Antimicrobial Resistance in Isolates from Inpatients and Outpatients in the United States: Increasing Importance of the Intensive Care Unit

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To compare the occurrence of antimicrobial resistance in hospitals with that in the community, we analyzed data for isolates collected from inpatients and outpatients in eight U.S. hospitals. The percentage of resistant isolates from inpatients was higher than that from outpatients for the following combinations of antimicrobials and organisms: methicillin/coagulase-negative *Staphylococcus* (49.0% vs. 36.0%, respectively; $P < .01$); methicillin/*Staphylococcus aureus* (33.0% vs. 14.5%, respectively; $P < .01$); ceftazidime/*Enterobacter cloacae* (26.0% vs. 12.0%, respectively; $P < .01$); imipenem/*Pseudomonas aeruginosa* (12.0% vs. 6.5%, respectively; $P < .01$); ceftazidime/*P. aeruginosa* (7.8% vs. 4.0%, respectively; $P < .01$); and vancomycin/*Enterococcus* species (6.3% vs. 1.4%, respectively; $P < .01$). There was a significant stepwise decrease in the percentage of resistant organisms isolated from patients in the intensive care unit (ICU), non-ICU inpatients, and outpatients. These results suggest that resources allocated to control antimicrobial resistance should continue to be focused in the hospital, particularly in the ICU.

Antimicrobial-resistant pathogens are challenges to progress in controlling emerging infections, especially hospital-acquired infections [1]. Increases in the rate of antimicrobial resistance are resulting in the use of much more expensive drugs, more prolonged hospitalizations, higher death rates, and higher health care costs. Yearly expenditures incurred from drug resistance in the United States are estimated to approach $4 billion and are rising [2].

Most, but not all [3], studies have found a higher prevalence of antimicrobial resistance in hospitals in general and in intensive care units (ICUs) in particular than in the community [4–6]. Such resistance presents a serious challenge for physicians. For example, data from the National Nosocomial Infections Surveillance (NNIS) system, currently the only national source of information on infections due to hospital-acquired pathogens and their associated antimicrobial susceptibility profiles, indicate that the rate of resistance to vancomycin in hospital-acquired *Enterococcus* species is increasing. As of December 1993, 14.2% of all enterococci associated with nosocomial infections in ICU patients were vancomycin-resistant. Most of these pathogens were resistant to all currently available antimicrobials [7].

Among certain gram-negative bacilli, the resistance rate is also increasing. In hospitals participating in the NNIS system, NNIS data indicate that the percentage of *Klebsiella pneumoniae* resistant to extended-spectrum β-lactam agents increased from 1.5% in 1986 to 12.8% in 1993 [8]. NNIS data also suggest that in one region these resistant *Klebsiella* strains first appeared in an ICU in one hospital and then spread to other hospitals in the surrounding area.

Unfortunately, antimicrobial resistance is not limited to the hospital setting. *Streptococcus pneumoniae* infections are a leading cause of morbidity and mortality in young children, persons with underlying debilitating medical conditions, and elderly persons. Multidrug-resistant strains of this organism are emerging throughout the United States [9, 10]. Methicillin-resistant *Staphylococcus aureus*, traditionally thought to be hospital-acquired but infrequently recognized in the community for over a decade, is now found outside hospitals in relatively large numbers [11].

Defining appropriate control measures for antimicrobial-resistant pathogens has been of particular concern for acute care hospitals. With a changing emphasis on integrated health care systems that provide care for patients in acute care, extended care, and ambulatory care settings, dwindling resources will need to be prioritized and appropriately focused on infection control in hospitals and prevention of antimicrobial resistance. This task has been complicated by the fact that the magnitude of antimicrobial resistance in the hospital compared with that in the community setting is not clear. In addition, the contribution of the ICU to overall resistance in the hospital needs clarification.

Therefore, to evaluate and compare resistance in these two settings, in 1994 the Hospital Infections Program and the Cen-

ters for Disease Control and Prevention (CDC), in cooperation with the Rollins School of Public Health at Emory University, began Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology). This project began with phase I in April 1994; a second phase started early in 1996. We present data from phase I of that project to assess the extent of antimicrobial resistance in hospitals, particularly in ICUs, compared with that in the community and to determine if pathogens isolated from inpatients are more resistant to antimicrobials than are pathogens from outpatients.

Methods

Eight hospitals that participate in the ICU component of the NNIS system were selected for the first phase of Project ICARE. The surveillance methodology of the NNIS system has been previously described [12]. The eight hospitals were chosen to be geographically separated (New York, Pennsylvania, Wisconsin, Michigan, North Carolina, Georgia, and California) and to represent various categories of bed size and teaching affiliation. Three of these hospitals had ⩾500 beds; the remaining five had <500 beds.

The study was conducted from April 1994 through March 1995. Each hospital collected data for 13 different antimicrobial/organism combinations (eight organisms and eight antimicrobials were represented in these 13 combinations). All isolates, whether responsible for hospital- or community-acquired infection, were to be reported. Duplicate isolates were excluded: these were defined as isolates of the same organism with the same antimicrobial resistance pattern that were recovered from the same patient whatever the site of isolation.

The susceptibility testing methods used by the participating hospitals for most isolates included the following: Kirby-Bauer disk diffusion; VITEK (bioMérieux Vitek, Hazelwood, MO); Microscan (Baxter Laboratories, West Sacramento, CA): Sceptor (Becton Dickinson Microbiology Systems, Cockeysville, MD); Sensititre (Sensititre, Salem, NH); Pasco (Difco, Wheatridge, CO); Micromedia (AcuMed, Westlake, OH); and broth microdilution and agar dilution methods. Only isolates of *Enterococcus* species had their identities and susceptibilities to vancomycin confirmed at the CDC by using the broth microdilution method [13].

We studied eight of the 13 sentinel antimicrobial/organism combinations because of their current and potential clinical importance. These combinations included methicillin/coagulase-negative *Staphylococcus;* methicillin/*S. aureus;* ceftazidime/*Enterobacter cloacae;* imipenem/*Pseudomonas aeruginosa;* ceftazidime/*P. aeruginosa;* vancomycin/*Enterococcus* species; ciprofloxacin/*Escherichia coli;* and ceftazidime/*E. coli.* In each hospital, the data were stratified by each ICU, all inpatient units combined, and all outpatients. The proportion of resistant isolates for each antimicrobial/organism combination was defined by dividing the number of resistant isolates by the total number of isolates for which tests of susceptibility

to the antimicrobial from the respective combination were performed.

For phase I of Project ICARE, data for each antimicrobial/organism combination in all eight study hospitals were pooled; resistance in organisms from hospitalized patients (ICU and non-ICU patients combined) was compared with resistance in isolates from outpatients. The isolates from inpatient areas in hospitals were further subdivided into pooled ICU and pooled non-ICU categories. Resistance in isolates from each of these location groups was compared with resistance in the isolates from outpatients.

For each of the eight antimicrobial/pathogen combinations, the influence of the data from an individual hospital upon the overall statistical analysis of pooled data was assessed by removing the data from each hospital in turn and analyzing the pooled data from the remaining seven hospitals according to the ICU and non-ICU inpatient/outpatient stratification described above to see if the data from the excluded hospital influenced the overall statistical analysis of pooled data. Statistical methods employed included the χ^2 test (with Mantel-Haenzel correction) and, where appropriate, Fisher's exact test.

We also examined the relative magnitude of the ICU population within all NNIS hospitals. Since 1988, NNIS hospitals have been surveyed approximately every 2 years regarding their number of licensed beds and their number of ICU beds. We analyzed the results of five surveys and plotted the mean number of total hospital beds and ICU beds by year; a regression line was fitted to these data.

Results

Ninety-six percent of vancomycin-resistant *Enterococcus* isolates received by the CDC were confirmed to have the identities and resistance profiles reported by the study hospitals. According to the pooled data from all eight hospitals, the proportion of antimicrobial resistance in isolates from inpatients was significantly higher than that in isolates from outpatients for all of the antimicrobial/organism combinations except ciprofloxacin/*E. coli* and ceftazidime/*E. coli* (table 1). This finding was also true when data from each hospital were examined individually, with two exceptions.

One hospital did not routinely check susceptibility to imipenem in pathogens from outpatients. In another hospital (hospital A), significantly more imipenem-resistant *P. aeruginosa* isolates were recovered from outpatients than from inpatients (11 of 93 vs. 7 of 162, respectively; $P < .05$). This finding was in stark contrast to similar comparisons made in the othe six hospitals where the percentage of imipenem-resistant *P. aeruginosa* was significantly higher among isolates from inpatients.

The direction of the difference between the percentage of imipenem-resistant *P. aeruginosa* among isolates from inpatients and that among isolates from outpatients actually reversed when we removed data from hospital A from the

Table 1. Resistance to specific antimicrobials in isolates from inpatients vs. outpatients for sentinel antimicrobial/pathogen combinations.

Antimicrobial/pathogen combination	No. of resistant isolates/total no. of isolates tested (%)		
	Inpatients	Outpatients	*P* value
Methicillin/coagulase-negative *Staphylococcus*	922/1,881 (49.0)	250/697 (35.9)	<.01
Methicillin/*Staphylococcus aureus*	861/2,633 (32.7)	233/1,594 (14.6)	<.01
Ceftazidime/*Enterobacter cloacae*	145/559 (26.0)	15/126 (11.9)	<.01
Imipenem/*Pseudomonas aeruginosa**	164/1,368 (12.0)	31/477 (6.5)	<.01
Ceftazidime/*P. aeruginosa*	147/1,889 (7.8)	25/631 (4.0)	<.01
Vancomycin/*Enterococcus* species	92/1,459 (6.3)	8/575 (1.4)	<.01
Ciprofloxacin/*Escherichia coli*	16/3,189 (0.5)	28/3,997 (0.7)	NS
Ceftazidime/*E. coli*	5/2,348 (0.2)	9/1,887 (0.5)	NS

NOTE. NS = not significant.
* Two hospitals not included (see text).

statistical analysis of pooled data. Therefore, data regarding imipenem-resistant *P. aeruginosa* from hospital A and the hospital that did not test susceptibility to imipenem in *P. aeruginosa* isolates were not included in the results of the statistical analysis of pooled data that appear in table 1. It is interesting that in hospital A the percentage of ciprofloxacin-resistant *E. coli* also was higher among isolates from outpatients (1.7% for inpatients vs. 5.9% for outpatients; *P* < .05).

The six antimicrobial/organism combinations with higher rates of resistance in isolates from inpatients were further categorized by ICU patients, non-ICU inpatients, and outpatients (figure 1). For all but imipenem/*P. aeruginosa,* the percentage of antimicrobial-resistant isolates was significantly higher in

Figure 1. Comparison of antimicrobial resistance in isolates from intensive care unit (ICU) patients, non-ICU inpatients, and outpatients in eight U.S. hospitals. MRSE = methicillin-resistant *Staphylococcus epidermidis;* MRSA = methicillin-resistant *Staphylococcus aureus;* CZIDREC = ceftazidime-resistant *Enterobacter cloacae;* IMIRPA = imipenem-resistant *Pseudomonas aeruginosa;* CZIDRPA = ceftazidime-resistant *P. aeruginosa;* VRE = vancomycin-resistant *Enterococcus* species; * = two hospitals were not included in the analysis of IMIRPA (see text); ■ = ICU patients; ▨ = other inpatients; ▥ = outpatients.

the ICU than in the other two settings. For all six combinations, the percentage of resistant isolates in the hospitals decreased in a stepwise manner. The highest resistance rates occurred among isolates from ICU patients followed in decreasing order by rates among isolates from non-ICU inpatients and rates among isolates from outpatients. All of the stepwise decreases were statistically significant with the exception of those for imipenem-resistant *P. aeruginosa* from non-ICU inpatients and outpatients and vancomycin-resistant *Enterococcus* species from ICU patients and non-ICU inpatients.

The importance of the ICU as a focus for antimicrobial resistance was underscored by the significant increase in the mean number of ICU beds in 70 NNIS hospitals that responded to each of four surveys from 1988, 1990, 1992, and 1995. The mean number of total licensed beds decreased slightly during the same period. This decrease, however, was not significant (figure 2).
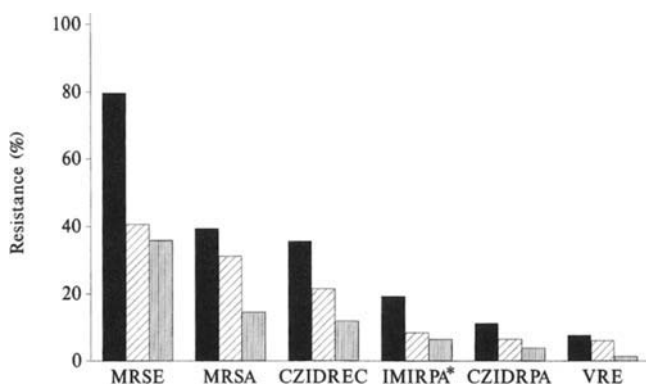
Discussion

Our analysis suggests that the rate of resistance in nosocomial pathogens to a variety of antimicrobials commonly used to treat nosocomial infections is significantly higher in the hospital setting than in the outpatient setting. Moreover, there appears to be a pattern of a stepwise decrease in the frequency of antimicrobial resistance (isolates from ICU patients > isolates from non-ICU inpatients > isolates from outpatients) for nearly all antimicrobial/pathogen combinations examined.

Analysis of data reported to the NNIS system between 1989 and 1993 demonstrated that the ICU was a major focus of resistance within hospitals [14]. This association between the ICU and antimicrobial resistance has been reported by other investigators [15]. Our data tend to support the presumption that control of antimicrobial resistance within hospitals should continue to be focused in the ICU.
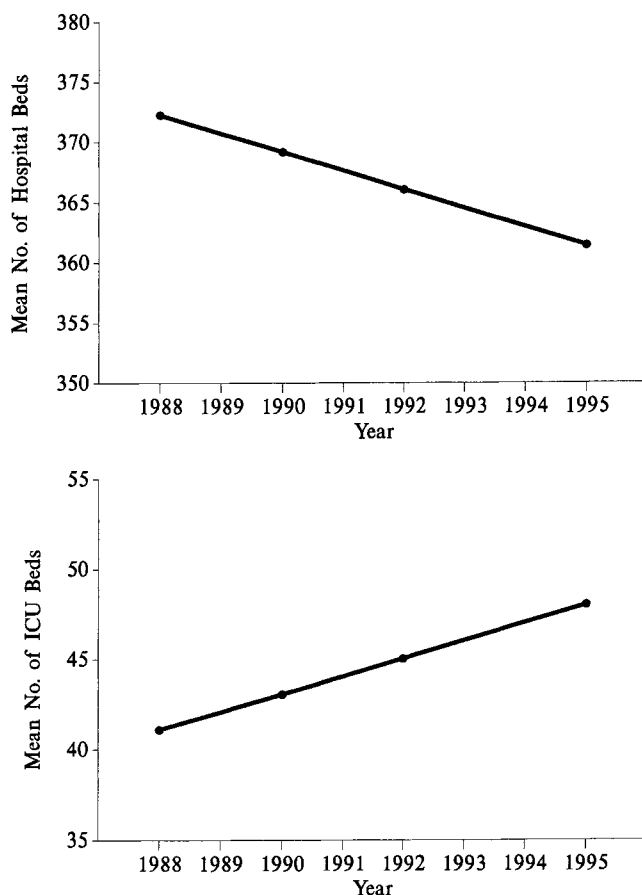
Figure 2. Results of five surveys of 70 hospitals participating in the National Nosocomial Infections Surveillance (NNIS) system from 1988 through 1995; the surveys examined the total number of licensed beds and the relative number of intensive care unit (ICU) beds. *Top:* a plot of the mean number of total hospital beds by year that fits a regression line. *Bottom:* a similar plot of the mean number of NNIS ICU beds by year. While there was a decrease in the mean number of total hospital beds during this period, it was not significant. In contrast, the increase in the number of NNIS ICU beds was statistically significant ($P < .05$).

Patients admitted to ICUs are at greatest risk of acquiring nosocomial infections, partly because of their serious underlying disease but also because of exposure to life-saving invasive procedures, prolonged use of in situ invasive devices, therapy with multiple antimicrobials, and extended hospital stays [5, 16]. Moreover, antimicrobial resistance in pathogens is more likely encountered in the ICU because of the selection effect of treatment with multiple antimicrobials for a single patient, which may result in amplification of antimicrobial resistance in organisms [17]. The increasing number of ICU beds in hospitals (figure 2) is an important development regarding both antimicrobial resistance and nosocomial infections. The relative magnitude of antimicrobial resistance in ICUs will increase as hospitals devote more beds and resources to those units.

Although our data found the hospital to be the focus of antimicrobial resistance, there were exceptions. The increasing

percentage of ciprofloxacin-resistant *E. coli* and imipenem-resistant *P. aeruginosa* among isolates from outpatients in one of our study hospitals (hospital A) suggests that some form of the selection effect on these isolates exists for the outpatients of this hospital. Discussions with the infection control department of hospital A revealed that most ciprofloxacin-resistant *E. coli* and imipenem-resistant *P. aeruginosa* isolated from outpatients came from the urinary tracts of patients who were residing in nursing homes and long-term rehabilitation facilities. The epidemiology of this emerging antimicrobial resistance phenomenon in isolates from outpatients of this hospital requires further elucidation.

This study had some limitations. First, we analyzed data from only eight hospitals. Therefore, our findings may not be representative for all hospitals in the United States. Phase II of Project ICARE, begun in early 1996, will encompass a study of resistance in a larger number of NNIS participants (~50 hospitals). Second, only isolates of *Enterococcus* species had their identities and susceptibilities to vancomycin confirmed independently at the CDC. More comprehensive confirmation studies of the identities and antimicrobial susceptibilities of organisms in the various antimicrobial/organism combinations will be conducted at the CDC for phase II.

Third, antimicrobial-prescribing practices may vary throughout the United States. It follows that the selection effect of a specific antimicrobial or resistance will probably vary from hospital to hospital. We are examining this issue by analyzing data from phase I in a separate study. Fourth, we combined data from the individual ICUs when a hospital had more than one of these units. Rates of nosocomial infections are dependent on the type of ICU and the rates of device use (a direct measure of invasive practices), which also vary widely [5]. It is likely that antimicrobial use and resistance also would vary in different types of ICUs. A larger study in which all data for ICU patients, non-ICU inpatients, and outpatients could be stratified by more specific medical categories, antimicrobial-prescribing practices, or other factors would help mitigate bias and permit more meaningful interhospital comparisons, an area of focused study for phase II of Project ICARE.

As the rate of antimicrobial resistance increases, more resources should be allocated to stem this problem within the ICU, including more surveillance activities, scrupulous and stricter infection control in hospitals, and improved use of antibiotics.

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