ORIGINAL ARTICLE

Association between Vancomycin-Resistant Enterococci Bacteremia and Ceftriaxone Usage

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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 that ceftriaxone may be associated with VRE proliferation. We measured antimicrobial usage and VRE bloodstream infection (VRE-BSI) incidence to test our hypothesis that increased ceftriaxone usage would be associated with a higher incidence of VRE-BSI.

DESIGN. Retrospective cohort study.

SETTING. University of Alabama at Birmingham Medical Center, a 900-bed urban tertiary care hospital.

PARTICIPANTS. All patients admitted during the study period contributed data.

METHODS. We conducted a retrospective analysis of antimicrobial usage and VRE-BSI from 2005 to 2008 (43 months). Antimicrobial usage was quantified as days of therapy (DOTs) per 1,000 patient-days. VRE-BSI incidence was calculated as cases per 1,000 patient-days. Negative binomial regression with adjustment for correlation between consecutive observations was used to measure 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 per 1,000 patient-days. Hospital VRE-BSI incidence was associated with prior-month ceftriaxone DOTs (incidence rate ratio, 1.38 per 10 DOTs; $P = .005$). After controlling for ceftriaxone, prior-month cephalosporin usage (class) was not predictive of VRE-BSI ($P = .70$). Similarly, prior-month usage of piperacillin-tazobactam, ceftazidime, cefepime, cefazolin, or vancomycin was not predictive of VRE-BSI when considered individually ($P \geq .4$ for all comparisons). The final model suggests that type of intensive care unit was related to VRE-BSI incidence.

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

Infect Control Hosp Epidemiol 2012;33(7):718-724

Vancomycin-resistant enterococci bloodstream infections (VRE-BSIs) are a major cause of morbidity and mortality for hospitalized patients. *Enterococcus* species 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 (ICUs) indicate that VRE represented less than 1% of enterococcal isolates in 1990 but currently exceed 30%.[1-4] On the basis of conservative incidence estimates, VRE-BSI leads to $2 billion in annual US healthcare costs and may be related to 10,000 to 25,000 deaths per year.[5-15] The Infectious Diseases 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 infections due to vancomycin-resistant *Enterococcus* species.[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 multidrug-resistant gram-negative rods and methicillin-resistant *Staphylococcus aureus*.[27-29] Multiple investigations report successful reductions in VRE incidence in

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Received November 15, 2011; accepted February 8, 2012; electronically published May 14, 2012.

 0899-823X/2012/3307-0011$15.00. DOI: 10.1086/666331

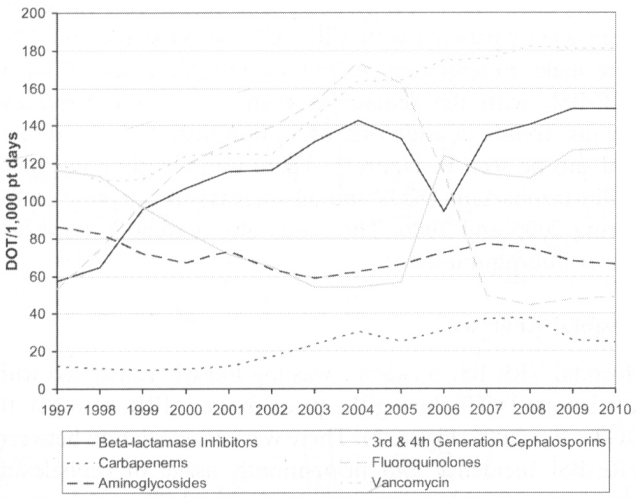

FIGURE 1. Antibiotic days of therapy (DOTs) per 1,000 patient-days of care at the University Hospital in Birmingham, Alabama, plotted per year. A sharp decline in fluoroquinolone DOTs is noted starting in 2004. This is coincident with the initiation of antimicrobial stewardship protocols limiting the use of fluoroquinolones. A sharp decline in β-lactamase inhibitors in 2006 was the result of nationwide shortages in piperacillin-tazobactam.

hospitals that use antimicrobial stewardship to restrict all cephalosporins.[18-26] However, given the clinical utility of the cephalosporin class, many hospitals (such as ours) determined that removing all cephalosporins from the hospital formulary would not be feasible.

On the basis of 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 the resultant derangement of intestinal microflora would encourage propagation of VRE.[30-36] The aim of this investigation was to determine whether 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 more than 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 2 medical ICUs, the medical ICU (MICU) and the cardiac ICU (CICU); 1 surgical ICU (SICU); and 2 medical floor units, the general medicine ward and the 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 for all patients with suspected BSI as a matter of routine clinical care. All blood cultures were analyzed with an automated culture system (BacT/ALERT, bioMérieux) and automated susceptibility testing (MicroScan WalkAway 96 SI, Siemens Healthcare Diagnostics). All patients who met Centers for Disease Control and Prevention (CDC) criteria for BSI with vancomycin-resistant *Enterococcus* species were included in the study.[37] For the hospital-level analysis, VRE-BSI incidence was calculated as the 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 (DOT) is represented by a patient receiving at least 1 dose of the selected antibiotic. Medication usage was quantified as DOTs per 1,000 patient-days. 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 fluoroquinolone use were in place during the entire study period. Specifically, fluoroquinolones could be prescribed only 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 relationships 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 DOTs (prior and concurrent

https://doi.org/10.1086/666331 Published online by Cambridge University Press

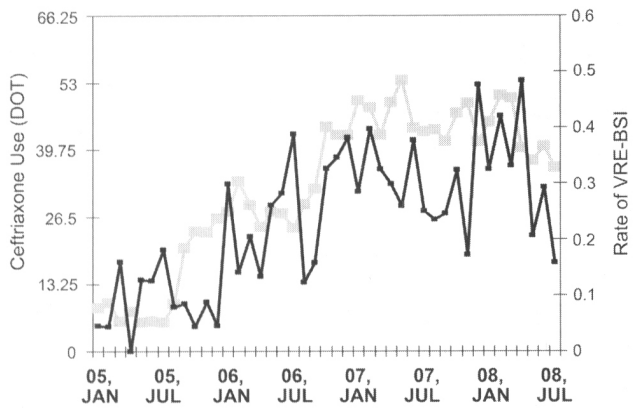

FIGURE 2. Number of patients with vancomycin-resistant enterococci bloodstream infections (VRE-BSIs) per 1,000 patient-days of care and antibiotic days of therapy (DOTs) per 1,000 patient-days of care plotted per month. Hospital VRE-BSI incidence was log-linearly associated with ceftriaxone DOTs during the prior month (incidence rate ratio, 1.38 per 10 DOTs; $P = .005$). Residual analysis confirmed that there was no trend in VRE-BSI incidence left unexplained once the association with ceftriaxone DOTs had been accounted for. Unexplained VRE incidence was generally less than ± 1 case per month.

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 (ie, using log VRE incidence as the outcome variable). In multivariable analysis, the association between monthly VRE-BSI incidence and DOTs 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 the relative incidence of VRE and the antimicrobial DOTs within individual care areas over the entire study period. We also investigated trends in the relative incidence of VRE-BSI (incidence rate ratio [IRR], with SICU as the reference group) in each care unit as a function of the relative usage of each individual antibiotic (DOTs, with SICU as the reference group) during the study period. We built a multivariable regression model to assess the time trend in VRE-BSI incidence as a function of the 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. The incidence of VRE-BSI increased from a baseline of 0.06 per 1,000 patient-days in January 2005 to 0.17 per 1,000 patient-days in July 2008. The mean age of patients with VRE-BSI was 54 years, and 42% were male. *Enterococcus faecium* caused 227 cases (97%) of VRE-BSI, with the remaining events due to *Enterococcus faecalis*. Trends in antibiotic utilization during the study period can be seen in Figure 1. There was a decline in piperacillin-tazobactam DOTs and an increase in cefepime DOTs 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 DOTs during the prior month (IRR, 1.38 per 10 DOTs; $P = .005$; 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 ($P > .05$ for all comparisons; Figure 3). After controlling for ceftriaxone use, no other antimicrobial agent was predictive of VRE-BSI incidence ($P \geq .4$). Residual analysis confirmed that there was no time trend in VRE-BSI incidence left unexplained after accounting for the association with ceftriaxone DOTs 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 level (eg, ICU) suggested a relationship between local ceftriaxone DOTs and local VRE-BSI incidence. A large proportion of the variance in VRE-BSI incidence across care units was explained by a linear relationship with relative ceftriaxone use across units ($R^2 = 0.8637$; $P = .05$). 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 ($P > .12$ for all comparisons).

Multivariable time-trend analysis of the relationship between monthly VRE-BSI incidence within a care area and prior-month antibiotic DOTs within the same care area found that prior ceftriaxone DOTs was directly and log-linearly associated with local VRE-BSI incidence (IRR, 3.34 per 10 DOTs [95% confidence interval, 1.2–8.9]; $P = .016$; Table 1). Concurrent cefepime DOTs was associated with an increased incidence of VRE in some models, but after backward elimination of nonsignificant antimicrobial covariates the only variable that remained statistically significant in the final model was prior-month ceftriaxone DOTs.

The final model also suggests that type of care unit is related to VRE-BSI incidence. Among ICUs, the SICU (IRR, 0.4 [95% confidence interval, 0.2–0.8]; $P = .2$) and the CICU (IRR, 0.4 [95% confidence interval, 0.2–0.9]; $P = .03$) had fewer VRE-BSIs than the MICU. There was no difference between the general medicine ward and the general medicine/hematology ward.

https://doi.org/10.1086/666331 Published online by Cambridge University Press

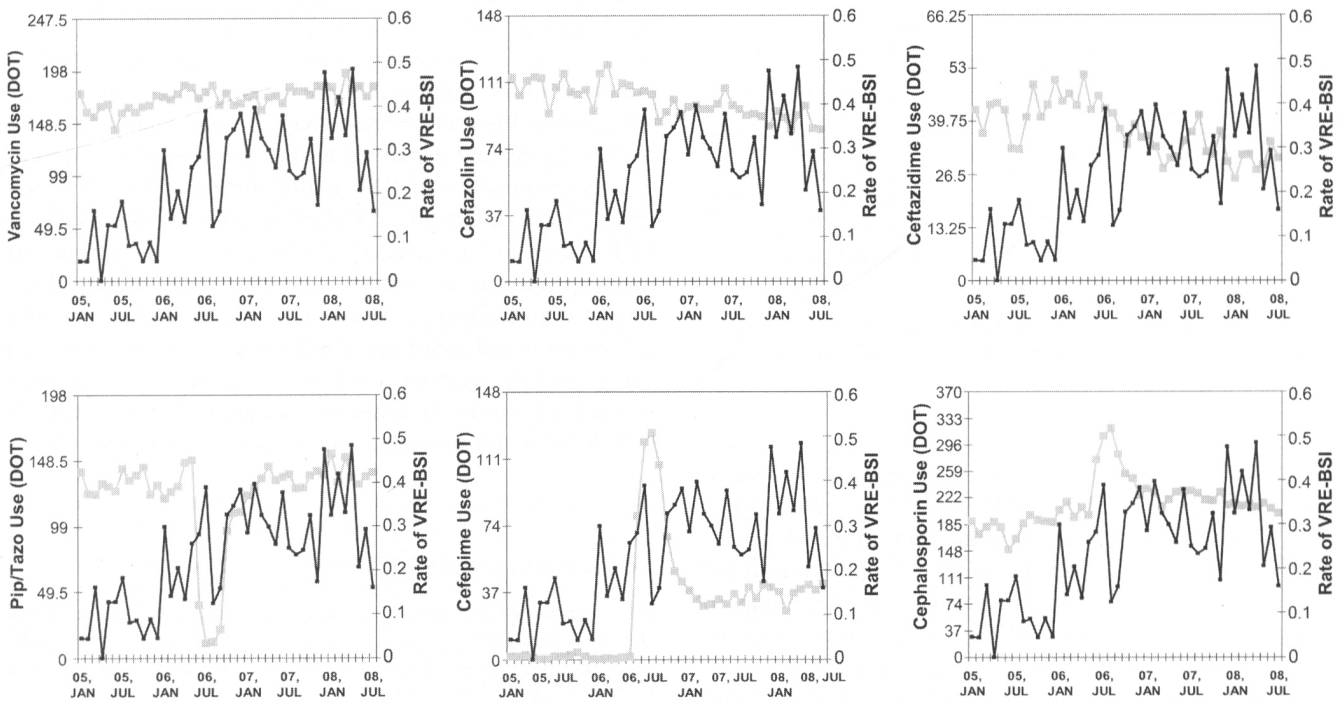

FIGURE 3. Number of patients with vancomycin-resistant enterococci bloodstream infections (VRE-BSIs) per 1,000 patient-days of care and antibiotic days of therapy (DOTs) per 1,000 patient-days of care plotted per month. Cephalosporin (class) DOTs were not predictive of VRE-BSI incidence ($P = .702$), nor were other antibiotics tested ($P \geq .4$ for all comparisons).

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 nonsignificant association between vancomycin exposure and acquisition of VRE (pooled odds ratio, 1.4 [95% confidence interval, 0.7–2.6]).[41] Importantly, previously published antimicrobial stewardship programs designed to limit the use of vancomycin have had little impact on VRE incidence without simultaneously improving infection control measures or limiting other antibiotics.[45]

In contrast, published reports on 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 a provider's options for therapy and could lead to poor patient outcomes and/or overuse of other classes of antimicrobials, which could lead to the emergence of other resistant pathogens. Although protocols for restriction of select cephalosporins could be a pragmatic alternative, investigations of 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 DOTs 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* species.[36] As a result, ceftriaxone is thought to significantly change intestinal flora, reducing microecologic

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TABLE 1. Multivariable Model of Association between Antibiotic Days of Therapy (DOTs) and Vancomycin-Resistant Enterococcal Bloodstream Infection within Individual Care Areas

Predictor variable	IRR (95% CI)	*P*
General medicine ward	0.5 (0.2–0.9)	.034
General medicine/hematology ward	0.3 (0.2–0.7)	.003
CICU	0.4 (0.2–0.9)	.026
SICU	0.4 (0.2–0.8)	.016
MICU	1.0 (referent)	
Ceftriaxone DOTs (prior month)	3.3 (1.2–8.9)	.016

NOTE. CI, confidence interval; CICU, cardiac intensive care unit; IRR, incidence rate ratio; MICU, medical intensive care unit; SICU, surgical intensive care unit.

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 the incidence of *Clostridium difficile* infections, lending further support to the idea that selective restriction of cephalosporins may have a beneficial impact on infection control and healthcare-related infections.[50,51] However, there are limitations to our investigation. As this was an ecologic study, we do not have data on individual patients and cannot adjust for important clinical cofactors, such as severity of illness or history of antibiotic exposure. The hospital formulary at UAB 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 to 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 DOTs, we performed a post hoc pilot analysis of VRE colonization in the MICU. After adjusting for days in the ICU and previous hospitalization, ceftriaxone DOTs was independently associated with increased risk of incident VRE colonization (odds ratio, 1.2 [95% confidence interval, 1.01–1.3]; $P = .046$).[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 (eg, improved hand hygiene and 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 at preventing the unacceptably high human and financial costs associated with VRE-BSI.

ACKNOWLEDGMENTS

We appreciate the assistance of Samantha Eells (Infectious Disease Clinical Outcomes Research Unit) in manuscript preparation and revision. J.A.M. appreciates the logistic support of the General Clinical Research Center at Harbor-UCLA Medical Center.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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REFERENCES

1. Hidron AI, Edwards JR, Patel J, et al. 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.
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.
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.
4. National Nosocomial Infections Surveillance System. 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.
5. Scott RD. *The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention.* Division of Healthcare Quality Promotion, National Center for Preparedness, Detection, and Control of Infectious Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention. Published March 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf. Accessed November 5, 2011.

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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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–S193.
17. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! an update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48(1):1–12.
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.
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.
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.
21. Smith DW. Decreased antimicrobial resistance after changes in antibiotic use. *Pharmacotherapy* 1999;19(8 pt 2):129S–132S; discussion 133S–137S.
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.
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.
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.
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.
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.
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.
28. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis* 2004;38(suppl 4): S341–S345.
29. Empey KM, Rapp RP, Evans ME. The effect of an antimicrobial formulary change on hospital resistance patterns. *Pharmacotherapy* 2002;22(1):81–87.
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.
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.
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.
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.
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.
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.
36. Rice LB, Hutton-Thomas R, Lakticova V, Helfand MS, Donskey CJ. β-Lactam antibiotics and gastrointestinal colonization with

vancomycin-resistant enterococci. *J Infect Dis* 2004;189(6): 1113–1118.
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.
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. *Ann Intern Med* 2001;135(3):175–183.
39. Kritsotakis EI, Christidou A, Roumbelaki 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.
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.
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.
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.
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.
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.
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.
46. Guggenbichler JP, Kofler J, Allerberger F. The influence of third-generation cephalosporins on the aerobic intestinal flora. *Infection* 1985;13(suppl 1):S137–S139.
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.
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.
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.
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. *Antimicrob Agents Chemother* 2009;53(5):2082–2088.
51. Kaier K, Frank U. Relationship between antibiotic consumption and *Clostridium difficile*–associated diarrhea: an epidemiological note. *Antimicrob Agents Chemother* 2009;53(10):4574–4575.
52. McKinnell JA, Powderly AL, Kunz DF, Patel M. Individual antimicrobials and risk of VRE colonization. Presented at: 48th Annual Meeting of the Infectious Diseases Society of America; Vancouver; October 21–24, 2010. 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.
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.