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Resistance of Gram-Negative Bacilli as Related to Hospital Use of Antimicrobial Agents

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The development of resistance of gram-negative bacilli, which are common nosocomial pathogens, is an increasing problem. It is generally accepted that this resistance may directly reflect the frequency of use of various antimicrobial agents. Because our institution experienced in 1976 a dramatic change in the pattern of antimicrobial use, primarily a marked decrease in prescribing cephalosporins, we attempted to evaluate retrospectively the effects of this change upon the resistance of gram-negative bacilli that are common nosocomial pathogens. Susceptibilities of *Klebsiella* and *Providencia* spp., *Pseudomonas aeruginosa*, and *Serratia marcescens* were determined for the years 1975 to 1979. Not unexpectedly, we observed a substantial decrease in cephalosporin resistance. An unexpected finding was a decrease in aminoglycoside resistance, despite increased use of these agents. The possibility that decreased cephalosporin use may lead to decreased aminoglycoside resistance is an intriguing and provocative thesis which can only be speculative at this time but which would seem worthy of additional formal investigation.

Most medical centers throughout the United States are experiencing a rise in antimicrobial resistance of gram-negative bacteria in both community-acquired and nosocomial infections (6, 16). Particularly problematic pathogens have been *Klebsiella* and *Providencia* spp., *Pseudomonas aeruginosa*, and *Serratia marcescens*. Many isolates have become resistant not only to gentamicin but also to the new aminoglycosides, such as tobramycin and amikacin (15, 17). This increase in resistance poses serious therapeutic problems for clinicians. Guidelines to monitor or control antimicrobial use have been established in many hospitals, with the hope of a resultant decrease in bacterial resistance as well as in hospital costs (4, 5, 20, 22).

It is clear that antimicrobial control programs can effect a decrease in the cost of hospital care, but the relationship of antimicrobial use to bacterial resistance remains to be fully defined (10, 11). It has been noted that wide or excessive use of some antimicrobial agents is correlated with increasing resistance to these agents (13, 18). However, it is not clear that appropriate use of an antimicrobial agent will necessarily lead to a decrease in reistance to the drug (3, 11, 21). Even less is known about the possible effects of decreased use of one class of agents upon the resistance to other, dissimilar drugs.

Because of a marked decrease in cephalosporin use which occurred in our institution in 1976 as a result of a control program, we attempted to assess its possible effects by reviewing the resistance of gram-negative bacilli isolated at our hospital during a 4-year period (1975 to 1979).

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MATERIALS AND METHODS

To investigate possible relationships between frequency of use of antimicrobial agents and bacterial resistance to these agents in a hospital setting we reviewed retrospectively the following data from 1975 to 1979.

(i) Demographic data obtained from medical records included average daily census, average length of hospital stay, and percent patient turnover rate. In addition, hospital records were reviewed to determine the numbers of physicians and students available for patient care during the 4-year period. Detailed records of numbers of nursing personnel were not available.

(ii) To determine the frequency of use of antimicrobial agents, we reviewed in-patient pharmacy records containing notations of every prescription for an antimicrobial agent and tabulated the numbers of patient courses for all cephalosporins (cefazolin, cephalexin, cephalothin, cephapirin, cephradine, and cefaman-

dole) and cephamycins (cefoxitin), all aminoglycosides (amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin), all penicillins (ampicillin, carbenicillin, penicillin G, ticarcillin, and semisynthetic penicillins), chloramphenicol, clindamycin, and erythromycin.

A patient course was defined as continuous therapy with any combination of agents of the same class, such as the cephalosporins and cephamycins or the aminoglycosides (excluding neomycin and streptomycin), prescribed for one patient regardless of route of administration, duration of therapy, or reason for administration (thus including prophylaxis). Therapy was considered to be continuous if the length of time between successive prescriptions was less than 2 weeks. Pharmacy policy is to require that antimicrobial agent prescriptions be renewed every 7 days.

(iii) Records of the microbiology laboratory were reviewed to determine the quarterly susceptibility to various antimicrobial agents of all organisms identified by standard criteria as *Klebsiella* or *Providencia* spp., *P. aeruginosa*, or *S. marcescens*. Susceptibility testing of isolates was performed by the disk diffusion method (2). Recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) were followed throughout the study period. Although media were obtained from two different companies, zone diameters of inhibition conformed to the standard proposed by the NCCLS. Quality control procedures and quality control zone size standards proposed by the NCCLS were used throughout the study period. Since no frozen isolates from 1975 to 1976 were saved, these organisms were not available for simultaneous testing with isolates from 1978 to 1979 by disk or minimal inhibitory concentration methods. The total number of strains of each isolate recovered by the laboratory during each quarter and the percentage of these isolates resistant to each antimicrobial agent were determined. There was no correction to exclude multiple measurements of the same strain isolated on separate occasions from the same patient, because the original records were not available.

(iv) During the study period, the following types of antibiotic control programs were in effect (12).

In the no-control program, each individual physician prescribed according to his or her own discretion. During this time, approximately 45% of cephalosporin use was for surgical prophylaxis for "clean" surgical procedures and occasionally in combination with clindamycin and an aminoglycoside for "dirty" surgical procedures (July 1975 to June 1976).

In the strict-control program, all controlled antimicrobial agents (all cephalosporins and cephamycins, as well as three aminoglycosides, amikacin, netilmicin, and tobramycin) required the approval of physicians of infectious diseases and a specialist in clinical pharmacy antimicrobial agents. During this period, approximately 10% of cephalosporin use was for surgical prophylaxis. This decrease in use of cephalosporins for prophylaxis was accompanied by increased use of penicillins for head and neck surgery, penicillin and oxacillin for orthopedic and thoracic surgery, and ampicillin and gentamicin for urological surgery. Prophylaxis for intraabdominal surgery was clindamycin plus an aminoglycoside, as in the period before strict control, but cephalosporins were added to this regimen less frequently (July 1976 to June 1977).

In the limited-control program, controlled antimicrobial agents required approval of infectious diseases physicians and a specialist in clinical pharmacy antimicrobial agents or a section chief but could not be prescribed by primary physicians alone. During this time, approximately 45% of cephalosporin use was for surgical prophylaxis (July 1977 to June 1979).

The use of oral neomycin for preoperative bowel preparation and for therapy of hepatic encephalopathy remained relatively constant throughout the entire 4 years.

(v) Calculation of correlation coefficients (r) comparing resistance to antimicrobial agents of gram-negative bacilli to use of the agents was performed with a programmable calculator (TI 59; Texas Instruments, Inc., Dallas, Tex.) by methods established by the Applied Statistics Library of Texas Instruments (1). For these calculations, a 6-month lag and a 1-year lag for bacterial resistance were selected arbitrarily in an attempt to provide a reasonable interval between changes in use of antimicrobial agents and possible effects upon resistance.

RESULTS

Demographic data were similar throughout the study period (Table 1). Numbers of physicians and students did not change significantly. As noted previously, specific details about numbers of nursing personnel could not be obtained. One factor not shown is that many patients were transferred to a newly constructed hospital facility in March 1977. However, in addition to patients, hospital personnel and hospital equipment were also transferred to the new facility. The hospital has 832 beds, of which 481 are medical, 260 are surgical, and 91 are for other specialty services. Data on use of cephalosporins and aminoglycosides are summarized in Table 2. Amikacin was used throughout the 4-year period under study but was available only as an investigational drug in the first 2 years. As indicated, a marked decrease in cephalosporin use (74.8%) occurred in the academic year 1976 to 1977 with the advent of strict control of antimicrobial prescribing. Use of aminoglycosides also decreased, but the change was of a much smaller magnitude (5.2% decrease for all aminoglycosides). The numbers of patient courses of specific aminoglycosides are indicated in Table 2. Gentamicin was by far the most frequently used aminoglycoside and constituted

TABLE 1. Annual demographic data

Academic yr (July–June)	No. of in-patients treated	Avg daily census	Turnover rate (days)	Avg hospital stay (days)
1975–1976	20,877	625	6.0	16.0
1976–1977	21,355	594	6.6	16.5
1977–1978	22,419	601	7.0	14.4
1978–1979	22,043	562	7.0	13.4

TABLE 2. Annual use of cephalosporins and aminoglycosides from 1975 to 1979

Academic yr (July–June)	Type of antimicrobial agent control	No. of patient courses of:			
		Cephalosporins	Aminoglycosides		
			Gentamicin	Tobramycin	Amikacin
1975–1976	None	1,502	990	7	23
1976–1977	Strict	379	932	2	32
1977–1978	Limited	601	1,071	4	160
1978–1979	Limited	533	1,313	4	189

approximately 85 to 95% of total aminoglycoside use throughout the study period. Changes in use of other classes of anitmicrobial agents occurred in conjunction with the marked decrease in cephalosporin use. Frequency of use of ampicillin, carbenicillin, and ticarcillin did not increase appreciably from 1976 to 1977, but use of penicillin G increased by approximately 150%, and use of semisynthetic penicillins increased by approximately 200% during this time. There was a marked increase in the use of erythromycin, a result of the increasing recognition of Legionnaires disease in the institution. A gradual small increase in the use of clindamycin occurred throughout the entire 4-year period, and a similarly gradual decrease in courses of chloramphenicol was observed. Frequencies of aminoglycoside resistance of selected gram-negative bacilli (*Klebsiella* and *Providencia* spp., *P. aeruginosa*, and *S. marcescens*) are shown in Table 3. Resistance to cephalothin is included only for *Klebsiella* sp. because, as would be expected, cephalothin resistance of the other genera remained extremely high and did not change appreciably throughout the study period. Resistance to cefoxitin and cefamandole was not examined because these agents became available for use only in the last months of the study. The numbers of isolates of gram-negative bacilli remained relatively constant throughout the 4 years, although obviously there were more fluctuations in the numbers of the less common organisms.

An obviously striking and not surprising finding is the substantial decrease in resistance of *Klebsiella* sp. to cephalothin (approximately 46%), which occurred in the year after decreased cephalosporin use. Correlation coefficients relating numbers of courses of cephalosporins to resistance of *Klebsiella* sp. to cephalothin were greater than 0.7 when either a 6-month or a 1-year lag was used, suggesting a highly likely correlation between the decreased use of cephalosporins and the decreased resistance to these agents.

An unexpected observation is that there was also a decline in resistance to some of the aminoglycosides from 1977 to 1978, the year after strict control of antimicrobial agents. Resistance to gentamicin decreased by 55.8% for *Klebsiella* sp., 63.0% for *Providencia* sp., and 21.3% for *S. marcescens*. Gentamicin resistance of *P. aeruginosa*, unlike that of the other organisms, rose during this time, increasing by approximately 15%. Tobramycin resistance also notably decreased for all species studied and ranged from 34.9% for *S. marcescens* to 78% for *Klebsiella* sp. Susceptibility testing with amikacin was not performed routinely until 1977 to 1978, and so changes in resistance could not be assessed for this agent. Therefore, data about resistance to this drug are given only for the last 2 years. Correlation coefficients obtained to relate gentamicin resistance with the use of this agent did not indicate any correlation. Correlation coefficients relating amikacin use to amikacin resistance could not be computed because of the lack of resistance data for the first 2 years. However, it was possible to examine the correlation between amikacin use and gentamicin resistance. A highly significant negative correlation was obtained for two genera, *Providencia* sp. ($r = -0.940$) and *Serratia* sp. ($r = -0.850$) when amikacin use was related to gentamicin resistance with no time lag. When a 1-year time lag was used, only *Serratia* sp. resistance to gentamicin appeared to correlate inversely with amikacin use ($r5 = 0.983$). Because tobramycin use accounted for such a small percentage of total aminoglycoside use (less than 1% in all years), it is unlikely that changes in use of this agent could be responsible for changes in gentamicin resistance. Thus, correlation coefficients relating tobramycin use to the various resistance patterns were not compared.

Although no highly significant correlation coefficients were obtained when a 6-month lag was used, there were some apparently significant correlations between cephalosporin use and aminoglycoside resistance for some of the organisms studied when a 1-year lag was used. Correlation coefficients relating cephalosporin use with gentamicin resistance of *Klebsiella* and *Providencia* spp. were only 0.6 and 0.2, respectively, when a 6-month lag was used, but were both greater than 0.7 when a 1-year lag was used. Correlation coefficients relating cephalosporin use with gentamicin resistance of *S. marcescens* were not as significant (0.4 with a 6-month lag and 0.5 with a 1-year lag).

DISCUSSION

It is generally accepted that bacterial resistance to antimicrobial agents parallels the frequency of use of the agents. The extensive use of gentamicin since its release for clinical use in

TABLE 3. Resistance of selected gram-negative bacilli to cephalosporins and aminoglycosides

Academic yr (July–June)	*Klebsiella* sp.					*Providencia* sp.			
	No. of isolates tested	% Resistant				No. of isolates tested	% Resistant		
		Cephalothin	Gentamicin	Tobramycin	Amikacin		Gentamicin	Tobramycin	Amikacin
1975–1976	1,019	25.2	14.6	33.0	NA[a]	173	63.6	47.6	NA
1976–1977	1,006	26.2	19.9	76.4	NA	125	74.4	80.0	NA
1977–1978	1,181	14.1	8.8	16.8	1.8	299	27.5	41.0	1.3
1978–1979	1,092	13.4	9.7	15.9	2.0	224	33.9	32.8	2.0

[a] NA, Not available; susceptibility testing not done routinely for this agent at this time.

the late 1960s and early 1970s has been considered to be the cause of the emergence of significant numbers of gentamicin-resistant organisms in many locations (7–9). Most institutions report an increase in resistance of many nosocomial pathogens, such as members of the family *Enterobacteriaceae* and *P. aeruginosa*, as well as an increase in frequency of use of cephalosporins and aminoglycosides.

Gentamicin was first used in 1969 at the University of Virginia Hospital, Charlottesville. In 1971, only 0.8% of more than 900 bacterial isolates were resistant to gentamicin, but by 1975, 7.7% were resistant (9). A similar pattern of increasing gentamicin resistance was noted at the Massachusetts General Hospital, Boston, where in 1974 20% of nosocomial bacteremias were due to gentamicin-resistant, gram negative bacilli (primarily *Klebsiella* sp. but also *P. aeruginosa* and *Enterobacter* and *Serratia* sp. (9). Gentamicin was released for clinical use at this hospital in March 1971.

Prescribing policies for antimicrobial agents may be introduced in hospitals when increasing resistance of pathogenic bacteria limits the clinical effectiveness of these agents. The basic concern is that the more an agent is used, the greater is the likelihood of bacterial resistance to it. In addition, there is the possibility that if the use of an antimicrobial agent is withdrawn or limited, there might be a resultant reduced resistance.

There is evidence from a number of studies that bacterial resistance to a given antimicrobial agent may indeed decrease if there is restriction or discontinuation of the use of the drug. In a neurosurgical intensive-care ward in Glasgow, Scotland, attempts to control an epidemic of *Klebsiella* sp. infection by isolation of infected cases and treatment with appropriate antimicrobial agents failed. It was only by the withdrawal of all of these agents, both therapeutic and prophylactic, that the incidence of *Klebsiella* sp. infection finally decreased (19). The relationship between bacterial resistance and consumption of antimicrobial agents was studied in a urological ward in Denmark over a 9-year period. It was noted that a decreasing incidence of resistance among gram-negative bacteria paralleled a decreasing use of antimicrobial agents. In addition, infections due to the more resistant organisms, such as *Enterobacter, Klebsiella, Proteus*, and *Providencia* spp. and *P. aeruginosa*, became less common during the study period (21). A survey of antibiotic resistance among isolates of *Escherichia coli* and *Klebsiella* and *Enterobacter* spp. showed a trend of decreasing resistance over a 10-year period at the University of Washington Hospital, Seattle, which was attributed partially to conservative and selective use of antibiotics and in part to the institution of a hospital infection control program (3).

In our hospital, a dramatic decrease in cephalosporin use occurred as a result of a control program. In an attempt to detect the possible effects of this decrease, we reviewed the resistance patterns of selected members of the family *Enterobacteriaceae* and *P. aeruginosa* isolates. We found a marked decrease in cephalothin resistance of *Klebsiella* sp., as would be expected. An unexpected finding was a decrease in gentamicin resistance of several genera of *Enterobacteriaceae* (*Klebsiella* sp., 33.6%; *Providencia* sp., 46.7%; and *Serratia* sp., 84.8%) and a decrease in resistance to tobramycin for all the organisms studied (*Klebsiella* sp., 78.0%; *Providencia* sp., 48.8%; *P. aeruginosa*, 49.5%; and *S. marcescens*, 34.9%). The discovery that some of these decreases in aminoglycoside resistance seemed to correlate well with decreased cephalosporin use led us to consider the intriguing possibility that decreased cephalosporin use might be associated with decreased resistance not only to cephalosporins but also to aminoglycosides.

For many reasons, the possibility of a relationship between decreased cephalosporin use and decreased aminoglycoside resistance of gram-negative bacilli can be only speculative. Our study consists of uncontrolled, retrospective observations, and consequently many other possible causes of decreased aminoglycoside resistance must be considered carefully. The observed changes in susceptibilities appear to be

TABLE 3—*Continued*

P. aeruginosa				*S. marcescens*			
No. of isolates tested	% Resistant			No. of isolates tested	% Resistant		
	Gentamicin	Tobramycin	Amikacin		Gentamicin	Tobramycin	Amikacin
1,091	13.2	14.8	NA	217	35.5	50.0	NA
898	15.6	41.2	NA	236	34.8	81.6	NA
1,143	18.0	20.8	11.5	285	27.4	53.1	3.1
1,073	21.4	21.0	14.4	224	5.4	31.5	3.9

reliable, because susceptibility testing was standardized and had proper quality control throughout the study period. However, because this was a retrospective study for which isolates were not saved, it was not possible to perform simultaneous testing with representative organisms at the end of the study to confirm that changes in test results were not a function of changes in methodology. Similarly, because isolates were not saved, it was not possible to investigate mechanisms of resistance.

Another difficulty inherent in our retrospective evaluation of bacterial susceptibility is the failure to exclude the influence of multiple isolates obtained on separate occasions from the same patient. Original records which would have permitted correction for this had been discarded. However, there was no known outbreak involving unusually resistant organisms, and it would seem unlikely that such marked changes in susceptibilities would be entirely due to multiple measurements of isolates from the same patient. The most obvious possible cause for change in aminoglycoside resistance is, obviously, change in aminoglycoside use. We cannot exclude the possibility that this was indeed the case in our institution, but there is reason to consider that this simple relationship may not be adequate to explain our observations. We could find no statistical correlation between gentamicin use and resistance to this agent. The one possibly significant change in aminoglycoside use was the increase in the use of amikacin. It would seem reasonable that, if amikacin replaced gentamicin to a substantial degree, this might result in decreased gentamicin resistance. Highly significant negative correlation coefficients were in fact obtained when amikacin use was related with gentamicin resistance for some organisms. However, the actual numbers of courses of amikacin were so small that it is difficult to believe that this change accounted for the dramatic changes in resistance which were observed.

An additional concern is the appropriate length of time at which to evaluate institutional bacterial susceptibility patterns in relation to the frequency of use of antimicrobial agents in the institution. We assumed that there should be some delay between change in antimicrobial use and observable effect upon susceptibility and arbitrarily selected 6 months and 1 year as lag periods before attempting to examine statistical correlations. It is of note that the apparently significant correlation between decreased cephalosporin use and decreased aminoglycoside resistance was demonstrated only when a 1-year lag was used. It may indeed be that this is an appropriate interval at which to observe such a correlation, but there is the concern that some unrecognized factor may have intervened in this period.

One obvious question is whether, instead of a direct correlation between decreased cephalosporin use and decreased aminoglycoside resistance, there might be some other concomitant-related or unrelated change in antimicrobial use responsible for the change in aminoglycoside resistance. There was, indeed, marked increase in the use of narrow-spectrum penicillins, largely as a direct result of change in cephalosporin use. In addition, erythromycin use increased because of the awareness of Legionnaires disease. However, as these agents are even less active than cephalosporins against the gram-negative bacilli in question, it seems unlikely that their use would affect resistance of these organisms. Even if this were the case, the premise that change in use of one class of agents might influence resistance to dissimilar agents would still be supported.

It is unfortunate that the transfer of many patients occurred after the time of dramatic change in cephalosporin use, because we cannot assess how this patient relocation may have affected bacterial resistance as an independent factor. Evidence against this possibility is provided by a study by Maki and colleagues (14). They reported significant changes in the presence of environmental bacteria in a newly completed hospital before and after it was opened for use, but found that the incidence of nosocomial infections in patients remained unchanged. They concluded that microorganisms in the inanimate hospital environment contribute negligibly to endemic nosocomial infections (14). Other fac-

tors of our demographic data, such as average daily census, percent turnover rate, and numbers of physicians and students, remained fairly constant. Average hospital stay did decrease somewhat over the 4 years, but the relationship of this change to changes in bacterial resistance is difficult to assess. Although specific numbers of nursing personnel could not be calculated, it is likely that hospital personnel and equipment were virtually unchanged.

Thus, despite our inability to exclude all other factors, our finding that decreased gentamicin resistance followed the decreased frequency of cephalosporin use leads us to the speculation that altered selective pressures on these microorganisms resulting from changes in use of one class of antimicrobial agents may have subsequently led to their increased susceptibility to another class of drugs. This intriguing possibility would seem to be worthy of additional formal investigation.

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