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Effects of an Antibiotic Cycling Program on Antibiotic Prescribing Practices in an Intensive Care Unit

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Various interventions have been proposed to combat the increase of antibiotic resistance and influence antibiotic prescribing practices. A prospective cohort study in a medical intensive care unit was conducted to determine the effect of an antibiotic cycling program on patterns of antibiotic use and to determine patient factors associated with cycling adherence. Four major classes of antibiotics for empirical therapy of suspected gram-negative bacterial infections were rotated at 3- and 4-month intervals. During the study, 1,003 patients received antibiotic therapy with at least one of the study drugs; of the 792 receiving cycle antibiotics during the cycling period, 598 (75.5%) received an on-cycle drug. Compared to the baseline, cycling recommendations increased the use of the target cycle agent: the use of cephalosporins increased during cycle 1 (56 to 64% of total antibiotic days, $P < 0.001$), fluoroquinolone use increased in cycle 2 (24 to 55%, $P < 0.001$), carbapenem use increased during cycle 3 (14 to 38%, $P < 0.001$), and use of extended-spectrum penicillins increased in cycle 4 (5 to 36%, $P < 0.001$). Overall, 48% of total cycle antibiotic days were compliant with the cycling protocol. On average, 8.8 days per patient were spent receiving on-cycle drugs (range, 1 to 109). Cycle periods that specified carbapenem and fluoroquinolone use had the highest number of off-cycle days (62 and 64%). Predictors of on-cycle antibiotic use were increased severity of illness, as measured by an acute physiology and chronic health evaluation II score, and greater length of intensive care unit stay. In conclusion, the successful implementation of this cycling protocol increased antibiotic heterogeneity over time in the study unit.

Antibiotic-resistant bacteria are an increasing problem in intensive care units (ICU). Infection with antibiotic-resistant organisms can cause increased hospital length of stay, mortality, and patient costs (18).

Multiple strategies have been employed to control the spread of these resistant organisms. Strategies to limit antibiotic resistance include increased adherence to infection control measures, therapeutic antibiotic substitution, prudent prescribing of antibiotics, and pharmacy-based computer antibiotic management programs (6, 9, 13, 18). In addition, the cycling or rotation of antibiotics for empirical therapy has been examined as a method for preventing the development of antimicrobial resistance (2, 3, 5, 8, 10, 12, 14, 15).

Data suggest that patterns of antibiotic use influence the development of resistance (11). Mathematical modeling suggests that heterogeneous antibiotic use may limit the emergence of resistance (15). Some studies demonstrate that cycling or switching of antibiotics with a gram-negative spectrum of activity may affect antibiotic resistance patterns within the ICU and may decrease the incidence of antibiotic-resistant gram-negative infections and infection-related mortality (5, 12, 14). In previous studies of antibiotic cycling, factors influencing compliance with rotation protocols have not always been analyzed. To truly understand the impact of antibiotic cycling programs, it is essential to demonstrate the extent of adherence or compliance with the targeted antibiotic switch and to understand the complete exposure of different classes of antibiotics in the study setting both at the individual patient level and at the ICU level.

The purpose of this study was to determine the impact of routine cycling of antibiotics for empirical therapy against gram-negative bacteria on the overall pattern of antibiotic use in a medical ICU (MICU). In addition, we wanted to determine the overall compliance with the antibiotic cycling regimen in the medical ICU and to examine patient characteristics associated with on- and off-cycle antibiotic use.

MATERIALS AND METHODS

Barnes Jewish Hospital is a 1,400-bed, urban, tertiary care, teaching hospital located in St. Louis, Mo. The study unit is a 19-bed MICU. The MICU is a closed unit with a multidisciplinary care team, which includes a full-time clinical pharmacist, eight resident physicians, one pulmonary or critical care fellow, and one attending physician, all of whom rotate on a monthly basis. All MICU attending physicians are board certified in critical care medicine. In 2000, there were 1,290 admissions, and the mean patient length of stay was 4.6 days.

Data were prospectively collected on all patients admitted to the MICU for more than two calendar days between 14 February 2000 and 30 June 2002. Data collected included patient demographics, past medical history, hospital and ICU admission dates, and acute physiology and chronic health evaluation II (APACHE II) score upon admission (7). In addition, process of care information, including use of mechanical ventilation, central venous catheter use, and enteral nutrition data, was collected. Data pertaining to ICU treatment and events, including organ failure and acquisition of *Clostridium difficile*-associated diarrhea were recorded. All definitions were selected prospectively as part of the original study design. The definitions for organ dysfunction were those originally described by Rubin and colleagues (17).

Baseline data were collected for 4.5 months (14 February to 30 June 2000). During this period, the prescription of antibiotics for the empirical coverage of presumed infections by gram-negative bacteria was at the discretion of the ordering physician. Barnes Jewish Hospital has an antibiotic management program, staffed by two full-time clinical pharmacists and infectious disease fellows. During the baseline period, all antibiotic classes with broad-spectrum activity against gram-negative bacteria (i.e., expanded-spectrum and "fourth-generation"

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TABLE 1. Cycling protocol for empirical gram-negative antibiotic use

Rotation	Cycle no.	Cycle drug class	Cycle length (mo)	No. of patients enrolled
Baseline		None	4.5	242
1	1	Cephalosporins	4	201
	2	Fluoroquinolones	4	158
	3	Carbapenems	4	145
	4	Extended-spectrum penicillins	4	109
2	5	Cephalosporins	3	111
	6	Fluoroquinolones	3	99
	7	Carbapenems	3	107

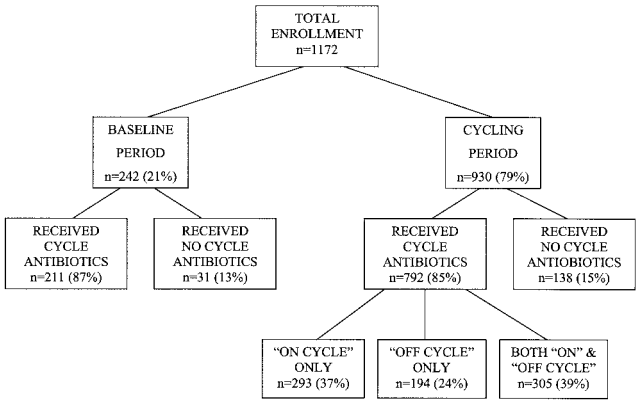

FIG. 1. Description of antibiotic use among study participants.

cephalosporins [e.g., cefepime], fluoroquinolones, and carbapenems and extended-spectrum penicillins) required approval by the hospital antibiotic management program prior to being dispensed. The only exception to this was cefepime, which could be prescribed for 72 h. After 72 h, the ordering physician had to get approval from the antibiotic management program for continued use of the drug.

After the baseline observation period, an antibiotic cycling protocol was then implemented which used four antibiotic classes with gram-negative activity for empirical use cycled every 3 to 4 months over a 2-year period. The four antibiotic classes that were cycled included cephalosporins, fluoroquinolones, carbapenems, and extended-spectrum penicillins. The cycle algorithm was developed with data from current MICU antimicrobial resistance profiles. This four-drug rotation was cycled twice, with the cycle drug changing every 4 months during the first year (rotation 1) and every 3 months during the second year (rotation 2) (Table 1).

On-cycle drug use was defined as use of the cycle antibiotic class during its assigned cycle period. An antibiotic was considered off cycle if an antibiotic class in the cycle protocol was ordered outside its scheduled time period (e.g., ciprofloxacin ordered during the extended-spectrum penicillin cycle). If an ICU stay crossed over a cycle end date, the antibiotic use was considered on cycle if the patient was kept on the cycle drug as determined by their ICU admission date. Patient level data were dichotomized into on- and off-cycle classifications according to the receipt of cycle antibiotics by the patient during the ICU stay. Patients given any on-cycle antibiotics were considered on cycle, whereas patients receiving only off-cycle antibiotics were categorized as off cycle. The percentage of total antibiotic days on cycle and the number of patients receiving any on-cycle antibiotics were the outcomes of interest in this analysis.

Under the direction of the MICU medical director, clinical pharmacists were responsible for promoting this system to guide antibiotic therapy for patients by using the chosen clinical cycling algorithms. MICU medical staff were educated about the cycling protocol and scheduled antibiotic changes through the use of posters, scheduled in-services, and staff meetings.

Orders for all antibiotic classes in the cycle protocol were reviewed daily by a clinical pharmacist and, in cases of empirical treatment, were automatically changed to the cycle antibiotic unless contraindicated (i.e., significant drug allergy or identification of a resistant target pathogen). Use of the cycle antibiotic was also encouraged for known pathogens if they were sensitive to the antibiotic.

Statistical analysis was performed by using SPSS, version 11.0, for Windows (SPSS, Inc., Chicago, Ill.). Categorical variables were compared by using the chi-square test or Fisher's exact test, as appropriate. Wilcoxon rank sum tests were utilized to compare continuous variables. The Bonferroni correction was used in univariate analysis to adjust for multiple comparisons, and a P value of <0.05 upon two-tailed testing was considered significant. Multivariate analysis was performed by using logistic regression. Variables considered for inclusion in multivariate analysis had a P value of less than 0.1 in univariate analysis after Bonferroni correction; variables were included in the final multivariate analysis if significant in the logistic regression model (1). To account for colinear variables, multiple models were run and the model with the highest log likelihood value was retained as the best explanatory model.

The Institutional Review Boards at both Washington University and Saint Louis University approved this study.

RESULTS

During the study period, 3,239 patients were admitted to the MICU; 1,172 (36%) were eligible for and enrolled in the study (MICU length of stay greater than 48 h) (Fig. 1). Of those enrolled, 1,003 patients (86%) received at least one of the cycle antibiotics. Data were collected for 242 patients during the baseline period; of these, 211 (87%) received one or more of the study antibiotics. Among the 792 patients who received a cycle antibiotic during the cycling period, 598 (75.5%) received an antibiotic defined as on cycle, 499 (63%) were given one or more off-cycle antibiotics, 293 (37%) received only on-cycle antibiotics, 194 (24%) were given only off-cycle antibiotics, and 305 (39%) received a combination of on- and off-cycle drugs (Fig. 1). Cycling protocol compliance as a function of total antibiotic days was 5,300 of 10,957 (48%). On average, 8.8 days per patient were spent taking on-cycle drugs (range, 1 to 109). On-cycle antibiotics started in one cycle period and continued into the next cycle time period accounted for 156 of the 5,300 (3%) on-cycle days. Cycles in which carbapenems and fluoroquinolones were the antibiotic class of choice had the greatest percentage of off-cycle antibiotic use (off-cycle antibiotics were used on 62 and 64% of total antibiotic days, respectively) (Table 2).

Of the seven patients requiring a prescription change during the cycling period, six (86%) were due to an inadequate coverage of a known pathogen. There were no definite adverse events (e.g., allergic reaction) related to antibiotic use, although there were three suspected allergic reactions and one suspected case of acute renal failure, possibly attributable to antibiotics.

Cycling recommendations influenced physician prescribing practices. Cephalosporins were the gram-negative antibiotic class of choice during the baseline period, but in all of the cycle periods, the designated on-cycle drug was used in the greatest quantity (Fig. 2).

Cephalosporin use increased during cycle 1 compared to the baseline (from 56% of the baseline to 64% of total antibiotic days, $P < 0.001$). Compared to the baseline, fluoroquinolone use increased in cycles 2 and 6 (from 24 to 55%, $P < 0.001$, and from 24 to 41%, $P < 0.001$, respectively).

In both cycles 3 and 7, the use of carbapenems increased

TABLE 2. Description of off-cycle gram-negative antibiotic use per cycle period

Cycle no.	Cycle drug class	No. (%) of off-cycle drug days for:				No. of off-cycle days/total no. of cycle days (%)
		Cephalosporin	Fluoroquinolone	Carbapenem	ES[a] penicillin	
1	Cephalosporins		426 (49)	330 (38)	112 (13)	868/2,424 (36)
2	Fluoroquinolones	340 (50)		287 (43)	48 (7)	675/1,489 (45)
3	Carbapenems	546 (48)	512 (45)		75 (7)	1,133/1,817 (62)
4	ES penicillins	307 (40)	359 (46)	110 (14)		776/1,204 (64)
5	Cephalosporins		406 (66)	144 (24)	61 (10)	611/1,353 (45)
6	Fluoroquinolones	330 (49)		282 (42)	57 (9)	669/1,128 (59)
7	Carbapenems	554 (60)	346 (37)		25 (3)	925/1,542 (60)

[a] ES, extended spectrum.

compared to the baseline period (from 14 to 38%, $P < 0.001$, and from 14 to 40%, $P < 0.001$, respectively).

Extended-spectrum penicillin use increased significantly from 5% in the baseline period to 36% during cycle 4 ($P < 0.001$). A comparison of patients receiving on-cycle antibiotics to other patients in the cohort is shown in Table 3. Baseline patient characteristics associated with on-cycle antibiotic use include congestive heart failure ($P = 0.03$) and increased APACHE II score ($P = 0.01$).

Process of care events related to on-cycle antibiotic use include sucralfate use ($P = 0.04$). On-cycle antibiotic use was also associated with a longer length of ICU stay ($P = 0.001$).

Length of ICU stay, APACHE II score, and use of H_2 blockers were included in the final multivariate model and independently associated with having received on-cycle antibiotics. Adjusted odds ratios for included variables were significant in the final model (Table 3).

DISCUSSION

In this prospective cohort study of MICU patients, we found that empirical antibiotic prescribing practices were influenced by an antibiotic cycling protocol. Compared to the baseline, cycling recommendations influenced prescribing in all seven of the cycles. The on-cycle drug was prescribed in the greatest quantities during its respective cycle(s), representing a significant change from baseline numbers. While a significant number of antibiotic days were considered off cycle, 64% of the study population was still exposed to on-cycle drugs during the cycling period. As shown in Fig. 2, successful implementation of this cycling protocol contributed to antibiotic heterogeneity over time in the study unit.

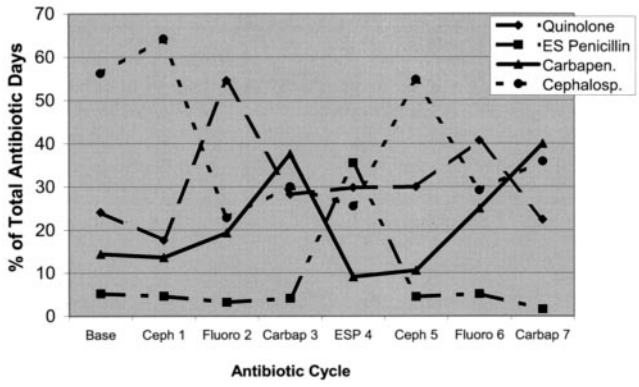

FIG. 2. Percentage of gram-negative antibiotic use in days per cycle period. ES, extended spectrum; Carbapen or Carbap, carbapenem; Cephalosp or Ceph, cephalosporin; Fluoro, fluoroquinolone; ESP, extended-spectrum penicillin.

Predictors of on-cycle antibiotic use were increased severity of illness and increased length of ICU stay. In addition, the use of H_2 blockers was significantly associated with not receiving on-cycle antibiotics. All are indicators of increased severity of illness and could explain the need for multiple antibiotics, therefore increasing the likelihood of getting the appropriate drug. In addition, a longer stay in the ICU will increase the likelihood of receiving an on-cycle antibiotic.

Cooperation from the unit medical director and the MICU medical and pharmacy staff were essential for the success of this project. Without staff buy in, effective implementation of a cycling protocol would be impossible. While cycling of antibiotics to decrease antimicrobial resistance has been studied previously (2, 12), issues of compliance with the protocol have not been addressed in a consistent manner. The clear definition and designation of antibiotic classes as either on or off cycle, as established by a predetermined cycling protocol and time parameters, allow for the quantitative analysis of the cycling protocol implementation in our study.

Due to multidrug therapies for different infections and other treatment situations, drug use at the patient level was not always clearly on or off cycle. Patients could receive both on and off-cycle antibiotics during their MICU stay, adding to the complexity of the data analysis. Patients could be grouped by any on-cycle drug use, any off-cycle drug use, or receipt of both on- and off-cycle drugs. In addition, data were examined at the unit level by using on- and off-cycle antibiotic days to compare the sheer volume of empirical antibiotic use in the MICU. The ability to examine the data in these various ways adds to the strength of the analysis.

The level of cycling compliance with the antibiotic rotation schedule was examined by Raymond et al. (16). In this study, the use of antibiotics to treat infection was classified into one of four compliance categories: three indicated acceptable antibiotic prescribing and the fourth represented an unacceptable deviation from the rotation protocol. The authors reported that only 3% of antibiotic therapy was unacceptable. Limitations to this analytical approach include the small sample size of antibiotics actually examined. Only patients with infections were included in the cohort; therefore, not all antibiotic use in the study unit was examined.

Moss et al. examined compliance by totaling the amount of

TABLE 3. Analysis of factors associated with on-cycle antibiotic use during ICU stay

Variable[c]	On-cycle drug use (n = 598)	Off-cycle drug use (n = 194)	P value	aOR (95% CI)[b]
Patient characteristics				
Mean age (yrs) (range)	59.1 (17–101)	59.4 (16–97)	0.78	
Caucasian	357 (59.7)	130 (67)	0.09	
Male gender	296 (49.5)	95 (49)	0.89	
CHF	114 (19.1)	24 (12.4)	0.03	
COPD	165 (27.6)	57 (29.4)	0.63	
Cancer	86 (14.4)	20 (10.3)	0.15	
Chemotherapy	12 (2)	3 (1.5)	0.48	
HIV	14 (2.3)	4 (2.1)	0.54	
Diabetes	210 (35.1)	62 (32)	0.42	
Cirrhosis	47 (7.9)	14 (7.2)	0.77	
Chronic renal failure	162 (27.1)	43 (22.2)	0.17	
Dialysis	64 (39.8)	13 (30.2)	0.25	
Bone marrow transplantation	33 (5.5)	12 (6.2)	0.73	
Surgery in last 28 days	40 (6.7)	18 (9.3)	0.23	
Mean APACHE II score(range)	24.4 (5–44)	22.9 (6–45)	0.01[a]	1.03 (1.01–1.05)
Processes of care				
Antacid use	96 (16.1)	31 (16)	0.98	
H_2 histamine antagonist	256 (42.8)	96 (49.5)	0.10	0.71 (0.51–0.98)
Sucralfate use	19 (3.2)	1 (0.5)	0.04	
Vasopressor use	294 (49.2)	85 (43.8)	0.16	
Corticosteroid use	220 (36.8)	71 (36.6)	0.96	
Enteral nutrition	381 (63.7)	115 (59.3)	0.27	
Mechanical ventilation	470 (78.6)	149 (76.8)	0.60	
Reintubation	112 (18.7)	25 (12.9)	0.06	
ICU-related events				
Tracheostomy in ICU	81 (13.5)	20 (10.3)	0.24	
Mean length of ICU stay (days) (range)	10.0 (3–64)	7.6 (3–37)	<0.01[a]	1.04 (1.02–1.07)
Acute hepatic failure	138 (23.1)	38 (19.6)	0.31	
Respiratory failure	473 (79.1)	149 (76.8)	0.50	
Acute renal failure	297 (49.7)	86 (44.3)	0.19	
Acute CHF	111 (18.6)	31 (16)	0.42	
Coma or seizure	60 (10)	14 (7.2)	0.24	
C. difficile-associated diarrhea	53 (8.9)	12 (6.2)	0.24	

[a] Significant P value after correction for multiple comparisons.
[b] aOR, adjusted odds ratio; 95% CI, 95% confidence interval.
[c] Variables considered for inclusion but not significant in the final model include congestive heart failure (CHF), sucralfate use, and reintubation. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus. Unless otherwise noted, values are numbers of patients with percentages of the total number of patients in parentheses.

each antibiotic used per month in the study unit in standardized units and then rated the application as either pro or con antibiotic cycling use (12). Pro use supported the cycling regimen, whereas con use was detrimental to the impact of the regimen. Pro use or cycling compliance in the various cycles ranged from 8 to 82%, indicating that physician prescribing preferences influenced compliance. In their cycling study, Gerding and colleagues were able to effectively alter aminoglycoside use by changing the formulary in a controlled Veterans Affairs Medical Center setting and to also influence antibiotic resistance (5). Changes in the hospital formulary were implemented to ensure cycling success, and the antibiotic rotations were strictly enforced. Compliance was tracked as the percentage of cycle antibiotic usage by cycle period. Due to vast differences in cycle lengths and the lack of a preset protocol, conclusions about ideal cycling conditions are hard to obtain (4). In other cycling studies, only the impact of the cycling and not the actual success of the implementation of cycling are addressed (2).

Certain limitations exist in our study design. In the first four cycles (rotation 1), cycles were 4 months in length. During rotation 2, cycles were 3 months in length. While this change might shed light on the question of appropriate cycle length for a successful cycling protocol, it also limits the generalizability of the data. Due to project funding limitations, there was only one cycle of extended-spectrum penicillins. In addition, the study unit has a dedicated clinical pharmacist, a resource many ICUs do not have. While compliance to the cycling protocol was voluntary on the part of the physician, off-cycle orders were often automatically changed by the pharmacist if not contraindicated.

Baseline physician prescribing practices of antibiotics with gram-negative activity were a strong predictor of cycling protocol prescribing practices. Baseline practices were influenced in part by the hospital formulary restrictions and prior approval requirements of the antibiotic management team. There were multiple patient-specific variables associated with on-cycle antibiotic use, and empirical antibiotic cycling recommendations did influence antibiotic ordering practices. In every cycle except for one, cephalosporins were the most frequent

off-cycle drug to be prescribed (Fig. 2). The ability to order cefepime for up to 72 h before getting approval from the antibiotic management team possibly encouraged its use. In the baseline and all of the cycles, cephalosporin use represented greater than 20% of all cycle antibiotic use. Also, a statistically significant reduction in the use of an antibiotic may not be ecologically significant. The high level of cephalosporin use in all cycles may provide enough selective pressure to promote resistance during the off-cycle periods.

Additional data analysis will be conducted to determine the implications and outcomes of this cycling intervention. Outcomes, including resistance patterns of gram-negative isolates collected during the study period and infection rates, will be explored in future reports.

We showed that a focused antibiotic cycling program could result in substantial changes in prescribing practices among physicians in an academic ICU setting. This is an important step in testing the validity of antibiotic cycling as a way of preventing the emergence of antimicrobial resistance.

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REFERENCES

1. **Concato, J., A. R. Feinstein, and T. R. Holford.** 1993. The risk of determining risk with multivariable models. Ann. Intern. Med. **118:**201–210.
2. **Dominguez, E. A., T. L. Smith, E. Reed, C. C. Sanders, and W. E. Sanders, Jr.** 2000. A pilot study of antibiotic cycling in a hematology-oncology unit. Infect. Control Hosp. Epidemiol. **21:**S4–S8.
3. **Fridkin, S. K.** 2003. Routine cycling of antimicrobial agents as an infection-control measure. Clin. Infect. Dis. **36:**1438–1444.
4. **Gerding, D. N.** 2000. Antimicrobial cycling: lessons learned from the aminoglycoside experience. Infect. Control Hosp. Epidemiol. **21:**S12–S17.
5. **Gerding, D. N., T. A. Larson, R. A. Hughes, M. Weiler, C. Shanholtzer, and L. R. Peterson.** 1991. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob. Agents Chemother. **35:**1284–1290.
6. **Jernigan, D. B., M. S. Cetron, and R. F. Breiman.** 1996. Minimizing the impact of drug-resistant Streptococcus pneumoniae (DRSP). A strategy from the DRSP Working Group. JAMA **275:**206–209.
7. **Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman.** 1985. APACHE II: a severity of disease classification system. Crit. Care Med. **13:**818–829.
8. **Kollef, M. H.** 2001. Is there a role for antibiotic cycling in the intensive care unit? Crit. Care Med. **29:**N135–N142.
9. **Kollef, M. H., J. Vlasnik, L. Sharpless, C. Pasque, D. Murphy, and V. Fraser.** 1997. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **156:**1040–1048.
10. **Labarca, J.** 2000. Antibiotic cycling tested in nosocomial infections. Lancet **355:**992.
11. **McGowan, J. E., Jr.** 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev. Infect. Dis. **5:**1033–1048.
12. **Moss, W. J., M. C. Beers, E. Johnson, D. G. Nichols, T. M. Perl, J. D. Dick, M. A. Veltri, and R. E. Willoughby, Jr.** 2002. Pilot study of antibiotic cycling in a pediatric intensive care unit. Crit. Care Med. **30:**1877–1882.
13. **Murray, B. E.** 1994. Can antibiotic resistance be controlled? N. Engl. J. Med. **330:**1229–1230.
14. **Puzniak, L. A., J. Mayfield, T. Leet, M. Kollef, and L. M. Mundy.** 2001. Acquisition of vancomycin-resistant enterococci during scheduled antimicrobial rotation in an intensive care unit. Clin. Infect. Dis. **33:**151–157.
15. **Rahal, J. J., C. Urban, D. Horn, K. Freeman, S. Segal-Maurer, J. Maurer, N. Mariano, S. Marks, J. M. Burns, D. Dominick, and M. Lim.** 1998. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. JAMA **280:**1233–1237.
16. **Raymond, D. P., S. J. Pelletier, T. D. Crabtree, T. G. Gleason, L. L. Hamm, T. L. Pruett, and R. G. Sawyer.** 2001. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. Crit. Care Med. **29:**1101–1108.
17. **Rubin, D. B., J. P. Wiener-Kronish, J. F. Murray, D. R. Green, J. Turner, J. M. Luce, A. B. Montgomery, J. D. Marks, and M. A. Matthay.** 1990. Elevated von Willebrand factor antigen is an early plasma predictor of acute lung injury in nonpulmonary sepsis syndrome. J. Clin. Investig. **86:**474–480.
18. **Shlaes, D. M., D. N. Gerding, J. F. John, Jr., W. A. Craig, D. L. Bornstein, R. A. Duncan, M. R. Eckman, W. E. Farrer, W. H. Greene, V. Lorian, S. Levy, J. E. McGowan, Jr., S. M. Paul, J. Ruskin, F. C. Tenover, and C. Watanakunakorn.** 1997. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin. Infect. Dis. **25:**584–599.