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Journal

Antimicrobial Agents and Chemotherapy, 58(3)

ISSN

0066-4804

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Publication Date

2014-03-01

DOI

10.1128/aac.01908-13

Peer reviewed

AAC
Journals.ASM.org

Trends in Antibiotic Resistance in Coagulase-Negative Staphylococci in the United States, 1999 to 2012

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Coagulase-negative staphylococci (CoNS) are important bloodstream pathogens that are typically resistant to multiple antibiotics. Despite the concern about increasing resistance, there have been no recent studies describing the national prevalence of CoNS pathogens. We used national resistance data over a period of 13 years (1999 to 2012) from The Surveillance Network (TSN) to determine the prevalence of and assess the trends in resistance for *Staphylococcus epidermidis*, the most common CoNS pathogen, and all other CoNS pathogens. Over the course of the study period, *S. epidermidis* resistance to ciprofloxacin and clindamycin increased steadily from 58.3% to 68.4% and from 43.4% to 48.5%, respectively. Resistance to levofloxacin increased rapidly from 57.1% in 1999 to a high of 78.6% in 2005, followed by a decrease to 68.1% in 2012. Multidrug resistance for CoNS followed a similar pattern, and this rise and small decline in resistance were found to be strongly correlated with levofloxacin prescribing patterns. The resistance patterns were similar for the aggregate of CoNS pathogens. The results from our study demonstrate that the antibiotic resistance in CoNS pathogens has increased significantly over the past 13 years. These results are important, as CoNS can serve as sentinels for monitoring resistance, and they play a role as reservoirs of resistance genes that can be transmitted to other pathogens. The link between the levofloxacin prescription rate and resistance levels suggests a critical role for reducing the inappropriate use of fluoroquinolones and other broad-spectrum antibiotics in health care settings and in the community to help curb the reservoir of resistance in these colonizing pathogens.

Coagulase-negative staphylococci (CoNS) are normal flora of the human skin and mucosa. Because they have long been considered contaminants rather than true clinical pathogens, there are few systematic studies describing their epidemiology in human infections. Nonetheless, colonizing CoNS pathogens have been reported to be responsible for infections in humans, particularly in immunocompromised hosts (1–3) and neonates (4, 5). Seventy-three percent of all neonatal bacteremia in the United States is caused by CoNS pathogens (4, 5). In addition, CoNS are typically resistant to multiple drug classes (3). The clinical presentations for patients infected with CoNS are often distinct from those caused by *Staphylococcus aureus* infections, which occur more commonly in patients on corticosteroid therapy, those undergoing hemodialysis, or those with implanted catheters or prosthetic valves (6). Of the CoNS pathogens, *Staphylococcus epidermidis* is the most abundant colonizer of human skin and mucous membranes and is the most common cause of catheter-associated bloodstream infections (7).

CoNS infections are most commonly treated with glycopeptides, including vancomycin, but there has been increasing concern regarding emerging resistance to these agents (3). Up to 90% of *S. epidermidis* strains are now resistant to methicillin, with resistance to aminoglycosides and macrolides noted among hospital-associated strains. Resistance to linezolid also occurs but is much less frequent (8, 9). Despite hospital-level reports of increasing resistance, there have been few recent national studies describing the prevalence of antibiotic resistance in clinically important CoNS pathogens. For example, previously reported surveillance data (10–12) are more than a decade old.

In this study, we examined national trends in antibiotic resistance of clinical CoNS isolates. We paid particular attention to *S. epidermidis* isolates obtained from blood specimens in hospitalized patients, given the important role of this pathogen in hospital-acquired infections associated with medical devices. Finally, we compared the resistance patterns in *S. epidermidis* with the overall resistance trends in CoNS pathogens and examined the correlations with antibiotic prescribing patterns.

MATERIALS AND METHODS

Data. We analyzed national trends in the frequency of resistance for *S. epidermidis* and all CoNS pathogens (*S. saprophyticus*, *S. lugdunensis*, *S. schleiferi*, and *S. caprae*), using antibiotic susceptibility data from The Surveillance Network (TSN) Database-USA (managed by Eurofins Medinet, Chantilly, VA). TSN is an electronic repository of susceptibility test results collected from more than 300 microbiology laboratories in the United States, representing a national sample of isolates tested for resistance. Laboratories were selected to be geographically and demographically representative of hospital and patient characteristics (bed size, age, race, and sex) in each of the nine U.S. Census Bureau regional divisions (13, 14). Testing of isolates occurs on-site as part of the routine diagnostic testing for susceptibility to different antibiotic agents using standards established by the Clinical and Laboratory Standards Institute (CLSI). Data from TSN have been used extensively to evaluate patterns and trends of antibiotic drug resistance (13–21).

Our data included CoNS isolates collected from inpatient areas of health care facilities from January 1999 to June 2012. To assess longitudi-

Received 3 September 2013 Returned for modification 14 October 2013
Accepted 9 December 2013
Published ahead of print 16 December 2013
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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.01908-13.

doi:10.1128/AAC.01908-13

nal trends in resistance, we examined two sets of isolates, (i) all *S. epidermidis* bacterial isolates for which the isolate source was blood and (ii) all CoNS isolates regardless of source. The former set reduces the likelihood of contamination, although without clinical indicators, it cannot be ruled out. The latter set of isolates forms the full reservoir of CoNS isolates, which can serve as an important indicator of possible changes in resistance levels. Isolates were tested for resistance to oxacillin (a proxy for all β-lactam antibiotic drugs, including methicillin), ciprofloxacin, clindamycin, levofloxacin, linezolid, and vancomycin individually. While both ciprofloxacin and levofloxacin are fluoroquinolones and thus have similar mechanisms of resistance (22), we examined them separately because levofloxacin has a broader spectrum of activity against Gram-positive organisms (see, e.g., references 23 and 24) and because differences in their resistance rates have been noted (25). In addition to defining individual resistance profiles, we operationally defined isolates as multidrug resistant if they were resistant to oxacillin, ciprofloxacin, clindamycin, and levofloxacin. Isolates were categorized for resistance according to the CLSI breakpoint criteria. Between 2004 and 2005, the resistance breakpoints for levofloxacin were modified; however, no other changes to data collection or processing methods occurred during the study period. Isolates that had intermediate resistance were classified as resistant because of the change in the resistance breakpoints for levofloxacin (the MIC values for resistance after the change include the intermediate values for the prior years). For comparison, we also examined the levofloxacin resistance rates in *S. aureus* (which were subject to the same breakpoint changes) and *Escherichia coli* (no breakpoint change) blood isolates using the same methods.

Trend analysis. The resistance rates for each year were calculated as the proportion of phenotypes resistant to the number of isolates tested. Confidence intervals (CIs) were calculated by using the Wilson score method incorporating continuity correction as detailed by Newcombe (26). The Mann-Kendall test for trend and the Wilcoxon-Mann-Whitney rank sum test, which tests whether the distribution from the first half of the study was the same as that from the second half, were used to evaluate the statistical significance of observed changes in the frequency of resistance. All data analysis was done using Stata version 10 software (Stata Corp LP, College Station, TX).

Correlation analysis. We also investigated the correlation between the yearly levofloxacin prescription rate and the percentage of *Staphylococcus epidermidis* isolates that were resistant. However, as has often been noted in the statistical literature, two time series can appear highly correlated without any statistical significance (or meaningful connection) (21). Accordingly, we used a time series analysis method similar to that of Sun and colleagues (21), which addresses this issue, to ascertain the statistical correlation. Briefly, we applied the Box-Jenkins approach to fit time-series data to autoregressive moving average (ARIMA) statistical models. This method removes the trend from the data and transforms it into a series of independent, identically distributed random variables. Time series were differenced, and the best ARIMA model was selected based on the Akaike information criterion (AIC). The residuals of the model were then diagnosed for acceptability using the Box-Ljung white noise test. The residuals from prescription and resistance models were then cross-correlated to examine their association.

Prescription data were obtained from IMS Health's Xponent database, which contains the number of dispensed drug prescriptions collected from retail pharmacies (chains, mass merchandisers, independents, and food stores) in the United States by month. The database covers >70% of all prescriptions filled in the United States, and records are then weighted to project 100% of total prescriptions dispensed. Because the fluoroquinolones may have similar mechanisms of action and thus contribute to cross-resistance, we examined the correlation between levofloxacin resistance in *S. epidermidis* infections and both ciprofloxacin and all fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin) prescriptions.

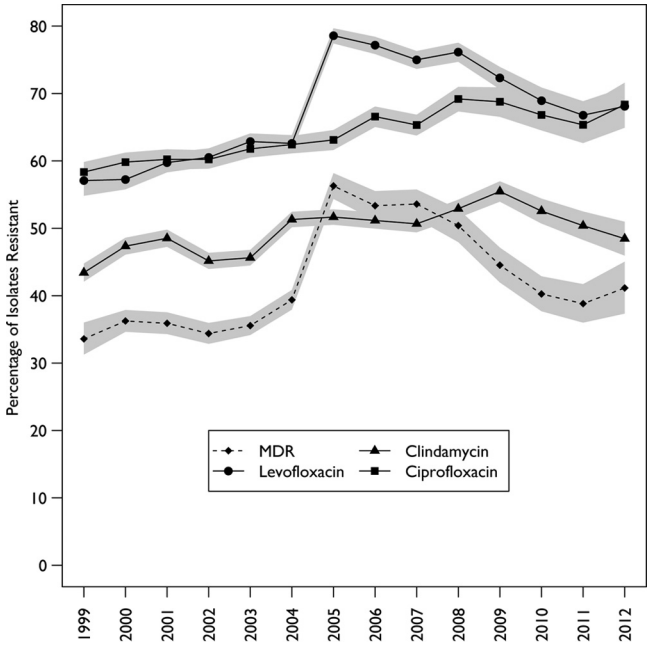

FIG 1 Percentage of resistant *Staphylococcus epidermidis* bloodstream isolates from inpatients, 1999 to 2012. Multidrug resistance (MDR) is defined as resistance to levofloxacin, clindamycin, ciprofloxacin, and oxacillin. Gray zones represent 95% confidence intervals.

RESULTS

Trend analysis. We evaluated resistance of *S. epidermidis* isolates from blood specimens obtained from hospitalized patients during the study period and compared their resistance patterns with those for all CoNS pathogens obtained from all clinical sites. Between 1 January 1999 and 30 June 2012, more than 540,000 CoNS isolates and 80,000 *S. epidermidis* blood isolates were submitted to TSN and included in our analysis.

Over the course of the study, resistance of *S. epidermidis* to ciprofloxacin, levofloxacin, and clindamycin individually increased, as did the resistance to a multidrug-resistant phenotype (Fig. 1). However, the patterns of resistance differed among drugs. Resistance to ciprofloxacin and clindamycin increased from 58.3% (95% confidence interval [CI], 56.8 to 59.8) in 1999 to 68.4% (95% CI, 64.9 to 71.6) in 2012 and from 43.4% (95% CI, 42.1 to 44.8) in 1999 to 48.5% (95% CI, 45.9 to 51.0) in 2012, respectively. Resistance to levofloxacin exhibited a different pattern. The percentage of isolates resistant to levofloxacin increased rapidly from 57.1% (95% CI, 54.8 to 59.3) in 1999 to a high of 78.6% (95% CI, 77.4 to 79.7) in 2005, followed by a significant decrease to 68.1% (95% CI, 65.1 to 70.9) in 2012. Multidrug resistance followed a similar pattern, ranging from 33.6% (95% CI, 31.3 to 36.0) in 1999 to a high of 56.3% (95% CI, 54.4 to 58.2) in 2005 and a subsequent decrease to 41.1% (95% CI, 37.3 to 45.0) in 2012. Oxacillin resistance remained generally constant at ~80% during the study period. Resistance to linezolid was first detected in 2004, and by 2012 had reached 1.1% (95% CI, 0.6 to 1.9) (see Fig. S1 in the supplemental material). Resistance to vancomycin was not observed over the study period.

The positive trends observed for ciprofloxacin and clindamycin were statistically significant ($P < 0.01$) by the Mann-Kendall test for trend. Because of the increase and decrease patterns asso-

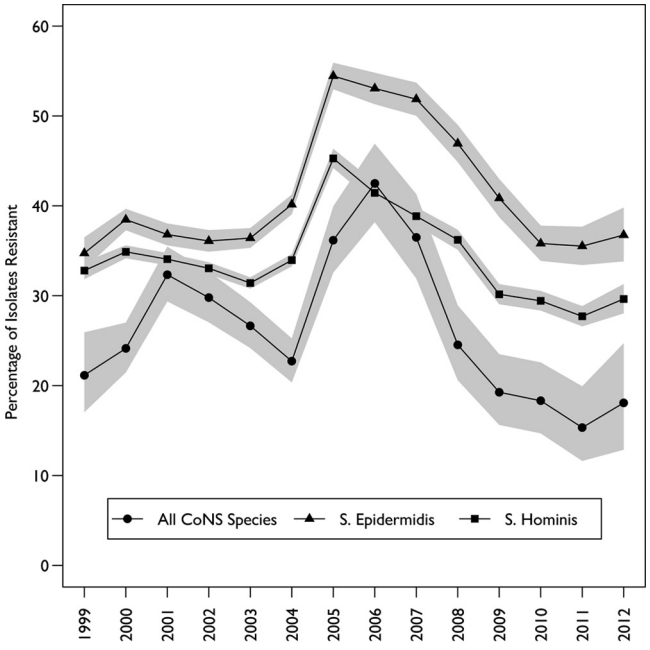

FIG 2 Percentage of all resistant coagulase-negative *Staphylococcus* sp. isolates from inpatients, 1999 to 2012. The CoNS species data include data for *S. epidermidis* and *S. hominis*. The data for these two species are included for comparison. Gray zones represent 95% confidence intervals.

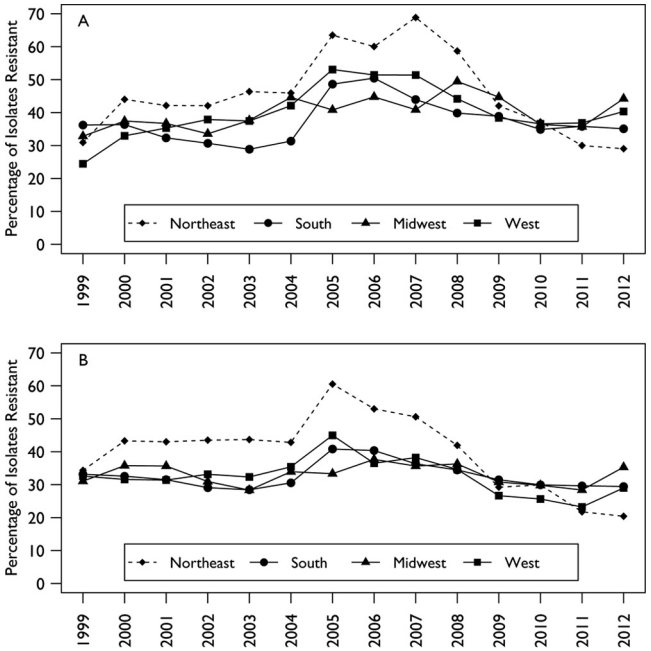

FIG 3 Regional variations in coagulase-negative staphylococcal resistance. There were significant variations in the rates of resistance between regions for *Staphylococcus epidermidis* blood isolates from inpatients (A) and all coagulase-negative species from all sources (B). In particular, the Northeast had high rates of resistance.

ciated with levofloxacin resistance, we used the Wilcoxon-Mann-Whitney rank sum test to determine whether the first half of the time series was statistically different from the second half. We found that this difference was statistically significant ($P < 0.01$), indicating highly significant trends in the patterns of resistance throughout the study period.

The pattern was similar when looking at all CoNS pathogens and at another common CoNS colonizer, *Staphylococcus hominis*, with multidrug resistance reaching a high of 45.3% (95% CI, 44.2 to 46.3%) in 2005 and a low of 29.6% (95% CI, 28.0 to 31.3%) in 2012 (Fig. 2; for more detail, see Tables S1 and S2 in the supplemental material). We also found that antibiotic resistance patterns varied by U.S. region, with the highest rates of resistance noted for the Northeast for both *S. epidermidis* isolates and all CoNS organisms (Fig. 3). Finally, we found that *S. aureus* isolates followed increase and decrease patterns similar to those of *S. epidermidis*, while *Escherichia coli* resistance increased rapidly from around 5% in 1999 to >30% in 2008 before leveling off (see Fig. S2 in the supplemental material).

Correlation analysis. We further examined the observed pattern of *S. epidermidis* resistance to levofloxacin because we found that it was correlated with the levofloxacin prescription rate (Fig. 4). Using time-series analysis, we constructed ARIMA models for each time series (all models were determined to be acceptable based on the AIC and Box-Ljung test for white noise of residuals; for a description of the ARIMA model parameters and diagnostics, see Table S3 in the supplemental data). The ARIMA residuals for the prescription and resistance time series were then cross-correlated, and we found positive and significant (*P* values at or below the 10% level) cross-correlation coefficients for levofloxacin prescriptions and levofloxacin resistance but not for ciprofloxacin or total fluoroquinolone prescriptions (Table 1; for fluoroquinolone prescription trends, see Fig. S3 in the supplemental data). The results were consistent whether we looked at all *S. epidermidis* isolates or only at bloodstream isolates. The *S. epidermidis* bloodstream isolate multidrug resistance rates were also highly correlated with levofloxacin prescriptions, but rates for all *S. epidermidis* isolates were not. Multidrug resistance rates were not correlated with ciprofloxacin or total fluoroquinolone prescriptions (*P* values not shown). Ciprofloxacin prescriptions were also not strongly correlated with ciprofloxacin resistance.

DISCUSSION

Infections caused by *S. epidermidis* are clinically important in hospitalized patients and play a significant commensal role in the community. Although previously considered contaminants, CoNS now account for 20 to 30% of all clinically relevant bloodstream infections and a significant proportion of catheter-related bloodstream infections (3). Nearly all CoNS strains display methicillin resistance, with 81% demonstrating resistance to multiple drugs (27). Difficult-to-eradicate bacteremia has also been associated with CoNS infection and biofilm formation (28) and, recently, some *S. epidermidis* clones (CC2) have been found to display particularly high rates of multidrug resistance. In addition, rapid development of antibiotic resistance to mupirocin, an agent used for topical decolonization for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis*, was described (29). The discovery of plasmid-mediated fluoroquinolone resistance mechanisms (30, 31) makes CoNS resistance more troubling because the CoNS pathogens are such abundant colonizers of human skin and mucous membranes. Thus, there are frequent opportunities for development of resistance that affects the downstream resistance of not only CoNS pathogens but

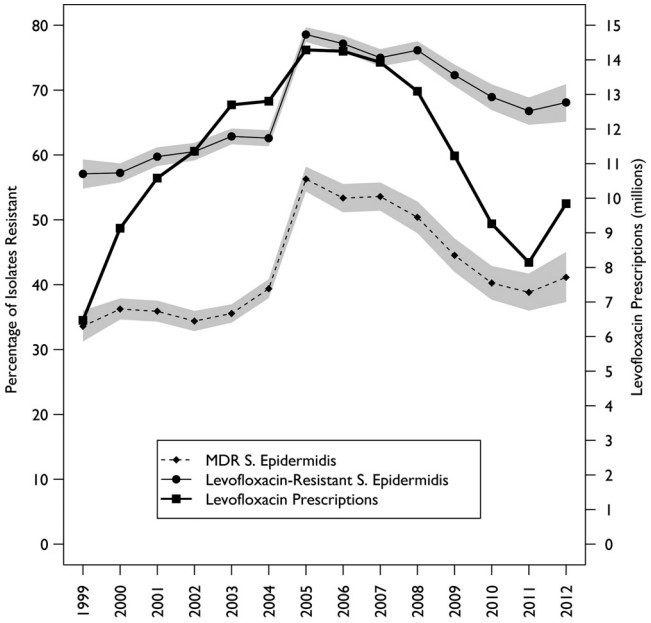

FIG 4 Correlation between levofloxacin drug use and resistance. Levofloxacin drug use increased significantly between 1999 and 2005, corresponding to a period of rising resistance rates for *S. epidermidis* to levofloxacin. As the number of prescriptions fell over the next several years, resistance also fell, although it did not fall as fast or as far as it rose, and increases in the number of prescriptions in 2012 are associated with increases in resistance rates. (Drug usage source, IMS Xponent, January 1999 to December 2010, IMS Health Incorporated; resistance data source, The Surveillance Network.)

also other bacteria, such as MRSA (32–34), a pathogen which is estimated to be responsible for more than 400,000 hospitalizations per year in the United States (35). However, despite the importance of CoNS as both a marker of drug resistance and a potential reservoir for resistance genes, there has been no recent estimate of the magnitude of resistance in CoNS, and our paper is the first we are aware of that describes longitudinal trends at the national level.

Consistent with prior reports (10, 12), we found high rates of resistance to oxacillin and high rates of multidrug resistance. However, our results also describe significant changes over the last decade in resistance to levofloxacin, which was observed to have a significant positive trend through 2005, corresponding to a period of increase in outpatient levofloxacin prescriptions. The subsequent decrease observed after 2005 was also correlated to a decrease in the volume of levofloxacin prescriptions provided during that time period. Using time-series analysis of prescription and resistance data, we found strong correlations between levofloxacin prescriptions and both levofloxacin resistance and multidrug resistance rates for *S. epidermidis* but no significant correlations with ciprofloxacin or total fluoroquinolone prescriptions. The time-series methods used suggest that the patterns in resistance rates observed are causally related to prescription rates for levofloxacin, suggesting that decreases in the use of levofloxacin after 2005 contributed significantly to the changes in the resistance profiles observed. Although cross-resistance with ciprofloxacin is possible and likely played a role as ciprofloxacin prescriptions surged in 2005 as well, our results suggest that the decrease in levofloxacin prescriptions was the main factor leading to reductions in resistance. The fact that ciprofloxacin usage did not seem to play a role in levofloxacin resistance is potentially due to the fact that levofloxacin has a broader spectrum of activity (23, 24) and equivalent or greater bioavailability, higher plasma concentrations, increased tissue penetration (36), and enhanced penetration of the bacterial cell (37) relative to those for ciprofloxacin. Alternatively, differences in the activity levels against DNA gyrase and topoisomerase IV, the primary targets of fluoroquinolones, may also account for these findings (22). Our results are also consistent with those of other reports showing a link between levofloxacin use and resistance in hospitalized patients (38).

The strong correlation with multidrug-resistant *S. epidermidis* rates raises an interesting ecological question for further study. In particular, this correlation may have occurred because levofloxacin use reduced the fitness costs associated with being resistant to other drugs. Alternatively, the decline in levofloxacin use may have been related to the use of another drug(s) that was more effective against multidrug-resistant strains. This result needs more study to understand the ecological and epidemiological consequences of exogenous changes in drug usage. The strong relationship between variations in levofloxacin prescriptions and resistance rates across the years suggests the importance of monitoring CoNS as a valuable surveillance tool. These results also suggest that antimicrobial stewardship programs that reduce prescription rates are likely to be effective in reducing resistance. However, the results also point to the strong connection between community antibiotic use and inpatient resistance rates (21). Stewardship programs must therefore encompass not just the hospital but the surrounding outpatient care centers as well.

In addition to changes in national resistance levels, we also describe variations in antibiotic resistance by region. We found disparities in the community-level antibiotic resistance across the United States that might lead to disparate downstream regional

TABLE 1 Cross-correlation coefficients between drug-resistant isolates and levofloxacin prescriptions, 1999 to 2010[a]

Isolate type and antibiotic prescribed	Cross-correlation coefficient	*P* value
Levofloxacin-resistant *Staphylococcus epidermidis* blood isolates		
Levofloxacin	0.53	0.07
Ciprofloxacin	0.32	0.29
Fluoroquinolone	0.48	0.11
Levofloxacin-resistant *Staphylococcus epidermidis*, all isolates		
Levofloxacin	0.71	<0.01
Ciprofloxacin	0.31	0.29
Fluoroquinolone	0.12	0.71
Multidrug-resistant *Staphylococcus epidermidis* blood isolates: levofloxacin	0.65	<0.02
Multidrug-resistant *Staphylococcus epidermidis*, all isolates: levofloxacin	0.34	0.23
Ciprofloxacin-resistant *Staphylococcus epidermidis* blood isolates: ciprofloxacin	0.33	0.27
Ciprofloxacin-resistant *Staphylococcus epidermidis*, all isolates: ciprofloxacin	−0.04	0.90

[a] Prescription data source, IMS Xponent, January 1999 to December 2010, IMS Health Incorporated; resistance data source, The Surveillance Network (TSN) Database-USA (managed by Eurofins Medinet, Chantilly, VA).

effects on health outcomes, such as hospital-acquired bloodstream infections. The reasons for these variations are likely multifactorial and involve factors such as antibiotic prescribing patterns, health care utilization, and clinical practices. Evaluation of these factors was beyond the scope of this study but remains an important area for future research. We also found that levofloxacin resistance has been increasing in a similar pattern for *S. aureus* and more dramatically for *E. coli* in concert with other observations (39).

The current study has several limitations. First, we could not account for patients' clinical characteristics or distinguish between confirmed infection and contamination, since our data sources did not include clinical information. However, by including only *S. epidermidis* isolates obtained from sterile sites (blood) rather than wound or skin specimens, as well as excluding outpatient specimens, we are confident that our data are more representative of clinically significant infection and do not include significant numbers of colonization site specimens. We included isolates from inpatients and a sterile site to serve as a surrogate for clinically relevant infections. Even with clinical information, it would have been difficult to distinguish between true infection and contamination; previous authors have documented the difficulties in determining contaminants versus true pathogens in clinical settings (40). In addition, despite the very restricted demographic data available, including the lack of diagnostic coding, our resistance trend findings have important implications for human health because of the potential for CoNS to cause clinically significant infections and promote antibiotic resistance in other species. Because our data included only outpatient prescriptions, we were not able to assess the consequences of hospital use of antibiotics on antibacterial resistance, nor were we able to evaluate inpatient versus outpatient use of antibiotics. In addition, the limitations of this data set did not allow us to compare MIC values for different antibiotic agents, which hinders the analysis slightly as there was a change in the CLSI interpretive criteria for levofloxacin for *Staphylococcus* species between 2004 and 2005. However, the testing procedure change was the same for *S. aureus* as it was for CoNS, and while resistance to levofloxacin increased over the same period it was not of the same magnitude, suggesting that changes in the criteria alone were not responsible for the increases. In addition, while the percentage of intermediate-resistant isolates was high in 2004, it fell to $<1\%$ in 2005 and stayed at that level for the rest of the study, so it is likely that this change did not significantly bias the results (see Fig. S4 in the supplemental material). Finally, characterizing the molecular epidemiology behind the trends reported was outside the scope of this study, since we lacked phenotypic or genotypic testing results that may have been able to aid in the tracking of multidrug-resistant CoNS strains, such as CC2. Further studies should include data on resistance mechanisms, particularly those that may confer resistance to other clinically important pathogens, such as *S. aureus*.

In conclusion, the prevalence of antibiotic resistance in CoNS pathogens, including multidrug resistance, increased significantly between 1999 and 2005, with a subsequent significant downward trend in multidrug resistance. The trends in multidrug resistance were driven largely by a decrease in levofloxacin resistance, which was associated with the prescription patterns for that antimicrobial agent. These findings suggest that antibiotic prescribing patterns, particularly those for broad-spectrum fluoroquinolones, have an important effect on multidrug antibiotic resistance of CoNS pathogens. These pathogens are ubiquitous and are associated with serious bacterial infections. The ability to transfer resistance mechanisms to other virulent pathogens, such as *S. aureus*, may give CoNS the potential to promote downstream resistance in other pathogens, although further research is needed to elucidate this potential. Our findings suggest the need for further surveillance of emerging resistance in CoNS. Better surveillance data are needed both to advance strategies to reduce the inappropriate use of fluoroquinolones and other broad-spectrum antibiotics and to guide the development of new antibacterial agents.

ACKNOWLEDGMENTS

L.M. is supported by awards UL1RR031988/UL1TR000075 and KL2RR031987/KL2TR000076 from the NIH National Center for Advancing Translational Sciences. E.Y.K. is supported by the Models of Infectious Disease Agent Study (MIDAS) under award U01GM070708 from the National Institute of General Medical Sciences, the National Center for the Study of Preparedness and Catastrophic Event Response (PACER) at the Johns Hopkins University, through U.S. Department of Homeland Security grant N00014-06-1-0991, and NIH Pioneer award DP1OD003874. Additional support for this report was provided by the Grand Challenges in Global Health program at Princeton University and the Extending the Cure Project, supported by the Pioneer Portfolio at the Robert Wood Johnson Foundation.

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We declare no conflicts of interest relevant to this article.

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