

Trends in Antibacterial Use in US Academic Health Centers

2002 to 2006

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Background: Antibacterial drug use is a major risk factor for bacterial resistance, but little is known about antibacterial use in US hospitals. The objectives of this study were to characterize trends in antibacterial use in a sample of US hospitals and to identify predictors of use.

Methods: We measured systemic antibacterial use from validated claims data at 22 university teaching hospitals from January 1, 2002, through December 31, 2006, and we examined potential predictors of use in 2006, including hospital and patient demographics and antibacterial stewardship policies.

Results: A total of 775 731 adult patients were discharged in 35 hospitals during 2006, and 492 721 (63.5%) received an antibacterial drug. The mean (SD) total antibacterial use increased from 798 (113) days of therapy per 1000 patient days in 2002 to 855 (153) in 2006 ($P < .001$). Fluoroquinolones were the most commonly

used antibacterial class from 2002 through 2006, and use remained stable. Piperacillin sodium–tazobactam sodium and carbapenem use increased significantly, and aminoglycoside use declined. Cefazolin sodium was the most commonly used antibacterial drug in 2002 and 2003 but was eclipsed by vancomycin hydrochloride in 2004. The strongest predictor of broad-spectrum antibacterial use was explained by differences across hospitals in the mean durations of therapy.

Conclusions: Total antibacterial use in adults increased significantly from 2002 through 2006 in this sample of academic health centers, driven by increases in the use of broad-spectrum agents and vancomycin. These developments have important implications for acquired resistance among nosocomial pathogens, particularly for methicillin-resistant *Staphylococcus aureus* (MRSA).

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ANTIBACTERIAL USE SELECTS for bacterial resistance, which may be amplified by patient-to-patient transmission of resistant isolates.¹ Infection with drug-resistant bacteria is associated with greater morbidity, mortality, and costs than infection with susceptible bacteria.^{2,3} Many professional societies and national agencies have recommended monitoring antibacterial use and linking patterns of use to resistance.⁴⁻⁷

However, measurement of antibacterial drug use in US hospitals has proved difficult, and few multicenter investigations have characterized use.⁸⁻¹¹ The largest multicenter antibacterial use surveillance program in the United States has been the Centers for Disease Control and Prevention's phases 1 through 3 (1995-2000) of the Intensive Care Antimicrobial Resistance Epidemiology project.¹²⁻¹⁴ This project measured intensive care unit use of antibacterial agents and did not report aggregated hospitalwide use. The objective of the present study was to characterize trends in aggregated antibacterial

drug use among adult inpatients in an alliance of US academic health centers from January 1, 2002, through December 31, 2006. We also sought to identify predictors of the use of antibacterial agents so that hospitals might benchmark their use in comparison with similar institutions.^{6,10}

METHODS

HOSPITAL DATA SOURCE

The institutional review board at Virginia Commonwealth University, Richmond, approved this investigation. The University Health System Consortium (<http://www.uhc.edu>) is an alliance of academic health centers that provides services for benchmarking and quality improvement initiatives to member hospitals. A subset of consortium hospitals subscribes to the Clinical Resource Manager (CRM) database, an electronic repository that collects data (including medication use) from participating institutions. The CRM database extracts medication use data from charge transaction masters and inpatient billing files and obtains demographic, procedure, and diagnosis data from discharge abstract summaries, includ-

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ing *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes. Data from the CRM database have been used in previous investigations.^{15,16} The number of hospitals subscribing to this database that agreed to provide data to the investigators increased from 23 hospitals in 2002 to 35 hospitals in 2006.

ANTIBACTERIAL USE DATA

Antibacterial drugs for systemic use (parenteral and oral) were characterized for adult (>18 years) inpatients discharged from January 1, 2002, through December 31, 2006. Patient-level data were aggregated to hospitalwide use. Ninety-one different antibacterial agents were searched for by generic drug codes. Many of these were rarely used such as streptomycin and sulfadiazine. We eliminated 48 antibacterial agents from further analysis; the sum use of these was less than 1% of total drug use. The remaining 43 drugs were categorized into 16 groups (**Table 1**). In addition, we were specifically interested in measuring and assessing the changes in the following 2 subgroups: (1) 5 classes of broad-spectrum antibacterial drugs that are commonly used for treatment of nosocomial infections (aminoglycosides, fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems, and piperacillin sodium–tazobactam sodium) and (2) vancomycin hydrochloride.

The days of therapy (DOTs) for each antibacterial drug administered to individual patients was determined. The mean duration of therapy for each drug was calculated, and the mean duration of therapy for all antibacterial drugs was determined. The aggregate of antibacterial use in each hospital for each year was expressed as DOTs per 1000 patient-days (PDs). For example, if a patient received a single dose of an antibacterial drug on a given day, whether or not multiple doses are usually administered, it was registered as 1 DOT. If a patient received more than 1 antibacterial drug on the same day, each antibacterial was counted as 1 DOT. Days of hospitalization for each patient at each hospital were summed to provide total PDs. Although the defined daily dose method is recommended by the World Health Organization to estimate drug use, important deficiencies of the defined daily dose method compared with direct measure of the DOTs have recently been reported.⁹ Specifically, the defined daily dose method is intended to estimate the DOTs from the quantity of drug purchased by the hospital. In most countries, purchase data are more readily available than measures of the DOTs. However, electronic capture of pharmacy dispensing and administration data now makes it feasible to measure DOTs directly.

VALIDATION OF ANTIBACTERIAL DRUG USE

Virginia Commonwealth University Health System is a participant in the CRM database. We validated the CRM database regarding the reported identity and DOTs of antibacterial agents that were received by patients at Virginia Commonwealth University Health System in the following manner. We obtained from the CRM database all adult inpatients at Virginia Commonwealth University Health System with a secondary diagnosis of *Clostridium difficile* disease by ICD-9-CM code 008.45 during the last 2 quarters of 2004 and during the first 2 quarters of 2005. The CRM database also identified all antimicrobial agents, proton-pump inhibitors, and histamine receptor blocking agents that were received, including the duration of therapy for each. This query identified 36 patients; for these patients, there were 232 exposures to the drugs already listed. These exposures were then compared with data obtained from manual review of the Virginia Commonwealth University Health System electronic medical record for the same patients. We de-

Table 1. Systemic Use of 43 Antibacterial Drugs Categorized Into 16 Groups

Group	Antibacterials
Tetracyclines	Tetracycline, doxycycline
β-Lactamase labile penicillins	Penicillin G sodium, penicillin G potassium, ampicillin, amoxicillin, piperacillin
Antistaphylococcal penicillins	Nafcillin sodium, oxacillin sodium, dicloxacillin
β-Lactam/β-lactamase inhibitor combinations	Amoxicillin–clavulanate potassium, piperacillin–tazobactam, ticarcillin–clavulanate, ampicillin–sulbactam
First-generation cephalosporins	Cefazolin, cephalexin
Second-generation cephalosporins	Cefaclor, cefuroxime, cefoxitin, cefotetan
Third- or fourth-generation cephalosporins	Ceftriaxone sodium, ceftazidime, cefotaxime sodium, cefepime, aztreonam
Carbapenems	Imipenem, meropenem, ertapenem sodium
Aminoglycosides	Gentamicin sulfate, tobramycin, amikacin
Fluoroquinolones	Ciprofloxacin, moxifloxacin hydrochloride, levofloxacin, gatifloxacin
Macrolides	Azithromycin, erythromycin, clarithromycin
Lincosamides	Clindamycin
Glycopeptides	Vancomycin
Oxazolidinones	Linezolid
Imidazoles	Metronidazole
Sulfonamides	Trimethoprim-sulfamethoxazole

termined that all drugs identified by the CRM database were actually administered to patients except for nonformulary antibacterials that were administered but not captured by the CRM database. The correlation of days of antimicrobial therapy from the CRM database with hospital electronic record review was excellent ($R^2=0.99$) when 10 nonformulary antibacterial courses were eliminated from the analysis.

HOSPITAL ANTIBACTERIAL STEWARDSHIP PROGRAM SURVEY

We hypothesized that the presence of an antibacterial stewardship program would affect antibacterial use. A 12-question survey was sent via e-mail in 2006 and 2007 to a pharmacist or physician infectious diseases specialist at each hospital for whom we had contact information ($n=30$). The questionnaire sought to determine if the hospital used strategies to influence antimicrobial drug use. One question asked if the hospital had an antimicrobial stewardship team and requested information about the functions of the team. The questionnaire is available from one of us (R.E.P.).

STATISTICAL ANALYSIS

Changes in drug use during the 5-year study period were assessed using repeated-measures analysis of variance. Because analysis of variance is robust to violations of the normality assumption, the analysis was performed on nontransformed data.

Univariate regression analysis sought to identify potential predictors of antibacterial use for (1) the sum of broad-spectrum use as already defined and (2) vancomycin. Relation-

Table 2. Characteristics of 35 Member Hospitals of the University Health System Consortium in 2006^a

Characteristic	Mean (SD)	Range
Bed size	533 (154)	216-905
Adult patient age	51.0 (4.1)	43-59
Discharges	22 165 (7611)	6631-43 512
Duration of total antibacterial therapy, d	4.99 (0.64)	3.91-6.30
Length of stay, d	5.64 (0.51)	4.90-6.97
Total patient days	124 385 (42 841)	41 591-234 919
Case mix index ^b	1.64 (0.16)	1.25-2.06
Surgical procedures per 1000 discharges	402 (62)	243-503
Diagnoses per 1000 discharges		
Urinary tract infections	81 (15)	48-130
Pneumonias	60 (14)	37-99
Bloodstream infections	48 (11)	29-74
Solid organ transplants	6.5 (4.9)	0-23
Bone marrow transplants	2.5 (2.3)	0-8.8

^aEight midwestern hospitals were located in the mid-Atlantic region, 7 midcontinent, 6 southeastern, 9 midwestern, 3 western, and 3 New England.

^bCase mix index equals the mean of diagnosis-related group weights for an individual hospital's diagnosis related group—paid Medicaid claims.

ships with $P < .25$ were then entered into a multiple regression model. Predictor variables (described herein) included selected hospital characteristics, aggregated patient variables, and selected ICD-9-CM codes for common infections treated in the hospital. We also examined whether the presence or absence of an antibacterial stewardship team was associated with use. Separate models were constructed for the dependent variables, namely, (1) the sum of broad-spectrum use and (2) vancomycin. Commercially available statistical software was used (JMP version 7.0; SAS Institute, Cary, North Carolina).

RESULTS

AGGREGATE ANTIBACTERIAL DRUG USE

Table 2 lists patient and hospital demographics for 2006 at 35 University Health System Consortium hospitals. In 2006, 775 731 adult patients were discharged from 35 hospitals, and 492 721 (63.5% [range, 51.0% to 72.8% per hospital]) received at least 1 dose of an antibacterial drug. Among adult patients who received antibacterial agents, 43.9% received a single agent, 27.4% received 2 agents, 14.1% received 3 agents, and 14.7% received 4 or more agents. **Figure 1** shows the use of antibacterial drugs at each hospital. The range in total mean antibacterial use was approximately 2-fold during 2006, from 589 to 1235 DOTs per 1000 PDs.

PREDICTORS OF ANTIBACTERIAL DRUG USE

Nineteen of the 35 hospitals (54.3%) completed the survey regarding antibacterial stewardship policies. Thirteen of the 19 hospitals (68.4%) reported that they had an antibacterial stewardship team that approved restricted antibacterial agents or reviewed selected antibacterial orders, with follow-up to the prescriber.

By univariate analysis, the sum of broad-spectrum antibacterial use was positively correlated with the mean

duration of total antimicrobial therapy ($r=0.59$, $P < .001$), case mix index ($P = .18$), bloodstream infections ($P = .03$), and pneumonias ($P = .07$) and was negatively associated with the presence of an antibacterial stewardship team ($P = .21$). When these variables were entered into the multivariate model, only the mean duration of total antimicrobial therapy remained predictive of broad-spectrum antibacterial use, and it explained 37% of the variability ($P = .03$).

Vancomycin use was positively correlated with the mean duration of total antimicrobial therapy ($r=0.50$, $P = .001$), bed size ($P = .08$), case mix index ($P = .17$), bloodstream infections ($P = .16$), and bone marrow transplantation ($r=0.48$, $P = .004$). When these variables were entered into the multivariate model, only the mean duration of total antimicrobial therapy and the rates of bone marrow transplantation remained predictive of vancomycin use; the model explained 46% of the variability in use ($P < .001$).

TRENDS IN ANTIBACTERIAL DRUG USE

Twenty-two hospitals provided 5 years of antibacterial use data for adult patients discharged between January 1, 2002, and December 31, 2006. Total antibacterial drug use increased each year, from a mean (SD) of 798 (113) DOTs per 1000 PDs in 2002, to 805 (121) in 2003, to 827 (137) in 2004, to 850 (152) in 2005, and to 855 (153) in 2006 ($P = .02$). A comparison of the most commonly used drug classes revealed the reasons for these changes.

The total use of 5 broad-spectrum antimicrobial drug classes increased significantly during 5 years, from a mean (SD) of 361 (75) DOTs per 1000 PDs in 2002, to 368 (78) in 2003, to 378 (80) in 2004, to 386 (84) in 2005, and to 386 (89) in 2006 ($P = .01$) (**Figure 2**). There were important differences within the 5 groups. The class of β -lactam and β -lactamase inhibitor drugs increased significantly, but the increase was confined to a single agent within the class, piperacillin-tazobactam (Zosyn; Wyeth, Madison, New Jersey). The mean (SD) use of piperacillin-tazobactam increased by 84% during 5 years, from 38 (32) DOTs per 1000 PDs in 2002, to 60 (36) in 2003, to 67 (36) in 2004, and to 75 (34) in 2005, and its use remained stable at 70 (35) DOTs per 1000 PDs in 2006 ($P < .001$). In addition, use of the carbapenem class increased by 59% during these 5 years, from a mean (SD) of 22 (14) DOTs per 1000 PDs in 2002 to 35 (21) in 2006 ($P < .001$). In contrast, total aminoglycoside use decreased by 29% during 5 years, from a mean (SD) of 39 (9) DOTs per 1000 PDs in 2002 to 27 (8) in 2006 ($P < .001$). During the study period, there was a slight increase in the mean (SD) use of third- and fourth-generation cephalosporins that was statistically nonsignificant, from 86 (28) DOTs per 1000 PDs in 2002 to 92 (38) in 2006 ($P = .70$), and there was a slight decrease in total fluoroquinolone use that was statistically nonsignificant, from 144 (39) DOTs per 1000 PDs in 2002 to 137 (46) in 2006 ($P = .62$).

The other change contributing to the increase in total use was the marked increase in the use of vancomycin. During 5 years, the mean (SD) vancomycin use in-

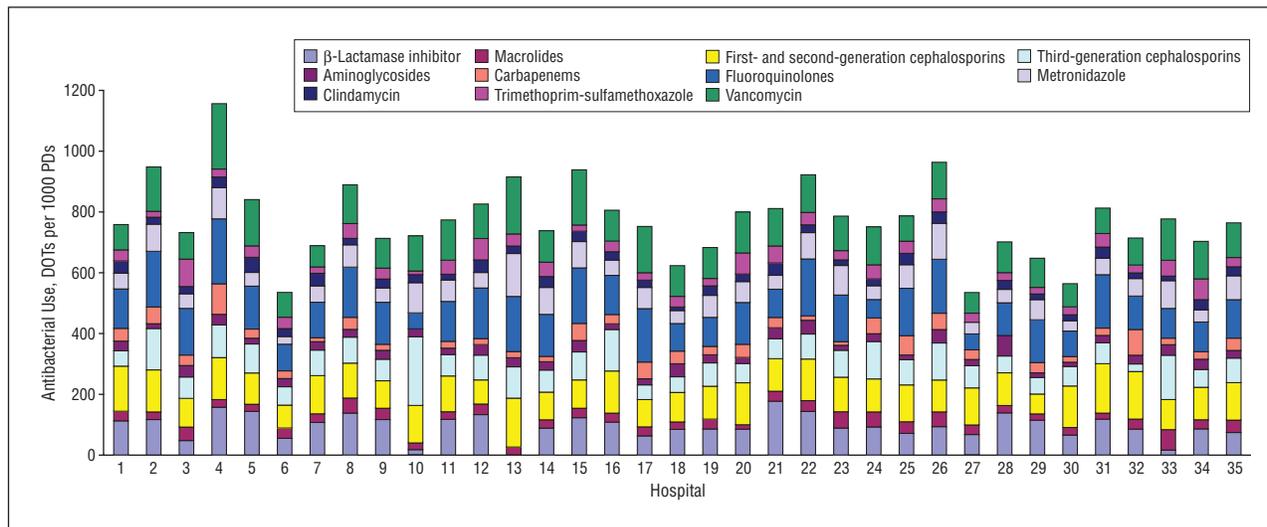


Figure 1. Antibacterial drug use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 35 US academic health centers in 2006. The height of each bar represents the total antibiotic use, and the composition of each bar represents 11 different antibacterial classes. The total use for a single agent reflects the sum of all oral and parenteral dosage formulations.

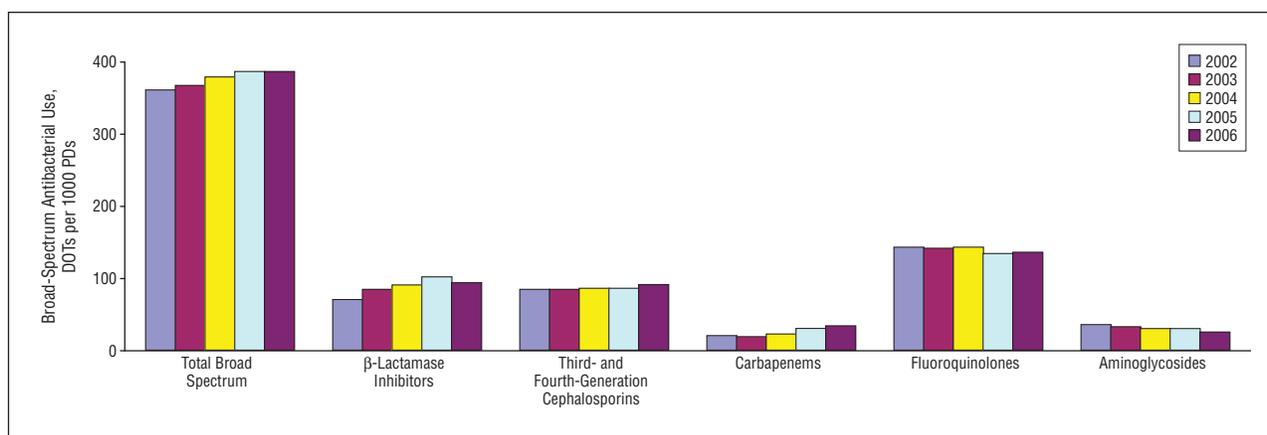


Figure 2. Trends in broad-spectrum antibacterial drug use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 22 US academic health centers from 2002 to 2006. There is a statistically significant increase in total broad-spectrum antibacterial use. Increases in carbapenem and piperacillin-tazobactam use were statistically significant, as was the decline in aminoglycoside use. There was no significant change in fluoroquinolone or cephalosporin use.

creased by 43%, from 87 (29) DOTs per 1000 PDs in 2002, to 91 (39) in 2003, to 104 (34) in 2004, to 113 (35) in 2005, and to 124 (37) in 2006 ($P < .001$) (**Figure 3** and **Figure 4**). Whereas vancomycin use increased within most hospitals during the study period, there were marked differences in vancomycin use among hospitals.

COMMENT

There are 4 important observations to be made from these data. First, this characterization of antibacterial drug use in US academic health centers is the largest and most current of such reports (to our knowledge) and was made possible by electronic collection of claims data. Previous multihospital investigations determined use from antibacterial purchase data for only selected drugs and expressed use in defined daily doses per 1000 PDs, making comparisons with these results problematic.^{8,12-14} Aggregated antibacterial drug use has been recently reported in adults by DOTs per 1000 PDs in 130 US general medical and surgical hos-

pitals in 2002 and 2003.⁹ The proportion of patients who received at least 1 dose of an antibacterial drug in the present investigation (57.3% in 2002) was similar to that in 2002 (59.8%) in these general medical and surgical hospitals. The mean (SD) total antibacterial drug use in the present investigation for 2002 (798 [110] DOTs per 1000 PDs) was also similar to that measured in the general medical and surgical hospitals (776 [120] DOTs per 1000 PDs). Agreement of the mean (SD) use for selected individual drugs in the present investigation for 2002 vs the use in the general medical and surgical hospitals was high for frequently used drugs, including cefazolin (99 [36] vs 94 [28] DOTs per 1000 PDs), levofloxacin (75 [57] vs 75 [56]), and azithromycin (18 [11] vs 18 [15]). There is a suggestion that academic health centers vs general medical and surgical hospitals may differ substantially in the mean (SD) use of other antibacterials, including ceftriaxone sodium (25 [20] vs 63 [26] DOTs per 1000 PDs), piperacillin-tazobactam (56 [40] vs 43 [28]), and vancomycin (87 [23] vs 53 [27]).

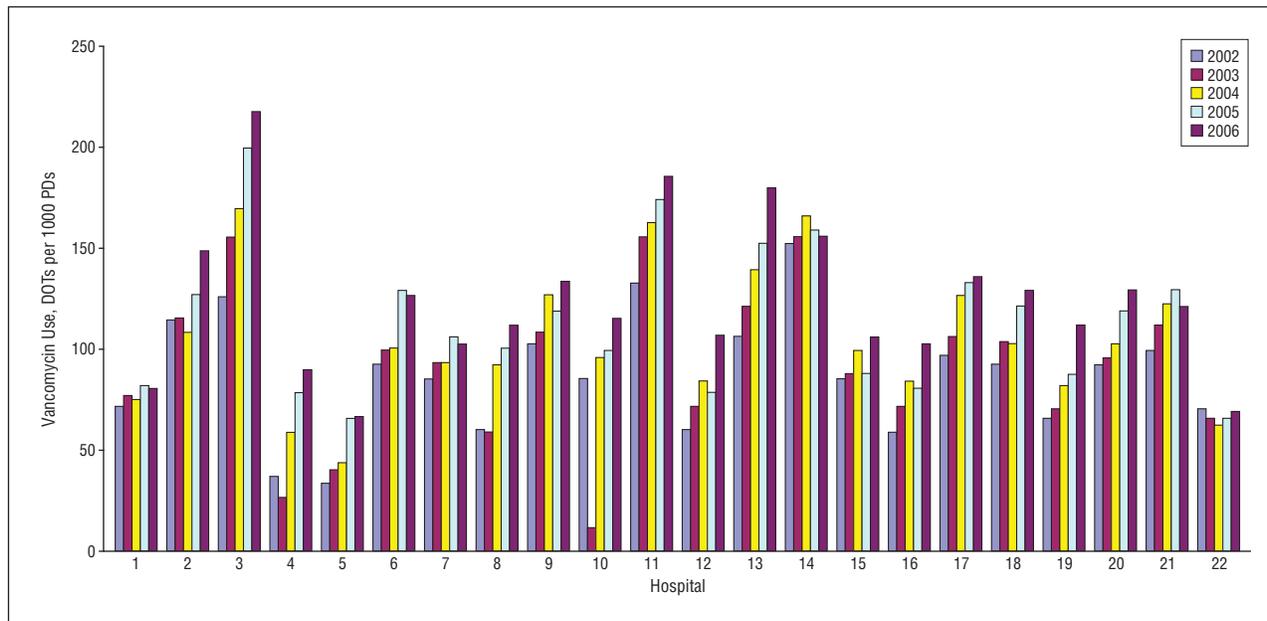


Figure 3. Changes in vancomycin use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 22 US academic health centers from 2002 to 2006. Vancomycin use increased in most individual hospitals during the 5 years of the study, although there was substantial variability in the use among hospitals.

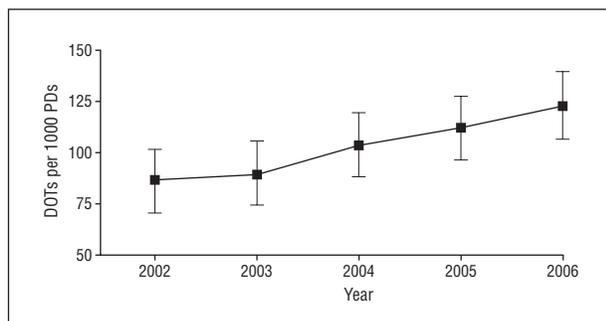


Figure 4. The mean (SD) vancomycin use at 22 hospitals increased significantly between 2002 and 2005 ($P < .001$). DOTs indicate days of therapy; PD, patient days.

The second observation is that total antibacterial use significantly increased during the 5-year period, driven to a large extent by increased broad-spectrum use and the use of vancomycin. With respect to broad-spectrum use, fluoroquinolones and third- and fourth-generation cephalosporin use did not change during the study period, and the increase was driven by increased use of other broad-spectrum agents. The most striking changes included a 59% increase in carbapenem use and an 84% increase in the use of piperacillin-tazobactam between 2002 and 2006. The increase in the use of these broad-spectrum agents occurred despite sporadic shortages of carbapenems and piperacillin-tazobactam during the study period, suggesting that the rate of increase may accelerate as the shortage is alleviated. Carbapenem use increased presumably because of increasing resistance among gram-negative organisms to the other more commonly used antimicrobial agents. The Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance program monitors carbapenem resistance among *Pseudomonas aeruginosa* and reported a 15% increase in carbapenem-resistant isolates in 2003 comparison with isolates obtained from 1998 through

2002.¹³ In 2005, piperacillin-tazobactam became the third most commonly prescribed antibacterial drug in this network of hospitals, behind vancomycin and cefazolin. Piperacillin resistance is not tracked by the Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance program, and it is unclear if increased use of piperacillin-tazobactam is associated with increased resistance. A final implication of this observation is that prior exposure to broad-spectrum agents is associated with a significant increase in the isolation of methicillin-resistant *Staphylococcus aureus* (MRSA). A recent systematic review of 76 investigations indicated that prior exposure to antibiotics increased the relative risk of isolation of MRSA by approximately 1.8-fold, with the highest relative risk of 3.0 for fluoroquinolones.¹⁷

Fluoroquinolones remained the most commonly used class of antibacterial agents throughout the study period, although their use was also stable during the study period. Linder et al¹⁸ previously reported that prescribing of fluoroquinolones increased 3-fold in US outpatient clinics from 1995 to 2002 and that fluoroquinolones became the most commonly prescribed antibacterial class in 2002. Levofloxacin was the most commonly used fluoroquinolone for all years in our study, followed by ciprofloxacin hydrochloride. The effect of fluoroquinolone use on bacterial resistance rates for nosocomial pathogens, including *P aeruginosa*, has been well documented.¹⁹ However, fluoroquinolone resistance in *P aeruginosa* seems not to be increasing, possibly related to static fluoroquinolone use,^{13,19} as observed in the present investigation.

The third significant observation is the marked increase in vancomycin use during the 5-year period such that it became the single most commonly used antibacterial in this sample of hospitals from 2004 to 2006. A rapid rise in vancomycin use has been previously noted at the University of Iowa Hospitals in 1993²⁰ and globally in 1998.²¹ In 1998, the Hospital Infection Control Practices Advi-

sory Committee of the Centers for Disease Control and Prevention issued a guideline designed to limit the use of vancomycin to delay the emergence of vancomycin-resistant enterococci and *S aureus*.²² The reasons for the continued increase in vancomycin use are likely multifactorial, including the increasing numbers of hospital-acquired infections caused by MRSA and the emergence of community-associated MRSA, all of which encourage greater empirical use of vancomycin.²³⁻²⁵ However, there are new and important implications of the increasing use of vancomycin that were not apparent when earlier guidelines to limit vancomycin use were published.²² Vancomycin use is a risk factor for emergence of vancomycin-intermediate *S aureus* and vancomycin-resistant *S aureus*, although these strains are rare in the United States.²⁶ Of greater concern may be the emergence of low-level resistance in MRSA to vancomycin, referred to as minimum inhibitory concentration (MIC) "creep," and this is far more common.²⁷⁻²⁹ Strains of MRSA having vancomycin MICs of 2.0 µg/mL are associated with longer median times to clearance of bacteremia compared with strains having MICs of 1.0 µg/mL or less, as well as frank treatment failures.³⁰⁻³² These findings have caused some to argue that vancomycin is becoming an "obsolete" antibacterial.³³ New glycopeptide antibacterial agents with a mechanism of action similar to that of vancomycin (such as telavancin and dalbavancin) may be less active in vitro against isolates of *S aureus*, with elevated MICs to vancomycin, although the numbers of isolates tested are few and the implications of reduced susceptibility are unknown.³⁴ Furthermore, evidence is emerging that increases in *S aureus* MICs to vancomycin are associated with increases in MICs to an unrelated drug, daptomycin.^{34,35} These data suggest that, if the clinical efficacy of vancomycin is compromised because of modest increases in MICs, this may be accompanied by reduced susceptibility in vitro and possibly in vivo for new and chemically unrelated drugs. Although the clinical significance of reduced susceptibility to newer agents (possibly promoted by vancomycin) is unclear, this would seem to be in urgent need of investigations in light of the changing demographics of infections caused by MRSA and the limited treatment options.³⁴ Renewed focus on the appropriate use of vancomycin, including ensuring that dosages are adequately high, discontinuing use if other drugs are active against isolated pathogens, and developing other creative strategies to reduce the selective pressure for these resistant strains, may help prolong the useful life of this important antibacterial.

The fourth significant observation relates to the identification of predictor variables to explain between-hospital differences in antibacterial use. We found that bed size and case mix index had little predictive value for broad-spectrum antibacterial use or vancomycin use. Broad-spectrum antibacterial use was weakly associated with the rates of selected common infections by univariate analysis, and vancomycin use had a strong positive association with rates of bone marrow transplantation. The presence of an antimicrobial management program was not significantly associated with reduced use of broad-spectrum antibacterials, but there were only 6 hospitals that did not have a stewardship program, with low power to detect a difference if one existed. The strongest pre-

dictor of antibacterial drug use was the mean duration of use for all antimicrobial drugs in the hospital. That the mean duration of therapy for all antimicrobials in a hospital, typically 4 to 6 days, is significantly correlated with the DOTs for selected antimicrobials is not surprising. What is surprising is that small differences in the mean duration of therapy had such a significant effect on predicting drug use in this investigation. Rice recently argued that in the face of increasing resistance among nosocomial pathogens and increasing rates of *C difficile* infections, "Studies are urgently needed to define minimal durations of therapy to ensure that efforts at reduced use are safe and effective."^{36(p491)} Additional investigations seem warranted to determine the reasons for these different durations of therapy in the current hospital network and their associated clinical outcomes.

The characterization of antibacterial use in this study has several limitations. First, administrative claims databases are rarely validated.³⁷ Although we validated antibacterial use data at 1 University Health System Consortium hospital, it is possible that this does not reflect all hospitals. Second, we did not attempt to quantify the use of newer antibacterials such as daptomycin and tigecycline that became commercially available in September 2003 and June 2005, respectively, because the use of these drugs may have been nonformulary in many hospitals during their early introduction into the US market. Third, the accuracy of ICD-9-CM diagnosis codes for quantifying hospital infection rates has been found to be poor,³⁸ and this likely hampered the predictions of antibacterial use. Fourth, we were unable to identify the appropriateness of antibacterial drug use in these hospitals. Consequently, what may be considered an acceptable benchmark based on these observations is probably excessive had we been able to eliminate inappropriate drug therapy from the dataset. Between-hospital differences in the proportion of drug use that is "inappropriate" is likely to contribute to the unexplained variability in antibacterial use.

In conclusion, total antibacterial drug use in academic medical centers is increasing, driven primarily by increased use of broad-spectrum agents and vancomycin. With few new antibacterials in development, antimicrobial stewardship programs in concert with aggressive infection control efforts represent the best chance for control of resistant pathogens. Stopping antibacterials when they are not needed, switching to more narrow-spectrum drug regimens, and optimal dosing using pharmacokinetic and pharmacodynamic principles are critical. Equally important will be investigations designed to identify shorter durations of antibacterial treatments for nosocomial infections that have the potential to dramatically decrease antibacterial exposure.

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the manuscript: Pakyz and Polk. *Critical revision of the manuscript for important intellectual content*: MacDougall, Oinonen, and Polk. *Statistical analysis*: Pakyz, MacDougall, and Polk. *Obtained funding*: Polk. *Administrative, technical, and material support*: Oinonen. *Study supervision*: Pakyz and Polk.

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