MH. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant *Enterococcus*. *Emerg Infect Dis.* 2002; 8(8):802–807. [PubMed: 12141965]

43. Ostrowsky BE, Venkataraman L, D'Agata EM, Gold HS, DeGirolami PC, Samore MH. Vancomycin-resistant enterococci in intensive care units: high frequency of stool carriage during a non-outbreak period. *Arch Intern Med.* 1999; 159(13):1467–1472. [PubMed: 10399898]
44. Carmeli Y, Samore MH, Huskins C. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci: a meta-analysis. *Arch Intern Med.* 1999; 159(20):2461–2468. [PubMed: 10665895]
45. de Bruin MA, Riley LW. Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review. *BMC Infect Dis.* 2007; 7:24. [PubMed: 17425800]
46. Guggenbichler JP, Kofler J, Allerberger F. The influence of third-generation cephalosporins on the aerobic intestinal flora. *Infection.* 1985; 13 (Suppl 1):S137–139. [PubMed: 4055044]
47. Donskey CJ, Hume ME, Callaway TR, Das SM, Hoyen CK, Rice LB. Inhibition of vancomycin-resistant enterococci by an in vitro continuous-flow competitive exclusion culture containing human stool flora. *J Infect Dis.* 2001; 184(12):1624–1627. [PubMed: 11740742]
48. Winston LG, Charlebois ED, Pang S, Bangsberg DR, Perdreau-Remington F, Chambers HF. Impact of a formulary switch from ticarcillin-clavulanate to piperacillin-tazobactam on colonization with vancomycin-resistant enterococci. *Am J Infect Control.* 2004; 32(8):462–469. [PubMed: 15573053]
49. Bonten MJ, Slaughter S, Ambergen AW, et al. The role of "colonization pressure" in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch Intern Med.* 1998; 158(10):1127–1132. [PubMed: 9605785]
50. Aldeyab MA, Harbarth S, Vernaz N, et al. Quasiexperimental study of the effects of antibiotic use, gastric acid-suppressive agents, and infection control practices on the incidence of *Clostridium difficile*-associated diarrhea in hospitalized patients. *Antimicrobial agents and chemotherapy.* 2009; 53(5):2082–2088. [PubMed: 19289520]
51. Kaier K, Frank U. Relationship between antibiotic consumption and *Clostridium difficile*-associated diarrhea: an epidemiological note. *Antimicrobial agents and chemotherapy.* 2009; 53(10):4574–4575. [PubMed: 19770290]
52. McKinnell, JA.; Powderly, AL.; Kunz, DF.; MP. Individual Antimicrobials and Risk of VRE Colonization. 48th Annual Meeting of the Infectious Disease Society of America; Vancouver BC, Canada. October 21–24, 2010; 2010. p. Abstract 3365
53. Ramsey AM, Zilberberg MD. Secular trends of hospitalization with vancomycin-resistant enterococcus infection in the United States, 2000–2006. *Infect Control Hosp Epidemiol.* 2009; 30(2):184–186. [PubMed: 19125679]
54. Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med.* 2011; 364(15):1407–1418. [PubMed: 21488763]

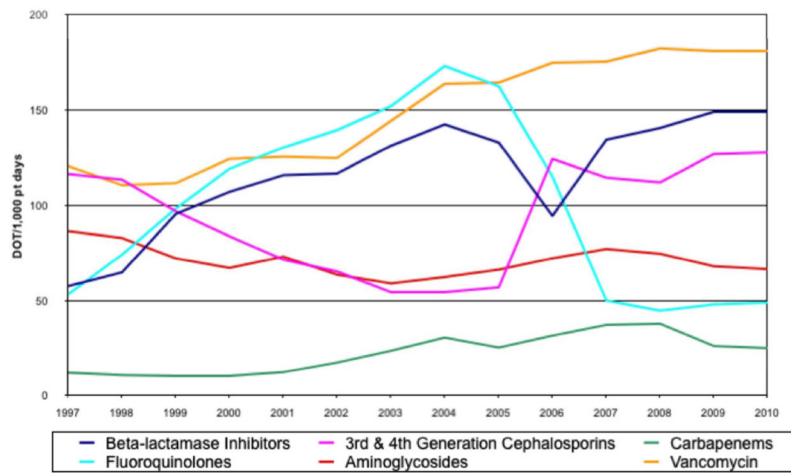


Figure 1.

Antibiotic Days of Therapy (DOT) per 1,000 patient days of care at the University Hospital in Birmingham, Alabama plotted per year. A sharp decline in fluroquinolone DOT is noted starting in 2004. This is co-incident with the initiation of antimicrobial stewardship protocols limiting use of fluroquinolones. A sharp decline in Beta-lactamase inhibitors in 2006 was the result of nationwide shortages in piperacillin/tazobactam.

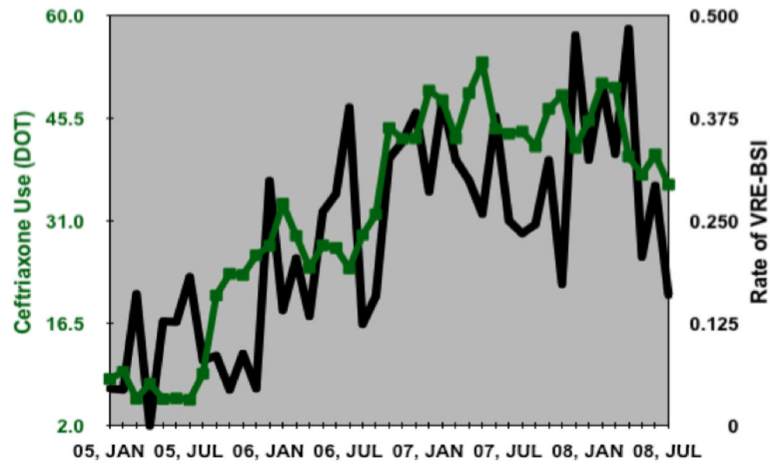


Figure 2.

The number of patients with VRE bloodstream infections per 1,000 patient days of care (shown in black) and antibiotic Days of Therapy (DOT) per 1,000 patient days of care (shown in green) plotted per month. Hospital VRE-BSI incidence was log-linearly associated with ceftriaxone DOT during the prior month (IRR of 1.38 per 10 DOT, $p=0.005$). Residual analysis confirms that there is no trend in VRE-BSI incidence left unexplained once the association with ceftriaxone DOT had been accounted for. Unexplained VRE incidence was generally less than ± 1 case per month.

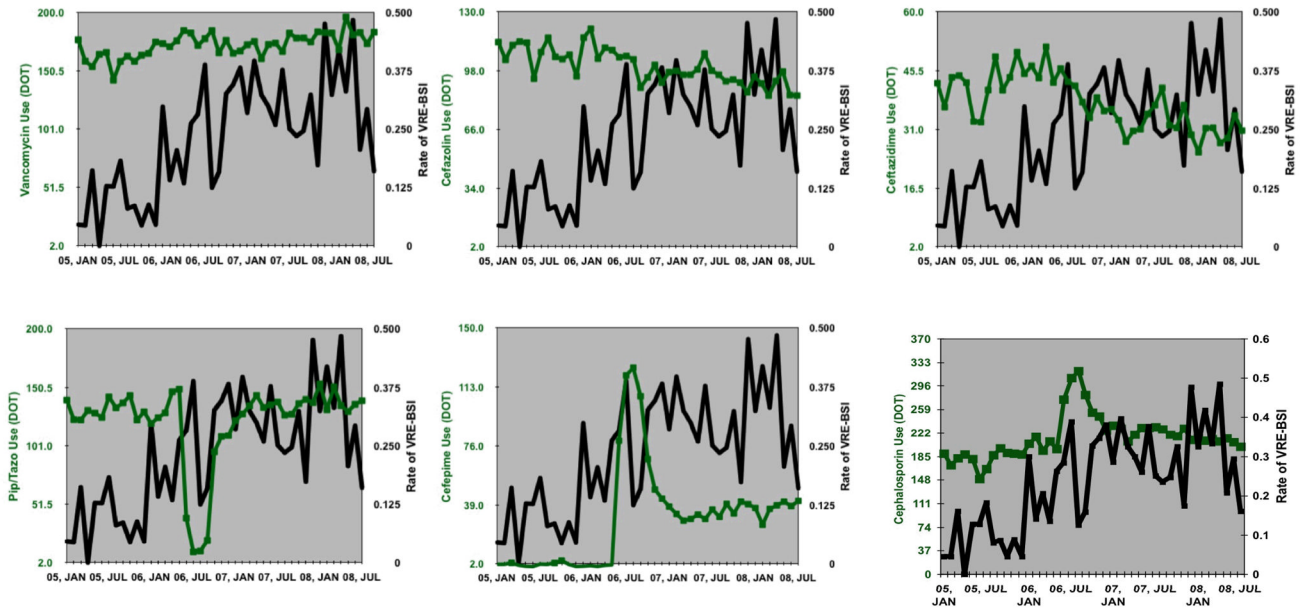


Figure 3. The number of patients with VRE bloodstream infections per 1,000 patient days of care (shown in black) and antibiotic Days of Therapy (DOT) per 1,000 patient days of care (shown in green) plotted per month. Cephalosporin (class) DOT were not predictive of VRE-BSI incidence ($p=0.702$), nor were other antibiotics tested ($p = 0.4$ for all comparisons)

Table 1
Multivariable Model of Association between Antibiotic DOT and VRE-BSI within Individual Care Areas

Predictor Variable	Incidence Rate Ratio	95% Confidence Interval	p-Value
General Medicine Ward	0.5	0.2–0.9	0.034
General Medicine-Hematology Ward	0.3	0.2–0.7	0.003
CCU	0.4	0.2–0.9	0.026
SICU	0.4	0.2–0.8	0.016
MICU (referent)	-	-	-
Ceftriaxone DOT (prior month)	3.3	1.2–8.9	0.016