Antimicrobial Resistance Rates Among Aerobic Gram-Negative Bacilli Recovered from Patients in Intensive Care Units: Evaluation of a National Postmarketing Surveillance Program

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We assessed the rates of antimicrobial resistance between 1990 and 1993 in intensive care units in the United States. A standardized microtiter minimal inhibitory concentration panel was used to test ~100 consecutive gram-negative aerobic isolates that were recovered primarily from blood, wounds, urine, and pulmonary sites in patients treated in each of 396 intensive care units in 45 states. Amikacin and imipenem were the agents most active against the 33,869 nonduplicate isolates (those recovered only once) tested. Resistance of aerobic gram-negative bacilli to third-generation cephalosporins was found to be an emerging problem. Increases in rates of resistance to ceftazidime among isolates of *Klebsiella pneumoniae* (from 3.6% to 14.4%; $P \ll .01$) and *Enterobacter* species (from 30.8% to 38.3%; $P = .0004$) were noted from 1990 to 1993; rates of resistance among *Pseudomonas aeruginosa* isolates remained stable. Ceftazidime-resistant bacteria were frequently resistant to aminoglycosides and ciprofloxacin. Risk factors for ceftazidime resistance included the number of beds in the hospital, the teaching status of the hospital, and specific body sites from which the isolates were recovered.

Awareness of antimicrobial resistance patterns within an institution is important. For clinicians, this information is crucial to the success of empirical antimicrobial therapy. In addition, as part of infection control surveillance, hospitals may be required by accrediting organizations and regulatory agencies to compare their resistance rates to regional or national aggregated rates and to develop a response when their rates are excessive. While the National Nosocomial Infections Surveillance (NNIS) system of the Centers for Disease Control and Prevention (CDC) [1] provides a sampling of national resistance rates, the intensity of data collection based on the NNIS system may not be feasible for all hospitals.

To assess the possibility of devising alternate ways of comparing rates, we reviewed the results of a multiyear, national survey of resistance rates among gram-negative bacilli recovered in intensive care units (ICUs), which was performed as part of a pharmaceutical manufacturer's postmarketing surveillance program. Because of increasingly frequent reports of resistance to newer cephalosporins [2], we also used this data base to evaluate the national rates of resistance to a representative third-generation cephalosporin (ceftazidime).

Received 30 November 1995; revised 12 April 1996.

Financial Support: Supported in part by a grant from Merck and Company and by the Research and Education Foundation of the Michael Reese Medical Staff.

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Clinical Infectious Diseases 1996;23:779–84

1058–4838/96/2304–0018$02.00

Methods

Between 1990 and 1993, hospital administrators were asked by regional educational representatives of Merck and Company, Inc., (Rahway, NJ) to submit susceptibility data for a minimum of 100 consecutive gram-negative aerobic isolates from patients in their ICUs. Organisms were identified to the species level by the method used within each institution, and susceptibility tests were performed with a standardized custom microtiter MIC panel (Microscan MKD MIC, Dade International MicroScan, Sacramento, CA) supplied by Merck. Testing procedures were validated by determining the MICs for reference strains, as recommended by the National Committee for Clinical Laboratory Standards; *Pseudomonas aeruginosa* ATCC (American Type Culture Collection) 27853 was tested weekly in each study hospital, and *Escherichia coli* ATCC 25922 and *E. coli* ATCC 35218 were tested at least twice during the study.

The classes of antimicrobials tested included aminoglycosides (amikacin, tobramycin, and gentamicin); third-generation cephalosporins (ceftazidime, cefotaxime, and ceftriaxone); extended-spectrum penicillins (ticarcillin, mezlocillin, and piperacillin); β-lactam/inhibitor combinations (ampicillin/sulbactam and ticarcillin/clavulanate); and aztreonam, imipenem, and ciprofloxacin.

Isolates were classified as either "nonduplicate" or "repeat;" the latter group consisted of isolates of the same species recovered two or more times from an individual patient, regardless of body site. All data refer to nonduplicate isolates unless otherwise stated.

Hospitals were categorized based on size (>500 beds [large], 200–500 beds [intermediate], and <200 beds [small]) and teaching status (nonteaching or teaching).

Statistical analyses were performed with Epi-Info Version 6.01 (CDC) with use of the χ^2 test with Yates' correction. *P* values of <.05 were considered significant.

Results

Hospital Demographics

A total of 396 study ICUs representing 45 states and the District of Columbia were included in this surveillance program; some hospitals participated in the program for several years. During each year of surveillance, teaching hospitals represented ~60% of participating institutions (except in 1993, when they represented 89% of all institutions). Large-sized and intermediate-sized teaching hospitals represented 26%–52% and 21%–37% of hospitals, respectively. Except for 1993, nonteaching hospitals were primarily represented by institutions with 200–500 beds (25%–33% of these hospitals). Small teaching hospitals and nonteaching hospitals represented <4% of participating institutions.

Organisms

During the 4-year surveillance period, 33,869 nonduplicate isolates were evaluated. The most common isolates, in order of frequency, were *Escherichia* species (21.3% of isolates); *P. aeruginosa* (19.7%); *Enterobacter* species (16.1%); and *Klebsiella* species (15.3%), which represented 72.4% of all initial isolates. The remaining isolates included *Acinetobacter* species (5.3%); *Proteus mirabilis* (4.8%); *Serratia marcescens* (4.3%); *Xanthomonas (Stenotrophomonas) maltophilia* (3.7%); *Citrobacter* species (3.6%); *Morganella morganii* (1.4%); and other gram-negative bacilli (4.5%).

Hospital size (the number of beds) and teaching status appeared to influence the species of bacteria detected. *P. aeruginosa* was more commonly found in teaching hospitals with >500 beds (21.2% of isolates vs. 19.0% of isolates from other hospitals; $P \leqslant .01$). Organisms more commonly found in hospitals with <200 beds were *Escherichia* species (29.1% of isolates from these hospitals vs. 21.0% of isolates from hospitals with ⩾200 beds; $P \leqslant .01$) and *Klebsiella pneumoniae* (14.7% of isolates vs. 12.3% of isolates from hospitals with ⩾200 beds; $P = .01$). The findings for *P. aeruginosa* correspond in part to the greater number of respiratory specimens submitted by teaching hospitals with >500 beds, and the findings for *Escherichia* species correspond with the greater number of urine specimens submitted by hospitals with <200 beds.

Body Sites

During the 4-year surveillance period, the rank order of body sites from which nonduplicate isolates were recovered did not change. The most common sites were the respiratory tract, (47%), urine (22.5%), blood (8.1%), and wounds (3.6%). *P. aeruginosa* was the most frequent respiratory isolate (24% of respiratory isolates), and *Escherichia* species were the most frequent isolates from urine (47%) and blood (30%). The distribution of organisms recovered from wounds was more even: *Enterobacter* species, *Escherichia* species, and *P. aeruginosa* were each recovered from 18%–21% of these specimens.

The respiratory tract was the most common site surveyed (44.3%–50.9% of specimens) in the teaching and nonteaching institutions with >200 beds; the urinary tract was the most common site surveyed (33%–50% of specimens) in teaching and nonteaching hospitals with <200 beds. Blood and wounds accounted for 8.1% and 3.6% of specimens, respectively, from all hospitals.

Susceptibility Patterns

Antimicrobials could be grouped into three categories based on the susceptibility of all species of nonduplicate isolates. These categories included agents active against ⩾90% of isolates, agents active against 80%–89% of isolates, and agents active against <80% of isolates (table 1). The ranking of ceftriaxone and cefotaxime is in part due to their lack of activity against *P. aeruginosa.*

Of the four major species studied, differences in susceptibilities to agents within antimicrobial classes were observed for *P. aeruginosa* and *K. pneumoniae* (table 2). Of the aminoglycosides, amikacin and tobramycin were more active against *P. aeruginosa* than was gentamicin, while all three aminoglycosides had similar activity against the other gram-negative bacilli. Piperacillin was more active than mezlocillin against *P. aeruginosa,* and it was more active than ticarcillin against *K. pneumoniae.*

Ceftazidime-Resistant Bacteria

K. pneumoniae. During the 4-year study period, 298 (7.1%) of 4,201 *K. pneumoniae* isolates were found to be resistant to ceftazidime. However, substantially higher rates of ceftazidime resistance (56%–75%) occurred in four hospitals, which accounted for 20% of all ceftazidime-resistant *K. pneumoniae* isolates. After excluding these four outlier hospitals from the analysis, the incidence of ceftazidime-resistant *K. pneumoniae* was 5.8% (table 3). The four outlier hospitals were excluded on the basis of the following results.

The rate of ceftazidime resistance among *K. pneumoniae* isolates increased progressively from 3.6% in 1990 to 14.4% in 1993 ($P \leqslant .01$). Factors associated with the presence of ceftazidime-resistant *K. pneumoniae* were the teaching status of the hospitals, size (>500 beds), and body site (wound) (table 3).

The increasing rate of resistance to ceftazidime could largely be attributed to teaching hospitals with >500 beds; in these hospitals, the rate of resistance increased from 5.4% (28 of 517 isolates) in 1990 to 21.8% (67 of 308 isolates) in 1993

Table 1. Overall antimicrobial susceptibility rates for isolates of aerobic gram-negative bacilli recovered from 396 intensive care units, by body site.

Antimicrobial	All sites* (n = 33,869)	Respiratory sites (n = 15,849)	Urine (n = 7,616)	Blood (n = 2,737)	Wounds (n = 1,232)
Group 1†					
Amikacin	92	88	97	94	93
Imipenem	91	88	97	95	93
Group 2†					
Tobramycin	88	85	93	89	87
Ciprofloxacin	89	87	94	93	89
Ceftazidime	84	81	91	86	81
Ticarcillin/clavulanate	81	78	86	81	75
Gentamicin	82	78	89	86	80
Group 3†					
Aztreonam	78	72	88	80	75
Piperacillin	67	67	70	65	65
Mezlocillin	61	60	66	60	59
Ticarcillin	58	58	61	55	56
Ceftriaxone	69	61	82	75	64
Cefotaxime	66	58	81	73	63
Ampicillin/sulbactam	40	34	54	47	37

NOTE. Numbers are percentages.
* Includes miscellaneous sites (n = 6,435).
† Groups based on overall susceptibility.

($P \ll .01$) (figure 1). The overall rates at which ceftazidime-resistant *K. pneumoniae* isolates were recovered from major body sites of patients in large teaching hospitals were two-to-seven times higher than rates at which they were recovered at all other hospitals from other sites including the respiratory tract (8.6% vs. 4.3%; $P \ll .01$), urine (10.2% vs. 3.2%; $P \ll .01$), blood (11.1% vs. 1.5%; $P \ll .01$), and wounds (25.6% vs. 7.8%; $P = .02$).

The progressive increase in the number of ceftazidime-resistant *K. pneumoniae* blood isolates from 1990 to 1993 for all hospitals was almost identical to the progressive increase observed in the number of nonblood isolates (figure 2).

For *K. pneumoniae* isolates, there was a significant relation between ceftazidime resistance and cross-resistance to other antimicrobial classes (table 4). Of the noncephalosporin antimicrobials, rates of cross-resistance were highest for gentamicin, ciprofloxacin, and amikacin. During consecutive years, there was little change in rates of cross-resistance to these classes of antimicrobials. The rate of cross-resistance to imipenem declined between 1990 (12.6%) and 1993 (2.4%); this

Table 2. Antimicrobial susceptibility rates for the four most common species of gram-negative bacilli recovered from 396 intensive care units, 1990–1993.

Antimicrobial by class	*Escherichia* species (n = 7,225)	*Klebsiella pneumoniae* (n = 4,205)	*Enterobacter* species (n = 5,451)	*Pseudomonas aeruginosa* (n = 6,682)
Amikacin	99	98	98	89
Tobramycin	96	92	93	93
Gentamicin	96	92	93	65
Piperacillin	72	44	63	90
Mezlocillin	71	36	62	78
Ticarcillin	70	6	55	86
Imipenem	99	98	97	87
Ciprofloxacin	99	95	96	89
Ceftazidime	98	93	67	86
Ceftriaxone	98	93	68	23
Cefotaxime	98	93	68	16
Aztreonam	97	92	71	77
Ticarcillin/clavulanate	90	89	60	87
Ampicillin/sulbactam	70	62	24	2

NOTE. Numbers are percentages.

Table 3. Rates of resistance to ceftazidime in selected bacteria, as determined by surveillance of intensive care units, 1990–1993.

	Klebsiella pneumoniae		*Enterobacter* species		*Pseudomonas aeruginosa*	
Variable	No. of strains tested	Percent resistant	No. of strains tested	Percent resistant	No. of strains tested	Percent resistant
Overall resistance	4,100	5.8	5,381	32.0	6,675	14.2
Site of recovery						
Urine	958	5.2	583	37.4*	996	9.3
Blood	417	6.5	384	35.7	370	12.7
Respiratory tract	1,885	5.9	3,102	31.0	3,888	15.2†
Wounds	120	14.2‡	220	35.5	262	15.6
Miscellaneous	720	4.4	1,092	29.9	1,159	15.3
Hospital status						
Teaching	2,521	7.3§	3,330	32.6	4,235	15.5§
Nonteaching	1,579	3.4	2,051	30.9	2,440	12.0
No. of beds						
<200	142	2.1	135	23.7	194	19.1
200–500	2,173	3.8	2,766	29.8	3,398	12.3
>500	1,785	8.6‖	2,480	34.9‖	3,083	16.1‖

NOTE. Data excludes outlier hospitals and were analyzed with use of the χ^2 test.
* $P < .01$ (urine vs. other sites).
† $P < .007$ (respiratory tract vs. other sites).
‡ $P < .001$ (wounds vs. other sites).
§ $P < .001$ (teaching vs. nonteaching hospitals).
‖ $P < .0003$ (>500 beds vs. other hospital sizes).

decline may be associated in part with improvements in the susceptibility testing methods used for this drug. Ticarcillin/clavulanate and ampicillin/sulbactam were inactive against 81% and 92% of ceftazidime-resistant *K. pneumoniae* isolates, respectively.

Enterobacter species. Ceftazidime resistance was found in 1,776 (32.6%) of 5,444 *Enterobacter* isolates. Substantially higher rates of resistance to ceftazidime (82%–100%) were identified in five hospitals, but these hospitals accounted for only 3% of all ceftazidime-resistant *Enterobacter* species. After these hospitals were excluded from the analysis, the incidence of ceftazidime-resistant *Enterobacter* species was found to be 32.0% (table 3). The frequency of ceftazidime-resistant *Enterobacter* species progressively increased from 30.8% in 1990 to 38.3% in 1993 ($P \leqslant .01$). Factors associated with higher ceftazidime resistance rates were hospital size and isolation of *Enterobacter* species from a urinary site (table 3).

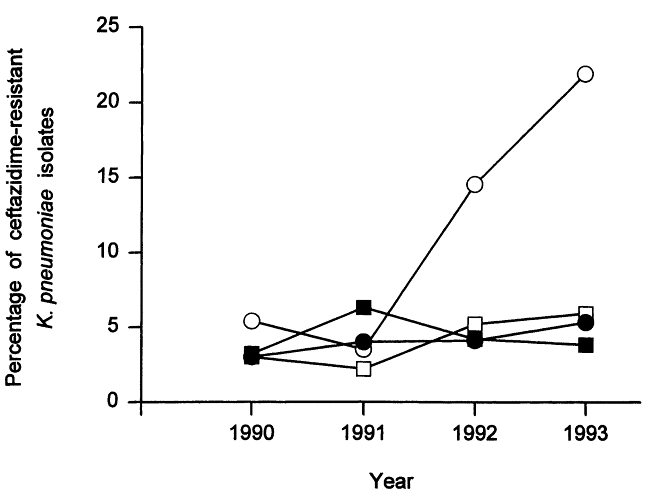

Figure 1. Ceftazidime resistance rates by hospital type and year for *K. pneumoniae.* ○ = teaching hospitals with >500 beds; ■ = teaching hospitals with 200–500 beds; □ = nonteaching hospitals with >500 beds; ● = nonteaching hospitals with 200–500 beds.

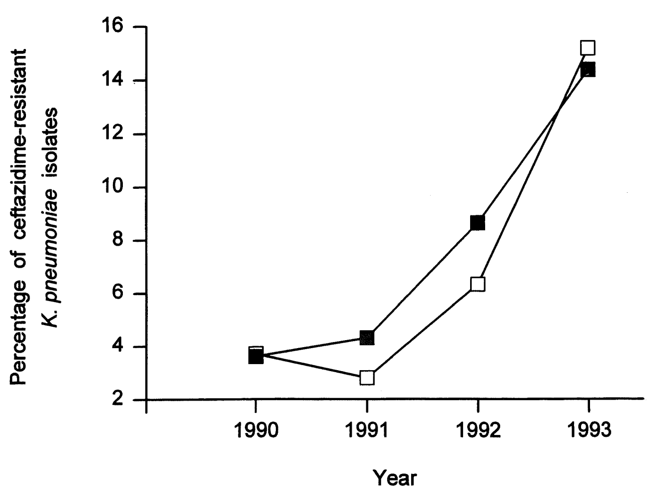

Figure 2. Ceftazidime resistance rates among blood vs. nonblood isolates of *K. pneumoniae.* □ = blood isolates; ■ = nonblood isolates.

Table 4. Rates of cross-resistance among selected gram-negative bacilli, as determined by intensive care unit surveillance, 1990–1993.

Antimicrobial	*Pseudomonas aeruginosa* Ceftazidime resistant (n = 950)	*Pseudomonas aeruginosa* Ceftazidime susceptible (n = 5,725)	*Enterobacter* species Ceftazidime resistant (n = 1,776)	*Enterobacter* species Ceftazidime susceptible (n = 3,668)	*Klebsiella pneumoniae* Ceftazidime resistant (n = 298)	*Klebsiella pneumoniae* Ceftazidime susceptible (n = 3,903)
Gentamicin	54.5	31.7	14.4	2.3	67.1	3.6
Ciprofloxacin	24.2	8.9	10.2	1.6	45.3	2.0
Imipenem	26.4	10.1	5.1	1.8	7.0	0.9
Amikacin	26.9	7.8	5.6	0.6	21.5	0.7

NOTE. Numbers are percentages.

The increase in the rate of ceftazidime resistance among *Enterobacter* species recovered from blood specimens was similar to the increase in the rate of resistance among isolates from nonblood sites.

Ceftazidime-resistant *Enterobacter* species were also frequently cross-resistant to other antimicrobial classes. Among the noncephalosporin antimicrobials, rates of cross-resistance were highest for gentamicin, ciprofloxacin, amikacin, and imipenem. Both β-lactam/inhibitor combinations tested (i.e., ticarcillin/clavulanate and ampicillin/sulbactam) were inactive against >95% of ceftazidime-resistant *Enterobacter* species.

P. aeruginosa. Of all *P. aeruginosa* isolates, 14.2% were resistant to ceftazidime. This rate remained stable (14%–15%) during the 4-year surveillance period.

Factors associated with ceftazidime resistance were isolation of *P. aeruginosa* from the respiratory tract and hospital size and teaching status (table 3). Teaching hospitals with >500 beds were more likely to have ceftazidime-resistant isolates recovered (17.1% vs. 12.5% for all other hospitals; $P \leqslant .01$).

Ceftazidime-resistant *P. aeruginosa* isolates demonstrated fluctuating degrees of multidrug resistance during the 4-year surveillance period. For example, cross-resistance to ciprofloxacin increased from 18.8% in 1990 to 34.3% in 1992; this rate then declined to 28.3% in 1993. Rates of cross-resistance to gentamicin and amikacin also fluctuated: for gentamicin, the rate increased from 37.5% in 1990 to 65.7% in 1992; for amikacin, the rate increased from 16.7% in 1990 to 30.7% in 1992. The highest rates of cross-resistance to these drugs were observed in 1992, and the lowest rates of cross-resistance were observed in 1993. Rates of cross-resistance to imipenem ranged from 25.6% in 1990 to 29.3% in 1992.

Repeated Isolates

Examination of isolates of a species recovered more than once from individual patients showed that these isolates occasionally differed from the initial isolates in terms of resistance patterns. For example, the rates of resistance to ceftazidime and ticarcillin/clavulanate among repeated isolates of *P. aeruginosa* was 1.5 to 2.4 times higher than the rates among initial isolates. Increases in rates of resistance to imipenem and amikacin (1.1–1.9 times higher) and to ciprofloxacin and gentamicin (1.3–1.5 times higher) were also found. When initial isolates of *P. aeruginosa* were resistant to ceftazidime, no increase in the rates of cross-resistance to other antimicrobials among repeated isolates was noted.

For *Enterobacter* species, the rates of resistance to ceftazidime, ticarcillin/clavulanate, and gentamicin were 1.1–1.9 times higher among repeated isolates than among initial isolates. Rates of resistance to imipenem, ciprofloxacin, and amikacin among both initial and repeated isolates were generally $\leqslant$5%. However, isolates were more resistant to these antimicrobials when they were also resistant to ceftazidime. For *K. pneumoniae,* there was little difference in rates of resistance to aminoglycosides (amikacin and gentamicin), β-lactams (ceftazidime, ticarcillin/clavulanate, and imipenem), and ciprofloxacin among initial and repeated isolates in most years.

Discussion

The initiation of rational empirical antimicrobial therapy is based on an awareness of resistance patterns within an institution. In this surveillance study, we found that the agents most active in vitro against gram-negative bacilli recovered from patients in ICUs were amikacin and imipenem. Although the use of third-generation cephalosporins for suspected or documented infections in ICU patients is an attractive, potentially less-toxic alternative to the use of aminoglycosides, we noted an increasing frequency of resistance to cephalosporins in study isolates.

In our analysis, ceftazidime was selected as the representative third-generation cephalosporin for the detection of resistance in strains that are hyperproducers of type I chromosomal β-lactamase (e.g., *Enterobacter* species) or that carry plasmid-mediated extended-spectrum β-lactamases [3]. In addition, another national analysis of this agent is available for benchmarking: a comparison of our data with the recently published NNIS ICU data [4] (based on exclusion of their outbreak hospital and our outlier hospitals) shows that the rate of resistance to ceftazidime among our *K. pneumoniae* isolates was higher

(5.8% vs. 2.6%), that the rate among our *Enterobacter* species was lower (32.0% vs. 39.6%), and that the rate among our *P. aeruginosa* isolates was similar (14.2% vs. 13.2%) [4].

There may be several reasons for differences between our findings and the NNIS results. First, our data were collected during a more recent period than were the NNIS data (i.e., 1990–1993 vs. 1987–1991). Second, the NNIS data represent only isolates from presumed nosocomial infections. Our data represent consecutive isolates and thus include organisms that may represent community-acquired infections and/or colonization. Nevertheless, our susceptibility data for blood isolates (which are probably representative of true infection) were similar to our data for nonblood isolates, at least with respect to *K. pneumoniae* and *Enterobacter* species.

Third, our data could have been biased by recruitment of hospitals known to have problems with resistant bacteria, as determined by postmarketing surveillance. Fourth, susceptibility surveillance results are dependent on the relative representation of organisms from teaching hospitals and from hospitals with >500 beds. The inclusion of more large teaching institutions in 1993 (52.2% of hospitals) than in 1990 (25.5% of hospitals) particularly contributed to the increasing rate of resistance among *K. pneumoniae* isolates.

On the basis of our results, multidrug resistance among *K. pneumoniae, Enterobacter* species, and *P. aeruginosa* isolates to unrelated classes of antimicrobials (e.g., aminoglycosides, β-lactams, and ciprofloxacin) was common; cross-resistance to ciprofloxacin appeared to trend upward. The extent to which this observation correlates with use of quinolone antibiotics both in and out of the hospital warrants study.

This study has several limitations. First, although microbiology laboratories were asked to submit 100 consecutive gram-negative isolates, it is unknown how rigidly the laboratories adhered to this protocol. Second, data on the use of antimicrobials in ICUs and hospitals was not available. Third, it is possible that some of our data may represent epidemics of resistant bacteria, even though we tried to correct for this by excluding outlier hospitals from our analysis of ceftazidime resistance. Fourth, susceptibility results for other potentially useful antimicrobial agents (e.g., trimethoprim-sulfamethoxazole) were not available.

Fifth, calculation of more sophisticated rates (e.g., rates of resistance per 1,000 patient days or by exposures to devices) is not possible because we do not have accurate denominator data for each ICU. Sixth, no epidemiologic typing was performed to prove that initial and repeated isolates with decreased susceptibilities were the same strain. Seventh, since we could not differentiate nosocomial isolates from community-acquired bacteria and we could not differentiate infection from colonization, these data do not necessarily serve as a guide for empirical antimicrobial selection. Eighth, these data are limited to only aerobic, gram-negative isolates, with the focus of susceptibilities limited to four major genera.

Finally, many factors correlate with the recovery of antibiotic-resistant bacteria, including the teaching status and size of the hospital; prior exposure to antimicrobials; sites of infection; and the population of patients, especially nursing home residents, from whom the isolates were recovered [3, 4]. However, given the limited demographics of our data base, we were able to analyze only the influences of hospital type and size and of body site. Future postmarketing surveillance programs should be designed on the basis of these limitations. For example, current efforts by the CDC to integrate data on antimicrobial use and resistance in ICUs in a subset of NNIS hospitals may yield important clinicoepidemiological information [5].

Despite these limitations, these data do provide a benchmark against which hospitals may gauge the rates of resistance among aerobic gram-negative bacteria in their ICUs. Moreover, our susceptibility data suggest that resistance rates for blood isolates closely parallel those for nonblood isolates. Thus, hospital administrators may find it useful to compare the susceptibilities of their ICU blood isolates with such data from other hospitals of similar size and teaching status and to confirm the validity of this approach prospectively. Our results emphasize that at a minimum, aggregate ICU surveillance data need to be risk-stratified by hospital size, teaching affiliation, and body site from which the isolate was recovered.

Finally, the increasing rates of antimicrobial resistance, especially in larger teaching hospitals, underscore the need for making control of resistance a strategic goal for hospitals; a series of potential prevention and control measures have been outlined recently [6].

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