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Impact of Use of Multiple Antimicrobials on Changes in Susceptibility of Gram-Negative Aerobes

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Evaluation of antimicrobial usage vs. susceptibility relationships typically involves single agents. However, susceptibility profiles may be affected by multiple drugs. From 1992 through 1996, we studied relationships between drug usage and the susceptibility (only susceptibility rates of ⩾70%) of *Acinetobacter anitratus (baumannii), Enterobacter aerogenes, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis,* and *Serratia marcescens* to 22 agents. Linear regression was used to assess usage of each agent vs. susceptibility to it and to all agents. Only relationships with a coefficient of determination of ⩾0.5 and a negative slope were evaluated and classified as increasing drug use and decreasing susceptibility (↑D, ↓%S) or decreasing drug use and increasing susceptibility (↓D, ↑%S). The mean numbers (range) of drugs associated with a change in susceptibility were 1.7 (0–14) and 0.6 (0–7), respectively, for ↑D, ↓%S and ↓D, ↑%S relationships. Multiple antimicrobials are associated with susceptibility to other drugs; thus, surveillance of these relationships should not be limited to single drugs.

The emergence of resistance to antimicrobials was detected soon after their introduction, and the current rate of resistance to a large number of antimicrobials is alarming [1–6]. Although many factors have been implicated as contributing to this increase, the selective pressures exerted by widespread and indiscriminate antibiotic usage are often cited as a major factor [2, 7–10]. Despite this assumption, only recently have urgent pleas been made for systematic surveillance of drug usage and susceptibility trends to better delineate relationships between drug usage and susceptibility [1, 5, 8, 11].

At first glance, it might seem that relating the intensity of antimicrobial usage and changes in susceptibility would be rather straightforward. However, establishing causality is fraught with many confounding factors [10, 12, 13]. Despite this, investigators have consistently reported an association between drug usage and susceptibility patterns [10, 14–36]. However, the focus of these studies was primarily on the use of a specific agent and how it related to the susceptibility of organisms to that agent alone. The impact of the use of multiple antimicrobials on the susceptibility pattern of the antimicrobial/organism of interest was frequently overlooked, except in a few studies [14, 26–31, 35, 36]. These studies suggested that usage of other agents was associated with the observed changes in susceptibility for the antimicrobial/organism of interest, indicating that the usage of multiple antimicrobials should not be ignored when susceptibility trends are evaluated. Thus, the objective of this study was to evaluate the impact of the usage of a variety of antimicrobials on changes in susceptibility of common nosocomial gram-negative aerobes.

Methods

Description of the Institution

The Medical University of South Carolina hospital is a 600-bed tertiary-care teaching institution, at which ~400 beds are utilized for nonpsychiatric adult inpatients. Intensive care units within the adults' hospital include neurosurgical, surgical/trauma, burn, cardiothoracic, medical, and cardiac units. Additional specialized patient populations include oncology, cardiac, renal, and bone marrow transplant patients.

Data Collection

Census, antimicrobial usage, and susceptibility data for adult inpatients were collected from January 1992 through December 1996. All data for the adults' hospital were collected on a quarterly basis and used to calculate annual totals, which were used for all subsequent analyses.

Census data. The number of patient-days for the adults' hospital were electronically transferred to this database from the hospital admissions department.

Antimicrobial usage. Antimicrobial drug usage data concerning adult inpatients were electronically transferred from the adults' inpatient hospital pharmacy computer system (Megasource, MSMEDS, Cerner Corp., Kansas City, MO) to a spreadsheet program (Excel, Microsoft Corp., Redmond, WA) written specifically for this analysis. For each drug order, the

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Table 1. Antimicrobials for which hospital-wide usage data were collected.

Penicillins	Cephalosporins	Aminoglycosides	Fluoroquinolones	Miscellaneous
Ampicillin	Cefazolin	Amikacin	Ciprofloxacin*	Aztreonam
Ampicillin/sulbactam	Cefuroxime	Tobramycin	Ofloxacin*	Imipenem
Piperacillin	Cefotetan	Gentamicin		TMP-SMZ*†
Piperacillin/tazobactam	Cefoxitin			
Ticarcillin	Ceftazidime			
Ticarcillin/clavulanate	Ceftizoxime			
	Ceftriaxone			
	Cefotaxime			

* Includes both oral and intravenous usage.
† Trimethoprim-sulfamethoxazole.

patient's name, hospital location, order number, dose, dosing schedule (e.g., every 6 hours), and beginning and ending days of therapy were collected. The drug order number was used to identify any duplicate orders, which were removed from the database prior to subsequent analyses. Data were screened quarterly for completeness, with use of the order date. In cases of missing data, the number of missing days per quarter was calculated and used to extrapolate the usage of all drugs in that quarter. Missing days represented only 9% of the total number of days over the entire study period.

Hospital-wide drug-usage data were collected for the antimicrobials listed in table 1. Oral drug usage data were included for ciprofloxacin, ofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMZ) in the calculation of total grams. All orders for TMP-SMZ were converted to milligrams on the basis of the trimethoprim component with use of standard conversions for the intravenous and oral suspension products, respectively. No data for ofloxacin and piperacillin/tazobactam were available prior to 1993 and 1994, respectively.

Susceptibility data. Susceptibility data were obtained for the following gram-negative aerobes isolated from hospitalized adult inpatients: *Acinetobacter anitratus (baumannii), Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Serratia marcescens.* All susceptibility results were categorized as susceptible according to the appropriate breakpoint concentrations, as established by the National Committee for Clinical Laboratory Standards during the study period. With use of the Vitek automated susceptibility testing system (bioMérieux Vitek, Hazelwood, MO), susceptibility was determined by the department of clinical microbiology. Data from the Vitek system are electronically transferred to a hospital mainframe computer that utilizes Cerner laboratory data management software. The Cerner software removes duplicate isolates that have been previously shown to alter susceptibility reports [37]. In this system, a duplicate isolate is defined as the same bacterial species from the same patient with the same susceptibility to a specific antimicrobial. All isolates tested and all susceptible isolates were collected from all nonurine cultures for every adult inpatient. Percentage of susceptibility was calculated as the number of susceptible isolates divided by the total number of isolates and multiplied by 100.

Data Analysis

Census data. The number of patient days were plotted against time to assess changes in the patient census. In addition, these data were used to normalize antimicrobial usage data (g/patient-day) and the number of isolates (isolates/patient-day) to account for any changes due to variations in the patient census over the study period.

Antimicrobial usage data. Days of therapy were used when antimicrobial usage was compared, since g/patient-day are not directly comparable, owing to differences in drug dosages. For each drug order, we calculated the days of therapy by subtracting the beginning day from the ending day of therapy. As we were most interested in assessing relationships when antibiotics were being used for therapeutic rather than prophylactic purposes, only those orders with $\geq$1 day of therapy were used. Data concerning orders with $<$1 day of therapy (primarily preoperative doses) were excluded, as were those instances for which days of therapy could not be calculated because of incomplete or missing information. These orders ($<$1 day of therapy) comprised $\sim$8.5% of the total number of drug orders.

The number of doses per day was derived from the dosing schedule (e.g., every 6 hours = 4 doses/d). The total number of grams for each individual drug order was calculated from the dose, the total number of daily doses, and the length of therapy in days. Data for each drug were then summed and normalized by dividing the grams of each drug by the number of patient-days (g/patient-day). Days of therapy and g/patient-day were plotted against time and assessed with simple linear regression to characterize changes over the study period. Only the direction (negative or positive) and not the magnitude of the slope was used to assess decreases or increases in drug usage.

Susceptibility data. The number of isolates, number of isolates/patient-day, and percentage of susceptibility over time were assessed by means of simple linear regression to characterize overall trends for each organism during the study period.

Susceptibility vs. antimicrobial usage relationships. The relationship between normalized antimicrobial usage (g/patient-day) and susceptibility (or %S, for percentage of susceptibility) for all antimicrobials and organisms was assessed by means of simple linear regression. From these data, clinically significant relationships were defined as those in which the annual percentage of susceptibility was ⩾70% at any time during the study period. This criterion was chosen because it likely represents a range of susceptibility that is clinically relevant in antimicrobial decision-making in our institution. Of this subset of data, only those relationships with a coefficient of determination (r^2) of at least 0.5 (corresponding to a correlation coefficient of ⩾0.70), based on simple linear regression, were further evaluated. Thus, the data utilized in this analysis were only for those individual antimicrobial/organism combinations in which %S was ⩾70% in any year and the r^2 for drug usage vs. susceptibility linear regression was ⩾0.5.

To assess the relationship between the use of an individual agent and the pattern of susceptibility to it, the %S for each antimicrobial/organism combination and normalized drug usage for that antimicrobial (e.g., susceptibility of *E. cloacae* to ceftazidime vs. ceftazidime, g/patient-day) over the entire study period were plotted and evaluated. To assess whether multiple antimicrobials were associated with the susceptibility of an individual agent, simple linear regression was performed for the usage (g/patient-day) of each individual drug vs. the %S of each antimicrobial/organism combination (e.g., susceptibility of *E. cloacae* to ceftazidime vs. ceftriaxone, g/patient-day) individually. Only those relationships with a negative slope (%S vs. drug usage) were further evaluated. These relationships were divided into two categories: (1) relationships in which drug usage increased and susceptibility decreased (↑D, ↓%S) and (2) relationships in which drug usage decreased and susceptibility increased (↓D, ↑%S). Analysis of variance with Tukey's standardized range post-hoc test ($P < .05$) were used to assess differences in the number of relationships among drugs with respect to their ability to affect organisms' susceptibility to them (e.g., susceptibility of *K. pneumoniae* to ceftriaxone vs. ceftriaxone, g/patient-day) as well as to other agents (e.g., susceptibility of *K. pneumoniae* to ceftazidime vs. ceftriaxone, g/patient-day).

Results

Over the entire study period, the number of patient-days decreased from 104,494 in 1992 to 95,411 in 1996. Patient-days steadily decreased from 1992 to 1995; however, a slight increase was observed from 1995 to 1996. The number of intensive care unit patient-days as a percentage of hospital-wide patient-days was constant over the course of the study, ranging from 18% to 19% each year.

Days of antibiotic therapy with the agents evaluated increased from 24,895 days in 1992 to 34,663 days in 1996.

Table 2. Antimicrobial usage (days of therapy) from 1992 through 1996 at the Medical University of South Carolina hospital.

Antimicrobial	Percentage of total days of therapy* (range during 1992–1996)
Penicillins	17
Piperacillin	5 (4–7)
Ampicillin/sulbactam	4 (2–7)
Ampicillin	4 (3–7)
Ticarcillin/clavulanate	2 (2–3)
Piperacillin/tazobactam	1 (<1–3)
Ticarcillin	<1 (<1)
Cephalosporins	34
Cefazolin	15 (13–16)
Cefotaxime	5 (3–5)
Ceftazidime	4 (3–4)
Ceftriaxone	3 (2–4)
Cefuroxime	3 (3–4)
Cefoxitin	2 (1–2)
Ceftizoxime	1 (<1–2)
Cefotetan	1 (1–2)
Aminoglycosides	17
Gentamicin	11 (10–12)
Tobramycin	5 (4–6)
Amikacin	1 (1–4)
Fluoroquinolones	17
Ciprofloxacin	16 (13–18)
Ofloxacin	1 (<1–2)
Miscellaneous	15
Imipenem	10 (6–13)
Aztreonam	3 (1–5)
TMP-SMZ	2 (1–4)

NOTE. TMP-SMZ = trimethoprim-sulfamethoxazole.

* Percentage of total days of use of drugs in this data subset (not total antimicrobial use in the hospital).

Data for the individual agents are presented in table 2. The percentage of the total days of therapy increased (from 1992 values) in 1996, by 54% and 31% for the fluoroquinolones and miscellaneous agents, respectively, while it decreased slightly for the penicillins (11%), cephalosporins (13%), and aminoglycosides (19%). Drug use (g/patient-day) increased for cefotaxime, ciprofloxacin, imipenem, ofloxacin, TMP-SMZ, ampicillin/sulbactam, cefazolin, cefotetan, ceftazidime, cefuroxime, gentamicin, ticarcillin/clavulanate, tobramycin, and ceftriaxone. Decreased drug use (g/patient-day) was noted for amikacin, aztreonam, cefoxitin, ceftizoxime, piperacillin/tazobactam, ticarcillin, piperacillin, and ampicillin.

The numbers of isolates tested for susceptibility during the period studied are displayed in table 3. In general, the number of isolates increased for all organisms except *E. coli. P. aeruginosa* was the most common organism, accounting for 25% of the total number of isolates over the entire study period. Although *A. anitratus* accounted for only ~7% of all isolates from 1992 through 1996, the number of isolates per patient-day increased steadily from 1994 through 1996. There was also a large increase in the number of *S. marcescens* and *K. pneumoniae* isolates over the study period.

Table 3. Number of isolates for which there were susceptibility test results, from 1992 through 1996.

Microorganism	No. of isolates tested (range)	Percentage of total (range)*
P. aeruginosa	1,503 (276–339)	25 (23–28)
E. coli	1,108 (208–233)	19 (16–20)
K. pneumoniae	996 (166–219)	17 (15–18)
E. cloacae	737 (129–174)	12 (11–15)
P. mirabilis	427 (80–91)	7 (7–8)
A. anitratus	394 (53–124)	7 (5–10)
S. marcescens	391 (62–104)	7 (5–9)
E. aerogenes	342 (57–84)	6 (5–7)
Total	5,898	

* Percentage of the yearly total number of isolates for which there were susceptibility test results (among the organisms studied).

Single-drug relationships. Twenty-three relationships that met the inclusion criteria, representing 15% of the number of single-drug/organism relationships evaluated, had a negative slope. Of these, 17 (74%) had increasing drug use and decreasing susceptibility (↑D, ↓%S), and six (26%) were those with decreasing drug use and increasing susceptibility (↓D, ↑%S) (figures 1 and 2). With the exception of cefotaxime, cefazolin, ceftriaxone, and cefotetan, for those drugs whose use increased, at least one relationship met our inclusion criteria. Although not statistically significantly different from other agents, increasing ticarcillin/clavulanate use was associated with decreasing susceptibility for four of the eight organisms studied. For those drugs with decreasing use, only piperacillin, amikacin, aztreonam, and ticarcillin were associated with changes in susceptibility to themselves. Drug-usage-vs.-susceptibility relationships that met the inclusion criteria were observed with all organisms except *E. cloacae.* The relative frequency of these relationships among organisms was as follows: *A. anitratus* > *P. aeruginosa* = *K. pneumoniae* > *E. aerogenes* > *E. coli* = *S. marcescens* = *P. mirabilis.*

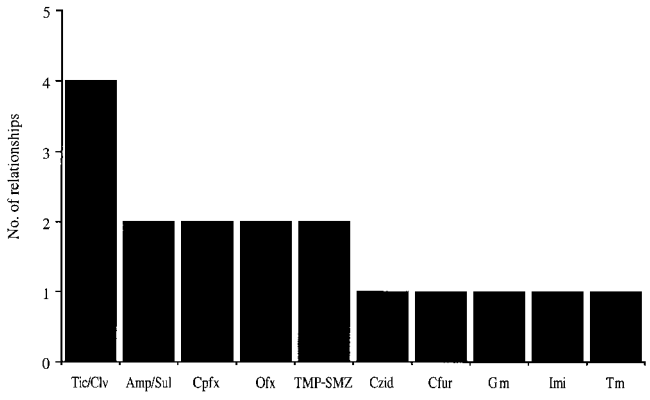

Figure 1. Number of drug/organism relationships involving increasing drug use and decreasing susceptibility that resulted from usage of an *individual* drug vs. susceptibility to it (Tic/Clv = ticarcillin/clavulanate; Amp/Sul = ampicillin/sulbactam; Cpfx = ciprofloxacin; Ofx = ofloxacin; TMP-SMZ = trimethoprim-sulfamethoxazole; Czid = ceftazidime; Cfur = cefuroxime; Gm = gentamicin; Imi = imipenem; Tm = tobramycin).

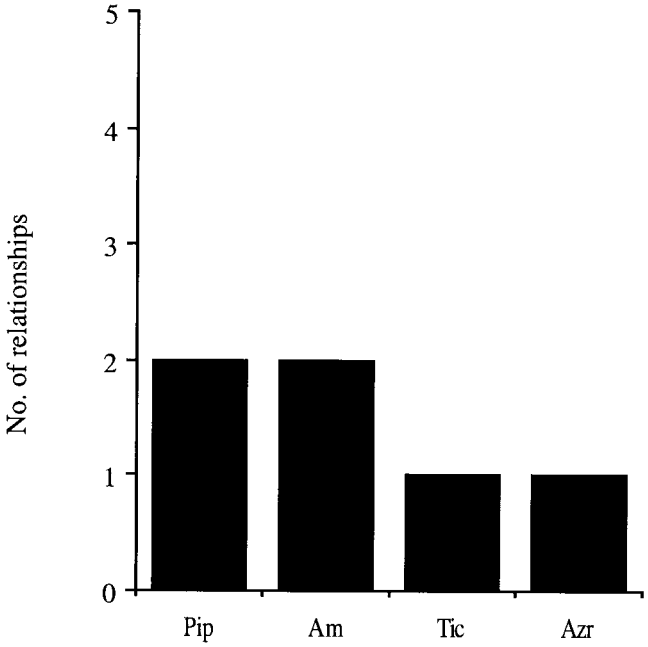

Figure 2. Number of drug/organism relationships involving decreasing drug use and increasing susceptibility that resulted from usage of an *individual* drug vs. susceptibility to it (Pip = piperacillin; Am = amikacin; Tic = ticarcillin; Azr = aztreonam).

Multiple-drug relationships. Of the 405 relationships with a negative slope that met our criteria, 75% were relationships with increasing drug use and decreasing susceptibility (↑D, ↓%S) and 25% were with decreasing drug use and increasing susceptibility (↓D, ↑%S). The number of each type of relationship resulting from individual drug usage vs. susceptibility of other agents is displayed in figures 3 and 4. For individual bacterial species, a change in susceptibility occurred to a mean of 1.7 antibiotics (range, 0–14) for the ↑D, ↓%S relationships and to a mean of 0.6 antibiotics (range, 0–7) for the ↓D, ↑%S relationships. Where ↑D, ↓%S relationships were detected, ticarcillin/clavulanate, TMP-SMZ, and ceftazidime were most commonly associated with decreased susceptibility of another agent, despite each of these accounting for only 2%–4% of the total days of therapy. Conversely, increasing usage of imipenem and ciprofloxacin, which accounted for 10% and 16% of the total days of therapy, were associated less often with a decrease in susceptibility to other agents. For ↓D, ↑%S relationships, decreased use of aztreonam and cefoxitin was associated most often with increased susceptibility of other agents. There were no statistically significant differences among drugs in either situation. Drug-usage-vs.-susceptibility relationships that met the inclusion criteria were observed with all organisms. The relative frequency of all relationships among the organisms

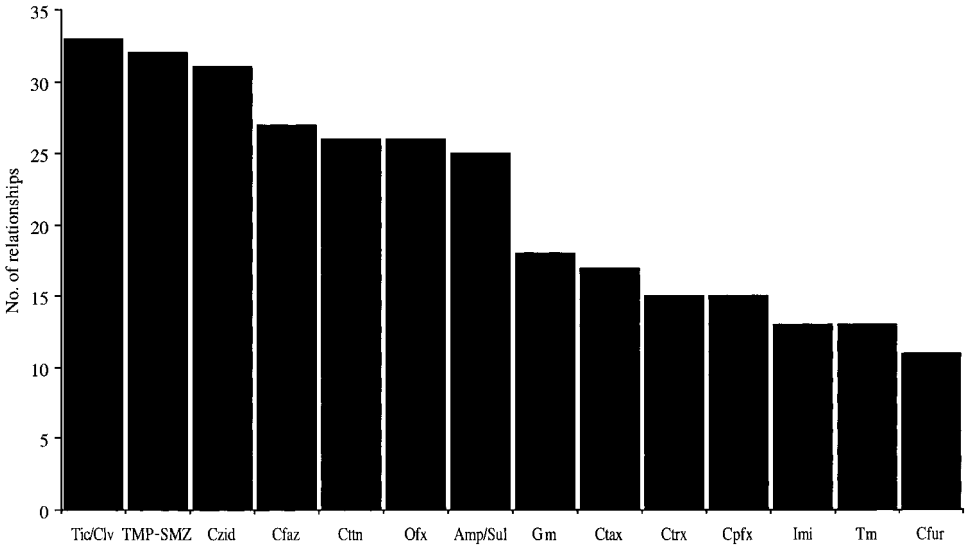

Figure 3. Number of drug/organism relationships involving increasing drug use and decreasing susceptibility that resulted from usage of an *individual* drug vs. *other* agents (Tic/Clv = ticarcillin/clavulanate; TMP-SMZ = trimethoprim-sulfamethoxazole; Czid = ceftazidime; Cfaz = cefazolin; Cttn = cefotetan; Ofx = ofloxacin; Amp/Sul = ampicillin/sulbactam; Gm = gentamicin; Ctax = cefotaxime; Ctrx = ceftriaxone; Cpfx = ciprofloxacin; Imi = imipenem; Tm = tobramycin; Cfur = cefuroxime).

evaluated was as follows: *A. anitratus* > *S. marcescens* > *K. pneumoniae* > *P. aeruginosa* > *E. coli* > *E. aerogenes* > *P. mirabilis* > *E. cloacae.*

Discussion

In most studies, antimicrobial usage has been assumed to be the major factor responsible for changes in susceptibility. Although one would expect a strong relationship between antimicrobial use and susceptibility patterns, other factors such as horizontal transmission of resistant isolates may obscure this relationship [9, 10, 32, 33]. Additionally, it should be recognized that multiresistant organisms can be selected as a result of the usage of antimicrobial agents unrelated to the agent of interest [18, 26]. Most studies have been on the relationship between an individual agent and its own susceptibility pattern. To date, limited data are available concerning the association between the use of multiple antimicrobials and susceptibility patterns.

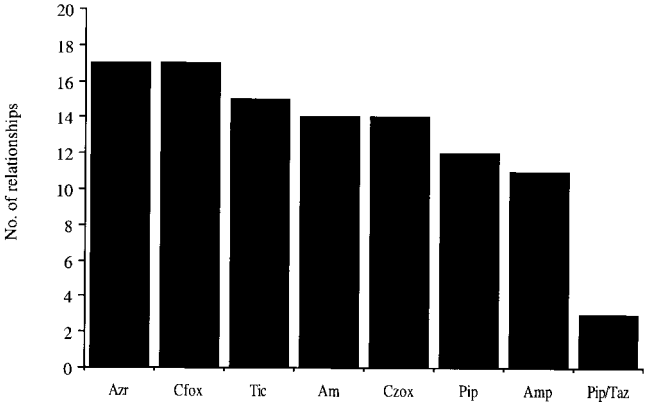

Figure 4. Number of drug/organism relationships involving decreasing drug use and increasing susceptibility that resulted from usage of an *individual* drug vs. *other* agents (Azr = aztreonam; Cfox = cefoxitin; Tic = ticarcillin; Am = amikacin; Czox = ceftizoxime; Pip = piperacillin; Amp = ampicillin; Pip/Taz = piperacillin/tazobactam).

In a recent report, the effect of changes in the consumption of macrolides on the susceptibility of group A streptococci to erythromycin in Finland was evaluated [21]. Macrolide use was restricted in response to a nationwide increase in erythromycin resistance. Following the implementation of the restriction policies, the number as well as the percentage of resistant isolates decreased. Data on the relative contributions of the individual agents to these decreases, however, were not reported. Stratton and co-workers tracked quinolone susceptibilities for *P. aeruginosa* during the process of replacing ciprofloxacin with ofloxacin [27]. The authors reported that a decrease in susceptibility was associated with an increase in the total usage of quinolones; however, it was not associated with the use of a specific agent.

Similar results were reported following the evaluation of penicillin use and susceptibility over 7 years in a university hospital [29]. It was noted that penicillin consumption alone was not correlated with changes in susceptibility of *S. aureus;* however, the correlation was greatly improved when the use of ampicillin was included in the analysis. Manian and coworkers found that drug usage was associated with loss of susceptibility to other agents in the same class [36]. An interesting finding was that, as in our study, ticarcillin/clavulanate was

most frequently associated with decreases in susceptibility of other agents. White et al. assessed susceptibility trends of *E. cloacae, S. marcescens, P. aeruginosa,* and *E. aerogenes* to seven β-lactams and the relationship with usage of these agents over 7 years [14]. The relationship between ceftazidime use and susceptibility of *E. cloacae* was poor ($r < 0.34$). However, aztreonam usage was strongly correlated to the decrease in susceptibility to ceftazidime for all organisms ($r = 0.84–0.89$). These reports illustrate the importance of including use of multiple drugs within the same drug class in the evaluation of susceptibility trends.

Other investigators have reported on the influence of dissimilar agents on susceptibility patterns [20, 26, 28, 30, 31, 35]. Chow et al. reported an increase in infections due to multiresistant *Enterobacter* species in patients having received prior therapy with a third-generation cephalosporin [26]. Resistance developed not only to other third-generation agents but also to extended-spectrum penicillins, chloramphenicol, tetracycline, norfloxacin, and TMP-SMZ. In contrast, Jacobson et al. did not demonstrate an association between the development of resistance to extended-spectrum cephalosporins and prior use of a number of different agents [20]. Søgaard demonstrated that the highest degree of correlation between antimicrobial usage and resistance to a single antimicrobial was obtained when the usage of multiple agents was incorporated into the analysis [31].

Similar findings were reported by Møller in the evaluation of resistance of *S. epidermidis, S. aureus,* and *E. coli* to a variety of antimicrobials studied over a 7-year period [30]. Decreased resistance of Enterobacteriaceae and *P. aeruginosa* to aminoglycosides has been associated with decreases in cephalosporin use [28]. Substantial decreases in resistance to gentamicin and tobramycin (34%–85% and 35%–78%, respectively) correlated well with decreased cephalosporin use. The authors hypothesized that the change in cephalosporin use, either by itself or in conjunction with a marked increase in penicillin and erythromycin use, may have been responsible. Other investigators have reported aminoglycoside use to be an independent predictor of resistance of *P. aeruginosa* to imipenem and ceftazidime [35]. These data lend credence to the premise that the use of one class of agents might influence the resistance to dissimilar agents.

The present study also demonstrates that use of multiple agents, similar and dissimilar, should be considered in evaluations of susceptibility trends. However, methodologic issues in our study as well as in other studies deserve comment. In this study, we evaluated only those susceptibility data that were values of at least 70% susceptibility. We chose this cutoff because an analysis of prescribing trends at our institution demonstrated that disproportionate decreases in drug use occurred when susceptibility to a given agent decreased to <70% (authors' unpublished data). This suggests that prescribers tend not to use a drug empirically when its susceptibility declines to <70%. Thus, evaluation of susceptibility data for rates of <70% may not be clinically relevant in empirical decision-making and therefore were not included. It is possible that important relationships between susceptibility and drug usage may have occurred below this susceptibility cutoff. However, the majority of the relationships meeting our criteria (73% and 76% of the single-drug and multiple-drug relationships, respectively) occurred with rates of susceptibility of ⩾70%.

In addition, the rate of the development of resistance and the point in that continuum at which one performs an evaluation may also hamper the ability to detect relationships between drug use and susceptibility. Should susceptibility change little, because of a ''lag phase'' or ''threshold'' effect or because maximal declines in susceptibility have already occurred, one will not be able to detect a relationship, despite changing drug use. This is illustrated by the relative lack of relationships observed with *E. cloacae* in the current study. Major decreases in susceptibility of *E. cloacae* to cephalosporins had already occurred at our institution before 1992. Moreover, drug-usage-vs.-susceptibility relationships involving decreased susceptibility are most likely found when the initial susceptibility is high, as was the case with ofloxacin, ticarcillin/clavulanate, and ampicillin/sulbactam.

The time unit of observation is also an important consideration in these types of analyses. We utilized annual data in assessing relationships. Preliminary analysis of quarterly data revealed more fluctuations in drug-usage-and-susceptibility relationships; however, this may simply be due to fewer observations being included in the percentage-susceptible calculations. Although relationships that occur within a shorter time frame may be missed with the use of aggregate/annual data, one is less likely to be misled by relationships based on dramatically fluctuating data.

Furthermore, most investigators utilize simple linear regression to characterize what may be nonlinear relationships [38]. Simple linear regression may not be an optimal method for analyzing these types of data; however, it fit our data well since we evaluated the subset of drug-use-vs.-susceptibility relationships with an r^2 of ⩾0.5. Since other factors may affect susceptibility patterns, explanation of at least 50% of the variability in the observed susceptibility trends was a reasonable objective. Others have suggested that a correlation coefficient of at least 0.7 is an appropriate marker for associations between drug use and susceptibility [17, 28, 30]. Currently, there is no consensus as to the magnitude of the correlation coefficient that should be used in analyses of this type. As an additional consideration, in our study, had a correlation coefficient of 0.8 ($r^2 = 0.64$) or 0.9 ($r^2 = 0.81$) been used, this would have resulted in the exclusion of 76% and 86%, respectively, of our data.

We focused on only those relationships with a negative slope, since this is what would likely draw the attention of most clinicians utilizing and evaluating these types of data. We, like other investigators, did note occasions when the slope was positive (increasing drug usage with increasing susceptibil-

ity or decreasing drug usage with decreasing susceptibility). However, these represented only 23% of the single-drug relationships and 27% of the multiple-drug relationships meeting our susceptibility and linear regression r^2 criteria. Potential explanations for these relationships include the influence of other agents, the period of observation, and the influence of other interventions (e.g., infection control measures).

This study investigated the possible relationships between the use of multiple antimicrobials and susceptibility for a number of common nosocomial pathogens. These results suggest that multiple antimicrobials may be associated with changes in susceptibility to other drugs and that surveillance of hospital susceptibility and drug use patterns should not be limited to single-drug relationships. Therefore, restricting use of a single drug in an attempt to prevent or reverse antimicrobial resistance in an institution may be ineffective. In light of the heightened emphasis on the relationship between drug usage and susceptibility, evaluation of the effect of multiple agents on susceptibility patterns appears justified.

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