ORIGINAL ARTICLE

Trends in Aminoglycoside Use and Gentamicin-Resistant Gram-Negative Clinical Isolates in US Academic Medical Centers: Implications for Antimicrobial Stewardship

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OBJECTIVE. To measure trends in aminoglycoside antibiotic use and gentamicin-resistant clinical isolates across a network of hospitals and compare network-level relationships with those of individual hospitals.

DESIGN. Longitudinal observational investigation.

SETTING. US academic medical centers.

PARTICIPANTS. Adult inpatients.

METHODS. Adult aminoglycoside use was measured from 2002 or 2003 through 2009 in 29 hospitals. Hospital-wide antibiograms assessed gentamicin resistance by proportions and incidence rates for *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli*. Mixed-effects analysis of variance was used to assess the significance of changes in aminoglycoside use and changes in resistance rates and proportions. Generalized estimating equations were used to assess the relationship between aminoglycoside use and resistance.

RESULTS. Mean aminoglycoside use declined by 41%, reflecting reduced gentamicin ($P < .0001$) and tobramycin ($P = .005$) use; amikacin use did not change. The rate and proportion of gentamicin-resistant *P. aeruginosa* decreased by 48% ($P < .0001$) and 31% ($P < .0001$), respectively. The rate and proportion of gentamicin-resistant *E. coli* increased by 166% and 124%, respectively ($P < .0001$), and they were related to increasing quinolone resistance in *E. coli*. Resistance among *K. pneumoniae* and *A. baumannii* did not change. Relationships between aminoglycoside use and resistance at the network level were highly variable at the individual hospital level.

CONCLUSIONS. Mean aminoglycoside use declined in this network of US hospitals and was associated with significant and opposite changes in rates of resistance for some organisms and no change for others. At the individual hospital level, antibiograms appear to be an unreliable reflection of antibiotic use, at least for aminoglycosides.

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Professional organizations have called attention to the growing problem of antibiotic-resistant gram-negative bacteria and the paucity of new antimicrobial drugs.[1] Three recent reviews reported that aminoglycoside use is increasing because of emerging gram-negative resistance to other available drugs, although supporting citations were not provided.[2-4] In contrast, we reported that mean aminoglycoside use between 2002 and 2006 decreased by 29% ($P < .001$) in a consortium of 22 US university teaching hospitals.[5] In addition, current data on the susceptibility of gram-negative isolates to aminoglycosides are limited and contradictory. A 2009 position paper from the Infectious Diseases Society of America (IDSA) states that "aminoglycoside resistance [among *Pseudomonas aeruginosa*] is emerging as a significant problem,"[1(p7)] but the most recent supporting reference was the 2004 National Nosocomial Infections Surveillance System, which did not report aminoglycoside susceptibility.[6] In contrast, a 2009 report from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) of 10-year surveillance trends in 10–15 US hospitals found that susceptibility to gentamicin and tobramycin for *P. aeruginosa* remained unchanged.[7] A 2008 report from the National Healthcare Safety Network reported only amikacin susceptibility among isolates of *P. aeruginosa* for 2006–2007.[8]

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Single-center investigations reported 20–30 years ago that declining aminoglycoside use is associated with improvements in aminoglycoside susceptibility.[9-11] If aminoglycoside antibiotics are currently used substantially less than in years past, we hypothesized that aminoglycoside susceptibility among gram-negative isolates may be improving. The purpose of this study was 3-fold: (1) to determine current trends in aminoglycoside use in a network of academic medical center hospitals, (2) to measure trends in aminoglycoside resistance for major nosocomial gram-negative pathogens by means of annual hospital antibiograms, and (3) to examine the relationships between mean aminoglycoside use and susceptibility at the network level versus the level of individual hospitals.

METHODS

Data Source

The University HealthSystem Consortium (UHC; http://www.uhc.edu) is an alliance of 115 academic medical center hospitals and more than 250 affiliated hospitals. A subset subscribe to the Clinical Resource Manager (CRM) database that extracts medication use from charge transaction masters and inpatient billing files. Twenty-nine CRM-subscribing hospitals that provided information on antibacterial drug use beginning in year 2002 or 2003 and through 2009 are the source of the data described in this investigation. We have described details of this database, its validation, and its assessment of hospital antibiotic use elsewhere.[5]

Antibiotic Use

Hospitals begin their participation in UHC at different times. The first year that drug use became available for a large number of hospitals was 2002 ($n = 23$), and an additional 6 hospitals began participation in 2003. Information on systemic aminoglycoside use in adult inpatients discharged between January 1, 2002 or 2003, through December 31, 2009, was obtained from patient-level billing records. These data were aggregated and reported annually for each hospital as days of therapy (DOTs) per 1,000 patient-days (PDs), as described elsewhere.[5] Any dose of antibiotic received by a patient during a 24-hour period (ending at midnight) is counted as 1 DOT. For example, administration of gentamicin every 8 hours for 3 doses or administration of the entire daily dose every 24 hours would be counted as 1 DOT. We have reported advantages of measuring antibiotic use by means of DOTs versus the metric usually recommended, the defined daily dose.[12] Changes in aminoglycoside use over time were defined as having increased over time (more than 10% increase comparing the baseline year to year 2009), decreased over time (more than 10% decrease comparing baseline to 2009), or not changed (2009 aminoglycoside use was within 10% of baseline).

Antimicrobial Susceptibility

We requested annual cumulative hospital antibiograms from the 29 hospitals for the years for which we had aminoglycoside use. We requested antibiograms that contained a full calendar year of susceptibility reported from all clinical isolates, at least 30 isolates for each organism, the number of isolates, and the proportion of resistant isolates. All hospitals received an online survey requesting information regarding susceptibility testing methods and antibiogram construction, including the inclusion or exclusion of duplicate clinical isolates, methods of susceptibility testing, policy regarding surveillance cultures, and whether Clinical and Laboratory Standards Institute (CLSI) interpretative breakpoints were used for all years. CLSI-recommended breakpoints for gentamicin and tobramycin are 4 μg/mL; the breakpoint for amikacin is 16 μg/mL.[2]

As recommended by Schwaber et al,[13] we recorded both proportions and rates of resistance for the following organisms: *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. The resistant "proportion" was the number of resistant isolates divided by the total number of isolates tested, and the resistant incidence "rate" was the number of resistant isolates per 1,000 adult patient discharges and per 1,000 adult PDs. The number of adult discharges and adult PDs were obtained from the UHC database.

Multidrug resistance among the targeted organisms is increasingly common.[14-17] We observed that gentamicin resistance among *E. coli* was increasing in most hospitals despite declining aminoglycoside use (see below). Consequently, we determined the proportions and rates of fluoroquinolone-resistant *E. coli* reported for ciprofloxacin or levofloxacin to assess the relationship to gentamicin resistance in *E. coli*.

Statistical Analysis

Mixed-effects analysis of variance (ANOVA) was used to assess the statistical significance of changes in aminoglycoside use and changes in resistance over the study years.[18] Relationships between aminoglycoside use and gentamicin-resistant organisms were assessed using generalized estimating equations (GEEs). GEEs account for nonnormal data distributions and for autocorrelation among observations from the same hospital over time. GEE analysis assesses drug use and resistance within and across hospitals to arrive at a population-averaged estimate of the relationship between aminoglycoside use and gentamicin-resistant *P. aeruginosa*. GEEs were also used to assess whether changes in gentamicin susceptibility among *E. coli* were related to changes in fluoroquinolone susceptibility among *E. coli*. The quasi-likelihood under the independence model criterion, an extension of the Akaike Information Criterion to the GEE method, was used to determine the best distribution and link functions, as well as working correlation structure.[19,20] A P value less than .05 was considered significant. Statistical software for the mixed-effects ANOVA was JMP, ver-

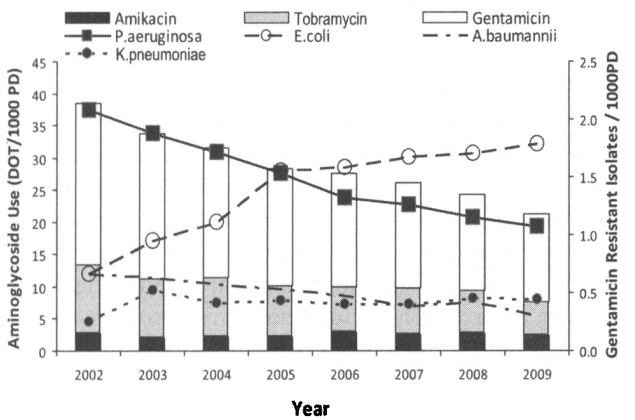

FIGURE 1. Changes in mean aminoglycoside use (days of therapy [DOTs] per 1,000 patient-days [PDs]) and associated changes in mean rates of gentamicin-resistant clinical isolates (isolates per 1,000 PDs). Total aminoglycoside use declined 41% over the period of study, caused by significant declines in use of gentamicin and tobramycin. The mean rates of gentamicin-resistant *Pseudomonas aeruginosa* declined ($P < .001$), the mean rates of gentamicin-resistant *Escherichia coli* increased ($P < .001$), and the mean rates of gentamicin-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* did not significantly change.

sion 8.0 (SAS Institute). The GEE analysis was conducted using Stata/SE, version 10.1 (StataCorp).

RESULTS

Hospitals

In year 2008, the mean bed size for the 29 hospitals providing data on aminoglycoside use was 534 (range, 333–905), the mean number of adult discharges was 24,793 (range, 13,404–44,448), and the case mix index for all adult patients was 1.63 (range, 1.22–1.85). The geographic distribution was Mid-Atlantic (9), Midcontinent (7), Midwestern (5), New England (2), Southeastern (4), and Western (2) states.

Aminoglycoside Use

The mean (± standard deviation) of total aminoglycoside use (the sum of gentamicin, tobramycin, and amikacin) decreased 41% over the period of this investigation, from 37.5 (±9.4) DOTs per 1,000 PDs in 2002 to 22.2 (±10.2) DOTs per 1,000 PDs in 2009 ($P < .0001$; Figure 1). Use decreased more than 10% in 24 hospitals; there was no appreciable change in 3 hospitals, and use increased by more than 10% in 2 hospitals (+13% in one hospital and +122% in another). Over all hospital-years, gentamicin comprised 63% of aminoglycoside use, tobramycin comprised 28%, and amikacin comprised 9%. Gentamicin use decreased by a mean of 45%, from 24.5 (±9.6) DOTs per 1,000 PDs in 2002 to 13.6 (±7.2) DOTs per 1,000 PDs in 2009 ($P < .0001$). Tobramycin use decreased by 38%, from 10.9 (±10.0) DOTs per 1,000 PDs in 2002 to 6.1 (±6.0) DOTs per 1,000 PDs in 2009 ($P = .005$). Amikacin use did not significantly change.

Testing of Susceptibility to Aminoglycoside Antibiotics

We obtained antibiograms from 28 of the 29 hospitals. Of 224 possible hospital-years, 202 antibiograms were used in the analysis (90%). We obtained 8 years of antibiograms from 16 hospitals, 7 years of data from 7 hospitals, 6 years of data from 2 hospitals, 5 years of data from 1 hospital, and 4 years of data from 2 hospitals. Twenty-six hospitals returned the survey on antibiogram construction. Twenty-two did not include duplicate isolates, 3 included some duplicates (depending on the time elapsed between culture results), and 1 included all duplicates. We included all hospitals in the analysis below, whether or not they included duplicate isolates. We excluded from analysis 1 hospital's data for *A. baummanii* because there were fewer than 30 isolates. All hospitals reported susceptibility to gentamicin; 8 hospitals also reported susceptibility to tobramycin and amikacin. All hospitals reported using CLSI breakpoints. Multiple methods were employed in year 2009 for routine susceptibility testing, including MicroScan ($n = 6$), Vitek ($n = 3$), Vitek 2 ($n = 3$), disk diffusion ($n = 5$), Phoenix ($n = 7$), and other ($n = 1$). Testing methods were often reported to have changed over time. Twenty-two hospitals reported that surveillance cultures were excluded; 4 hospitals included surveillance cultures.

The mean incidence rate for gentamicin-resistant *P. aeruginosa* (per 1,000 PDs) decreased by 49%, from 2.1 in year 2002 to 1.1 in 2009 ($P < .0001$; Table 1 and Figure 1), and the proportion of gentamicin-resistant *P. aeruginosa* decreased by 31%, from a mean of 29% in year 2002 to a mean of 20% in year 2009 ($P < .0001$). (The statistical assessment of resistance rates expressed per 1,000 discharges and per 1,000 PDs produced similar results [Table 1]; we report in the text only rates per 1,000 PDs, for clarity.) In contrast, both the incidence rates and the proportions of gentamicin-resistant *E. coli* increased over the study period, by 166% and 120%, respectively ($P < .0001$; Table 1 and Figure 1). Over the same period, the mean incidence rate of fluoroquinolone-resistant *E. coli* (per 1,000 PDs) increased from 1.2 in year 2002 to 4.2 in year 2009 ($P < .0001$), and the proportion of fluoroquinolone-resistant isolates increased from 8.7% in year 2002 to 26.7% in year 2009 ($P < .0001$). By GEE analysis, the change in the rate of gentamicin-resistant *E. coli* was statistically linked to the change in the rate of fluoroquinolone-resistant *E. coli* ($P < .001$).

There was no significant change in either the mean proportions or the rates of gentamicin-resistant *A. baumannii* and *K. pneumoniae* (Table 1 and Figure 1).

Relationship between Aminoglycoside Use and Gentamicin-Resistant *P. aeruginosa*

By GEE analysis, there was no significant relationship between total aminoglycoside use over time and either the rate or the proportion of resistant *P. aeruginosa*.

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TABLE 1. Changes in Gentamicin Susceptibility among Targeted Gram-Negative Clinical Isolates

Organism, resistance measure	2002	2003	2004	2005	2006	2007	2008	2009	*P*
Pseudomonas aeruginosa									
Proportion (%)	29 (12)	28 (12)	28 (11)	25 (9)	25 (8)	25 (8)	21 (8)	20 (7)	<.0001
Rate per 1,000 patient-days	2.1 (1.1)	1.8 (1.1)	1.7 (1.3)	1.5 (0.9)	1.3 (0.7)	1.3 (0.8)	1.2 (0.9)	1.1 (.06)	<.0001
Rate per 1,000 discharges	11.9 (6.9)	10.8 (7.0)	9.8 (7.8)	8.5 (5.4)	7.4 (4.2)	7.1 (4.5)	6.5 (4.8)	8.5 (4.0)	<.0001
Escherichia coli									
Proportion (%)	5 (2)	6 (4)	7 (4)	9 (4)	10 (4)	11 (4)	10 (3)	11 (3)	<.0001
Rate per 1,000 patient-days	0.7 (0.5)	0.9 (0.7)	1.1 (0.8)	1.6 (1.2)	1.6 (0.9)	1.7 (0.9)	1.7 (1.0)	1.8 (0.8)	<.0001
Rate per 1,000 discharges	4.2 (2.7)	5.7 (4.2)	6.4 (4.8)	8.6 (6.3)	8.8 (5.5)	9.3 (5.1)	9.4 (5.5)	9.7 (4.4)	<.0001
Klebsiella pneumoniae									
Proportion (%)	5 (4)	8 (7)	8 (9)	8 (7)	8 (7)	7 (6)	7 (6)	7 (6)	.0882
Rate per 1,000 patient-days	0.3 (0.4)	.05 (1.0)	0.4 (0.6)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.3)	0.4 (0.5)	.3953
Rate per 1,000 discharges	1.4 (1.9)	3.0 (5.9)	2.3 (3.3)	2.5 (2.4)	2.3 (2.7)	2.3 (2.7)	2.1 (2.3)	2.5 (2.7)	.3910
Acinetobacter baumannii									
Proportion (%)	32 (21)	37 (21)	37 (21)	37 (22)	39 (21)	41 (18)	37 (20)	39 (23)	.5173
Rate per 1,000 patient-days	0.7 (1.1)	0.6 (1.0)	0.6 (1.1)	0.5 (0.8)	0.5 (1.1)	0.4 (0.4)	0.4 (0.5)	0.3 (0.4)	.1320
Rate per 1,000 discharges	4.0 (6.9)	3.8 (6.3)	3.4 (7.1)	3.1 (5.2)	2.7 (3.3)	2.2 (2.1)	2.4 (2.8)	1.7 (2.2)	.4174

NOTE. Data are mean (standard deviation), unless otherwise indicated. Three measures of susceptibility are reported: the resistant proportions (% resistant) and 2 measures of the resistant incidence rates (no. of resistant isolates per 1,000 patient-days and per 1,000 discharges).

Contrast of Individual Hospital-Level Observations to the Network-Level Observation

Figure 2 illustrates changes in aminoglycoside use and resistance rates for 4 hospitals. Two hospitals (Figure 2*A* and 2*B*) observed substantial reductions in aminoglycoside use, 1 hospital had a substantial increase (Figure 2*C*), and 1 hospital (Figure 2*D*) did not appreciably change. At the level of the individual hospital, changes in aminoglycoside use were often not accompanied by changes in resistance rates for *P. aeruginosa* that would be predicted from the mean relationship (Figure 1). Furthermore, gentamicin resistance over time in *K. pneumoniae*, *A. baumannii*, and *E. coli* appeared to be unrelated to aminoglycoside use.

DISCUSSION

In 1994, McGowan[21] reviewed the available literature assessing whether antimicrobial control programs (now referred to as "stewardship" programs) had demonstrated a benefit in reducing bacterial resistance. He concluded, "Because these studies were performed in single institutions, their power to distinguish associations was poor. Cooperative multicenter studies are needed in which selection and classification biases are addressed prospectively, and in which confounding factors are controlled."[21(p478)] This reasoning supported early investigations by the CDC project ICARE (Intensive Care Antimicrobial Resistance Epidemiology), which attempted to link antibiotic use patterns in multiple intensive care units to rates of resistance for selected organisms.[22]

We believe that the present investigation, while not meeting all of McGowan's criteria, illustrates that this goal is closer to becoming reality. First, these data provide an assessment of current aminoglycoside use in a relatively large sample of US academic medical centers. In contrast to recent statements that aminoglycoside use is increasing in response to greater β-lactam and fluoroquinolone resistance,[2-4] aminoglycoside use in most hospitals is clearly decreasing; in only 2 hospitals did aminoglycoside use increase over the years of study.

Second, these observations are consistent with prior single-center investigations that reported that reductions in aminoglycoside use are accompanied by reductions in some resistant organisms, particularly *P. aeruginosa*.[9-11] The GEE analysis, however, did not find a statistically significant association between aminoglycoside use over time and change in resistant *P. aeruginosa*. This may reflect relatively low aminoglycoside use and low selective pressure at the beginning of the investigation that continued to remain low through 2009. Alternatively, there was substantial variability over the multiple years of analysis, increasing the likelihood that a true relationship between use and resistance, if one exists, would be missed by the GEE analysis. It is also possible that the decline in gentamicin resistance in *P. aeruginosa* is unrelated to aminoglycoside use and may reflect instead, for example, an increase in the use of carbapenems,[5] to which these organisms often remain susceptible.[7] While we believe that a network of hospitals is more likely to reflect true relationships than any single member of the network, it is also possible that the network analysis did not adequately address important predictors and confounders (see below). Currently there is no model that allows for simultaneous assessment of the use of multiple drug classes and other predictors and confounders on a particular resistance phenotype.[23]

Third, rising aminoglycoside resistance in *E. coli* concomitant with a decline in aminoglycoside use was unanticipated and found to be statistically linked to increasing fluoroquinolone resistance in *E. coli*. The rise in gentamicin-resistant *E. coli* during declining use is contrary to reports from 20–30

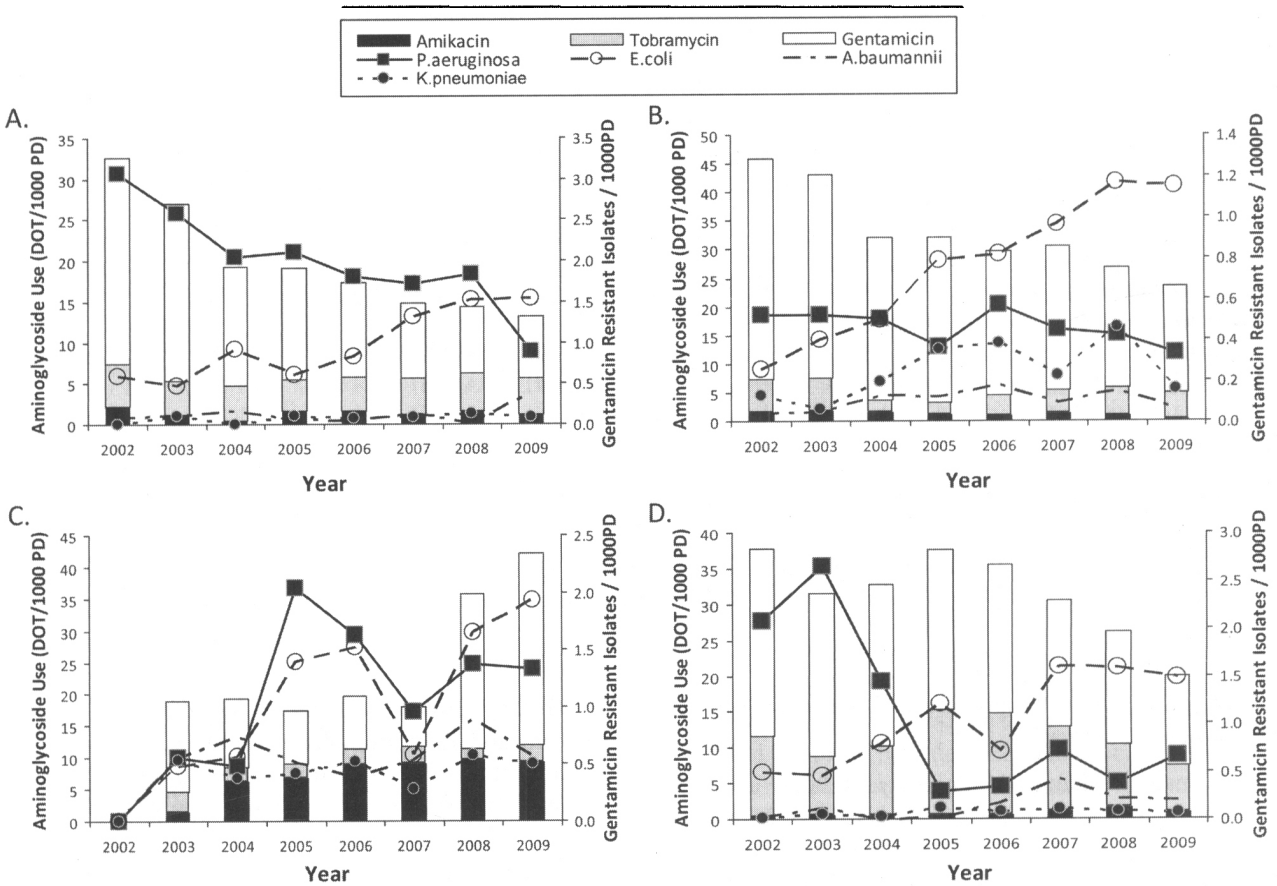

FIGURE 2. Hospital-level variability in the relationship between changes in aminoglycoside use (days of therapy [DOTs] per 1,000 patient-days [PDs]) and resistance rates (isolates per 1,000 PDs) in 4 hospitals. *A* and *B* illustrate declining aminoglycoside use in both hospitals and declining gentamicin resistance in *Pseudomonas aeruginosa* in one hospital (*A*) and no change in another (*B*). In *C*, gentamicin-resistant *P. aeruginosa* increased and then declined during 2002–2006, when aminoglycoside use was stable. Resistance did not substantially change during 2008–2009, when aminoglycoside use increased. In *D*, gentamicin resistance in *P. aeruginosa* declined substantially during a period of stable aminoglycoside use. In all 4 panels, gentamicin-resistance in *Escherichia coli* appeared to increase, and there appeared to be no substantial or sustained change in gentamicin susceptibility among *Acinetobacter baumannii* or *Klebsiella pneumoniae.*

years ago[9-11] and recent single-center investigations.[24] However, our observation is consistent with the MYSTIC report that found a large increase in aminoglycoside-resistant *E. coli* among hospital isolates between 1999 and 2008,[7] and this appears to be a worldwide phenomenon.[25] Recent investigations of multidrug-resistant *E. coli* provide a mechanistic link between fluoroquinolone resistance and aminoglycoside resistance.[15,26]

Finally, these observations would appear relevant to antimicrobial stewardship programs. A recent survey of the Society for Healthcare Epidemiology of America (SHEA) membership identified emerging resistance in gram-negative nosocomial pathogens and antimicrobial stewardship as the top 2 priorities for the SHEA research agenda.[27] Furthermore, the 2007 IDSA/SHEA guidelines for antimicrobial stewardship recommend that "programs must establish process and outcome measures to determine the impact of antimicrobial stewardship on antimicrobial use and resistance patterns."[28(p171)] However, the guidelines provide little advice regarding the specific methods that an antimicrobial stewardship program should use to assess these relationships. The most rigorous method to link stewardship interventions to bacterial resistance in a hospital is interrupted time-series analysis.[32] However, most hospitals are unable to obtain predictor variables and outcomes data in sufficiently small increments to allow interrupted time-series analysis to be routinely applied. Consequently, some investigations have attempted to link changes in aggregate susceptibility in unit-specific or whole-house annual antibiograms to assess changes in resistance following stewardship interventions,[10,11,30,33] although there are few critical assessments of its validity and limitations.[34-36] In contrast, a network of hospitals such as that described in this investigation may be able to link interventions and changes in antimicrobial drug use to changes in resistance using whole-house antibiograms because of greater statistical power and the potential to adjust

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for confounders, such as patient mix and methodological differences in antibiogram reporting methods. This interpretation is supported by findings from the MYSTIC surveillance project,[37] where significant positive relationships between mean drug use and antimicrobial resistance rates across all hospitals were observed for a number of "drug-bug" pairs, whereas no relationships were observed at individual institutions. In addition, a counterintuitive observation, such as a relationship between declining aminoglycoside use and increasing gentamicin resistance in *E. coli*, might well be dismissed by an individual hospital, even though this was a consistent observation across the network.

Large networks of hospitals in the United States are being organized to implement antimicrobial stewardship programs, including the Hospital Corporation of America Healthcare System (E. Septimus, personal communication, December 19, 2011), Cardinal Health Pharmacy Solutions (K. Kuper, personal communication, December 19, 2011), and the California Antimicrobial Stewardship Program Initiative in the Healthcare-Associated Infections Program at the California Department of Public Health (K. K. Trivedi, personal communication, December 19, 2011). The limited available data suggest that annual antibiograms from multihospital networks correlate well to more established surveillance programs.[36,38,39] Additional research is necessary to determine whether this approach is a valid strategy for monitoring emerging resistance and assessing the effect of antimicrobial stewardship interventions on microbiology outcomes. Although there is a natural tendency to interpret changes in an institution's antibiogram susceptibility as a reflection of the institution's antibiotic use, our data suggest that these complex relationships cannot be reliably assessed at the level of the individual hospital, at least for the aminoglycosides. Furthermore, aminoglycoside use is largely confined to hospitalized patients, and the relationships between aminoglycoside use and resistance in clinical isolates should be more straightforward than those for antibacterial drugs used in both the hospital and the community, such as fluoroquinolones.

This investigation describes a program to link longitudinal changes in multihospital antibacterial drug use and resistance, and there are a number of limitations and additional questions. First, there was variability between hospitals with respect to the method of measuring bacterial susceptibility, and we did not include adjustments in the analysis for some of them, including the reporting of duplicate isolates and changes in testing vendors. These concerns are less likely to be an issue in the future as hospitals adopt consistent methods to construct and report antibiograms.[40] Second, whether changes in aminoglycoside susceptibility are related to changes in aminoglycoside use is unclear, although this has been the interpretation of prior investigations.[9-11,17] Consequently, additional research will be required to identify whether residual "selection and classification biases" and "confounding factors," as described by McGowan[21] (above), will explain our observations. It is also possible that in some hospitals there were true relationships between antibiotic use and resistance, such as improvements in gentamicin susceptibility for *Acinetobacter* or *Klebsiella*, that were obscured by aggregation in the database. Third, we reported only gentamicin resistance, since all hospitals tested for susceptibility to gentamicin, but there are some differences in in vitro activity among the aminoglycosides that may have had an unmeasured impact on resistance rates.[2,41] Fourth, this investigation included only university-affiliated hospitals; community hospitals are not represented, and aminoglycoside use and rates of resistance may be different. Furthermore, not all academic medical center hospitals in this investigation are alike in important determinants of resistance, such as infection control efforts, patient mix, admissions from nursing homes and long-term care hospitals, and geographic distribution. We were unable to measure and did not include in our analysis all of these potential variables that may have impacted the microbiology outcomes. Finally, administrative claims data are subject to coding biases and other sources of error that may have influenced these results.[41]

In summary, we have described an observational investigation where aminoglycoside use naturally declined in a multihospital network and was associated with opposite changes in rates of resistance for some organisms and no changes in others. There are a variety of outcome measures that an antimicrobial stewardship program may wish to investigate as a result of an intervention, including financial benefits, clinical response, adverse events, drug interactions, and bacterial resistance. The later outcome may be the most difficult to convincingly link to changes in drug use, but from a clinical and society perspective it is one of the most important. We believe that emerging networks of hospitals are best equipped to address this issue, but many challenges remain. In the meantime, these data suggest that antimicrobial stewardship programs should remain skeptical of drawing conclusions regarding inpatient antibiotic use and changes in resistance as reflected by the hospital antibiogram.

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