

Overview of Nosocomial Infections Caused by Gram-Negative Bacilli

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We analyzed data from the National Nosocomial Infections Surveillance (NNIS) System from 1986–2003 to determine the epidemiology of gram-negative bacilli in intensive care units (ICUs) for the most frequent types of hospital-acquired infection: pneumonia, surgical site infection (SSI), urinary tract infection (UTI), and bloodstream infection (BSI). We analyzed >410,000 bacterial isolates associated with hospital-acquired infections in ICUs during 1986–2003. In 2003, gram-negative bacilli were associated with 23.8% of BSIs, 65.2% of pneumonia episodes, 33.8% of SSIs, and 71.1% of UTIs. The percentage of BSIs associated with gram-negative bacilli decreased from 33.2% in 1986 to 23.8% in 2003. The percentage of SSIs associated with gram-negative bacilli decreased from 56.5% in 1986 to 33.8% in 2003. The percentages pneumonia episodes and UTIs associated with gram-negative bacilli remained constant during the study period. The proportion of ICU pneumonia episodes associated with *Acinetobacter* species increased from 4% in 1986 to 7.0% in 2003 ($P < .001$, by the Cochran-Armitage χ^2 test for trend). Significant increases in resistance rates were uniformly seen for selected antimicrobial-pathogen combinations. Gram-negative bacilli are commonly associated with hospital-acquired infections in ICUs. The proportion of *Acinetobacter* species associated with ICU pneumonia increased from 4% in 1986 to 7.0% in 2003.

The gram-negative bacilli vary in the frequencies that they cause the 4 most frequent types of hospital-acquired infection: pneumonia, surgical site infection (SSI), urinary tract infection (UTI), and bloodstream infection (BSI) [1]. During the past 20 years, changes in health care, infection-control practices, and antimicrobial use and resistance may have influenced the frequency that these gram-negative organisms are associated with hospital-acquired infection. We endeavored to determine the frequencies that various species of gram-negative organisms are associated with these 4 hospital-acquired infections and whether the frequencies have changed over time.

METHODS

Data from the National Nosocomial Infections Surveillance (NNIS) system were analyzed. The NNIS system was established in 1970, when selected hospitals in the United States routinely

began reporting their nosocomial infection surveillance data for aggregation into a national database at the Centers for Disease Control and Prevention (CDC) [2, 3]. Participation in the NNIS system is voluntary and involves only acute care general hospitals in the United States. Until 1986, surveillance was hospital wide: all hospitalized patients were monitored for nosocomial infections at all sites. Baseline data comprised data on bacterial pathogens associated with the 4 most common types of nosocomial infections from an internal NNIS report on hospital-wide surveillance in 1975 (unpublished data). Because data reported to the CDC from the hospital-wide component progressively decreased, this component of the NNIS system was discontinued in 1999. In 1986, the intensive care unit (ICU) surveillance component was introduced.

Data from the ICU component were used for the trend analysis in our study. Data were collected between 1986 and 2003 for patients in intensive care units (ICUs). All patients in the ICU were monitored for nosocomial infection at all body sites for a period of at least 1 calendar month. Standard definitions for nosocomial infections were used [3]. The data collected on each infection included the date of ICU admission, the site of infection, and demographic characteristics. Up to 4 pathogens for each infection could be recorded. Infections were considered to be associated with ICU stay if they developed within 48 h

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Table 1. Percentage of bacterial isolates associated with nosocomial infection recorded during hospital-wide surveillance and reported to the National Nosocomial Infections Surveillance system, 1975.

Pathogen	Percentage of isolates, by infection type			
	Pneumonia (n = 4018)	Bloodstream infection (n = 1054)	Surgical site infection (n = 7848)	Urinary tract infection (n = 16,434)
Gram negative				
<i>Escherichia coli</i>	11.8	15.0	17.6	33.5
<i>Klebsiella pneumoniae</i>	8.4	4.5	2.7	4.6
<i>Enterobacter</i> species	9.6	6.0	4.6	4.7
<i>Serratia marcescens</i>	2.2	2.6	0.5	1.4
<i>Pseudomonas aeruginosa</i>	9.6	4.8	4.7	9.3
<i>Acinetobacter</i> species	1.5	1.8	0.5	0.6
Other	31.0	22.4	22.8	24.4
Gram positive				
Coagulase-negative staphylococci	2.6	10.3	7.4	3.2
<i>Staphylococcus aureus</i>	13.4	16.5	18.5	1.9
Enterococci	3.0	8.1	11.9	14.2
Other	6.9	8.0	8.8	2.2

NOTE. Data are previously unpublished.

after discharge from the unit, unless the clinical evidence strongly suggested otherwise.

Analysis was limited to bacterial pathogens, and they were classified as either gram positive or gram negative. After fungal, viral, and other nonbacterial pathogens were excluded, the annual percentages of gram-positive and gram-negative bacterial pathogens associated with each type of infection were determined for trend analysis. For each infection type, the most commonly reported gram-negative bacteria were analyzed by year. Statistical analysis was performed using the Cochran-Armitage χ^2 test for trend.

Each hospital in the NNIS system performed susceptibility tests and classified isolates as susceptible, intermediately susceptible, or resistant. Because the same panel of antimicrobials was not tested at each hospital, our analysis was limited to pathogen-antimicrobial combinations for which results of susceptibility tests were reported at all participating ICUs during 1986–2003. Isolates that were intermediately susceptible or susceptible to the specified antimicrobials were considered to be susceptible, with the exception of *Escherichia coli* and *Klebsiella pneumoniae* isolates, which were considered to be resistant to third-generation cephalosporins if they were intermediately susceptible or resistant to cefotaxime, ceftriaxone, ceftazidime, and/or aztreonam. We chose to combine intermediately susceptible and resistant results for these latter 2 pathogen-antimicrobial combinations for consistency with a previous analysis [4] and current recommendations.

Under Section 308(d) of the Public Health Service Act (42 USC 242b, k, and m[d]), the identities of patients and NNIS hospitals are confidential. Because the NNIS is an established

surveillance system, collection of data is not considered to be research and, therefore, is not subject to requirements for the protection of human research subjects.

RESULTS

In 1975, NNIS hospitals performing hospital-wide surveillance reported 29,354 bacterial isolates associated with the 4 most common types of nosocomial infection. The most commonly reported species are summarized in table 1. The majority of bacterial pathogens associated with each of these 4 types of infection in 1975 were gram negative. Because the amount of data from the hospital-wide component reported to the CDC steadily decreased from 1983 to 1999 (when the hospital-wide component was eliminated from the NNIS system), the remainder of the analysis is limited to data from the ICU component.

Gram-negative versus gram-positive pathogens, by type of ICU infection, 1986–2003

From 1986 through 2003, data on 410,503 bacterial isolates associated with nosocomial infections were submitted from ICUs in NNIS hospitals. The mean annual number of bacterial isolates reported was 24,129 (range, 10,128 in 1986 to 26,026 in 2000). The percentages of gram-negative and gram-positive bacteria associated with each of the 4 major types of infection are shown in figure 1. The percentage of bacteria that were gram negative was stable throughout the study period for pneumonia and UTI; the majority of bacterial isolates associated with these 2 infection types were gram negative. However, for

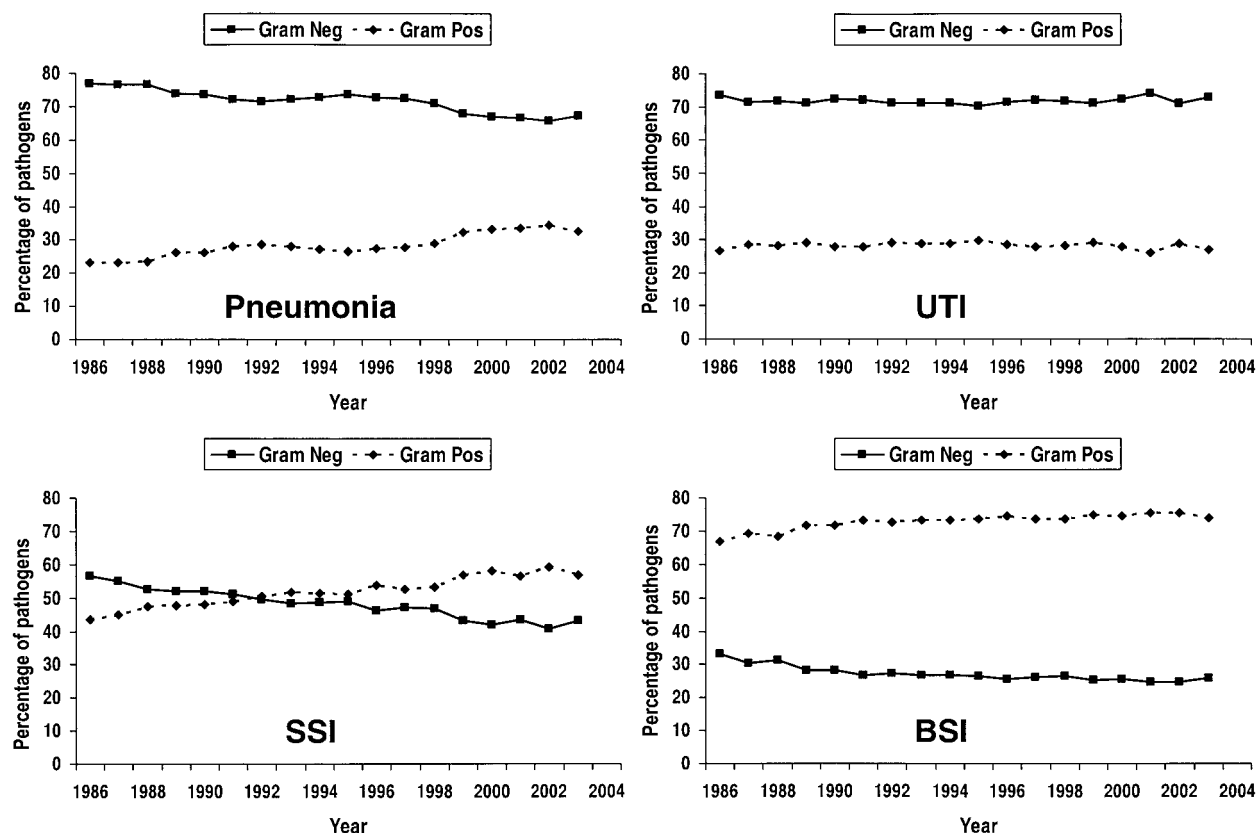


Figure 1. Results of intensive care unit surveillance revealing percentages of gram-positive (Gram Pos) and gram-negative (Gram Neg) pathogens associated with pneumonia, urinary tract infection (UTI), surgical site infection (SSI), and bloodstream infection (BSI)—National Nosocomial Infections Surveillance system, 1986–2003.

SSIs, the percentage of bacterial isolates that were gram negative decreased during the study period. By the middle of the 1990s, gram-positive bacterial pathogens were more commonly reported in association with SSIs than were gram-negative pathogens. Throughout the study period, gram-positive bacterial pathogens were much more commonly associated with BSIs than were gram-negative pathogens.

Trends in gram-negative pathogen distribution in ICUs, 1986–2003

Nosocomial pneumonia. Gram-negative aerobes (65.9%) remained the most frequently reported bacterial pathogens associated with pneumonia in 2003 (table 2). There was little change in the distribution of these pathogens during the 17-year study period, with the following exception: the proportion of *Acinetobacter* species was significantly higher in 2003, compared with 1986 ($P < .001$) (figure 2). This increase was noted at multiple hospitals and was not seen in 1 geographic region or in only 1 hospital contributing large number of *Acinetobacter* infections.

UTI. The distribution of gram-negative pathogens associated with UTIs in ICUs changed very little during the study

period. In 2003, *E. coli* was the most commonly reported gram-negative pathogen, followed by *Pseudomonas aeruginosa* (table 2). The percentage of *K. pneumoniae* and *Acinetobacter* isolates increased significantly ($P < .001$) but comprised only 9.8% and 1.6%, respectively, of isolates associated with UTIs in 2003.

SSI. The distribution of gram-negative pathogens associated with SSIs in ICUs changed during the study period. *E. coli* and *Enterobacter* isolates were significantly less commonly reported. *Acinetobacter* isolates were more frequently reported ($P < .001$) but comprised only 2.1% of the isolates associated with SSIs in 2003.

Primary BSI. The distribution of gram-negative pathogens associated with BSIs in ICUs changed very little during the study period. *E. coli* was somewhat less frequently reported (4.6% of isolates reported in 1986, and 3.4% of isolates reported in 2003), but the change was not statistically significant.

Trends in antimicrobial susceptibilities for selected gram-negative pathogens in ICUs, 1986–2003

Overall trends for selected gram-negative pathogens in ICUs showed significant increases during 1986–2003. The number of *E. coli* and *K. pneumoniae* isolates that were intermediately

Table 2. Percentage of bacterial isolates associated with nosocomial infection recorded during intensive care unit surveillance and reported to the National Nosocomial Infections Surveillance system, 2003.

Pathogen	Percentage of isolates, by infection type			
	Pneumonia (n = 4365)	Bloodstream infection (n = 2351)	Surgical site infection (n = 2984)	Urinary tract infection (n = 4109)
Gram negative				
<i>Escherichia coli</i>	5.0	3.3	6.5	26.0
<i>Klebsiella pneumoniae</i>	7.2	4.2	3.0	9.8
<i>Enterobacter</i> species	10.0	4.4	9.0	6.9
<i>Serratia marcescens</i>	4.7	2.3	2.0	1.6
<i>Pseudomonas aeruginosa</i>	18.1	3.4	9.5	16.3
<i>Acinetobacter</i> species	6.9	2.4	2.1	1.6
Other	14.1	3.8	9.8	10.7
Gram positive				
Coagulase-negative staphylococci	1.8	42.9	15.9	4.9
<i>Staphylococcus aureus</i>	27.8	14.3	22.5	3.6
Enterococci	1.3	14.5	13.9	17.4
Other	3.2	4.5	5.8	1.2

susceptible or resistant to 1 of several cephalosporins (or aztreonam) increased, although the increases were dramatically different. For *E. coli*, the increase was steady and consistent throughout the study period, whereas for *K. pneumoniae*, the increase was sudden and remained somewhat stable until 2003. In both instances, results of the Cochran-Armitage χ^2 test for trend were significant ($P < .001$) (figure 3).

Rates of resistance to ceftazidime and imipenem among *P. aeruginosa* isolates are summarized in figure 4. Rates of resistance to ceftazidime, imipenem, and ceftazidime among *Acinetobacter* isolates are summarized in figure 5. In all instances, results of Cochran-Armitage χ^2 tests for trend were significant ($P < .001$).

DISCUSSION

Our study shows that gram-negative bacilli continue to be associated with hospital-acquired infections in ICUs. In the 1970s, gram-negative bacilli constituted the majority of bacterial pathogens associated with the 4 major types of hospital-acquired infections. Although the data in table 1 are from hospital-wide surveillance, the predominance of gram-negative bacilli is a relevant reminder that these pathogens were once the most common human pathogens in hospitals. For approximately the past 2 decades, gram-negative bacilli have been the pathogens most frequently associated with pneumonia and UTIs. However, gram-positive bacterial pathogens are currently most frequently associated with BSIs and SSIs. Methicillin-resistant *S. aureus* has undoubtedly contributed to this shift, especially in ICUs. The increase in the percentage of BSIs due to gram-positive bacteria was first observed in the 1980s, when coag-

ulase-negative staphylococci were recognized as important BSI pathogens [5]. The shift to gram-positive pathogens as the predominant etiologic agents of SSIs occurred in the 1990s. The reasons for this shift may be related to antimicrobial use, especially for prophylaxis, or to a shift in the type of procedures performed. Notably, the dramatic increase in the use of laparoscopy may have decreased the incidence of SSIs, resulting in fewer reports of gram-negative bacilli infection associated with abdominal procedures [6].

Overall trends in the percentages of gram-negative bacilli associated with each type of hospital-acquired infection remained relatively stable during 1986–2003, with the following

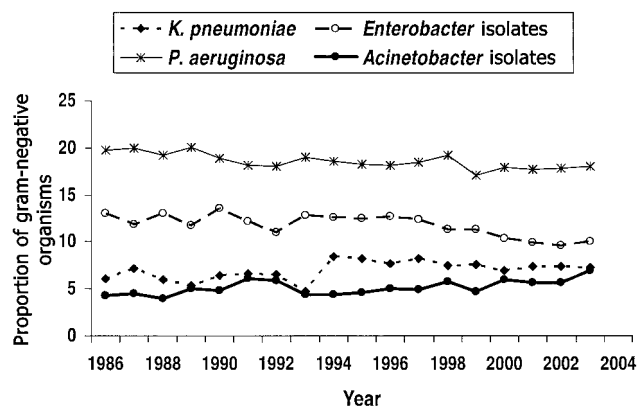


Figure 2. Results of intensive care unit surveillance for the proportion of selected gram-negative organisms reported for pneumonia from the National Nosocomial Infections Surveillance system, 1986–2003. The proportion of *Acinetobacter* species was significantly higher in 2003, compared with 1986 ($P < .001$, by the Cochran-Armitage χ^2 test for trend).

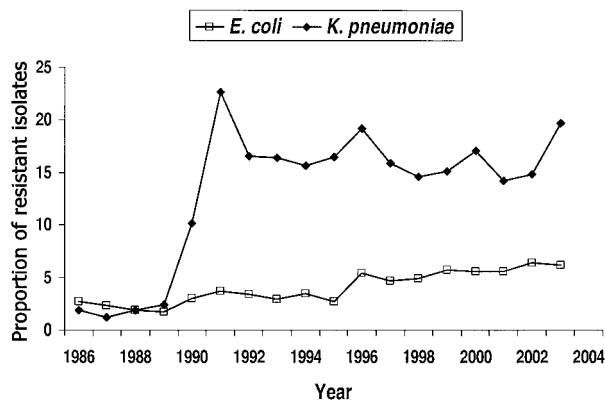


Figure 3. Results of intensive care unit surveillance revealing rates of antimicrobial resistance to third-generation cephalosporins among *Klebsiella pneumoniae* isolates (which includes isolates that were either intermediately susceptible or resistant) and *Escherichia coli* isolates—National Nosocomial Infections Surveillance system, 1986–2003. The proportions of *K. pneumoniae* and *E. coli* that were resistant were significantly higher in 2003, compared with 1986 ($P < .001$ for both, by the Cochran-Armitage χ^2 test for trend).

exceptions: *E. coli* was less commonly reported for SSIs and, to a lesser extent, for BSIs in 2003, compared with 1986. *Acinetobacter* organisms were the only gram-negative pathogens associated with consistently increasing proportions of hospital-acquired pneumonias, SSIs, and UTIs in nearly all NNIS hospitals during the study period. *Acinetobacter* organisms are intrinsically resistant to many antimicrobials and can acquire resistance to others [7]. The bacilli from this genus may become an even more predominant cause of hospital-acquired infections, as a result of selective pressure from antimicrobials in ICUs [8].

Changes in surveillance in hospitals may provide a limitation in interpreting these shifting trends. Before 1986, only hospital-wide surveillance was performed by hospitals in the NNIS system. The hospital-wide component in the NNIS system was the only one in which risk-adjusted nosocomial infection rates could not be calculated. Additionally, as resources for this activity became more limited, interest in the more efficient targeted surveillance methods increased. To enable calculation of risk-adjusted infection rates and to achieve more efficient surveillance, the hospital-wide component was eliminated from the NNIS system in 1995, and the ICU became an important area for targeted monitoring. The ICU is the focal point of more-recent surveillance programs, and this focused surveillance in an area of very high antimicrobial pressure could be one reason for the shift away from *E. coli* toward more resistant pathogens as causes of hospital-acquired infection.

A recent review by Archibald [9] showed that the types of pathogens encountered in health care institutions in North America, Europe, Asia, Australia, and even Africa are, for the

most part, similar [10–14]. This suggests that the reservoirs of these pathogens, which are often the patients themselves, and the risk factors for hospital-acquired infection, such as invasive devices, are also similar worldwide. Temporal changes in the types of bacterial pathogens observed may be due to changes in risk factors for infection or in characteristics of patients with underlying diseases. However, the observed changes, fewer reports of infections due to *E. coli*, and increasingly frequent reports of infections due to *Acinetobacter* species suggest that antimicrobial use is becoming a more important influence on which pathogens are isolated from a site of hospital-acquired infection. The increase in the frequency of hospital-acquired infections due to *Acinetobacter* species will be reviewed in a future issue of this journal [15].

For each of the antimicrobial-pathogen combinations tested, the increasing trend of resistance during the study period was significant. A previous report of results of proficiency testing at NNIS hospitals showed that the NNIS hospitals accurately performed susceptibility tests [16]. The increasing trends of resistance suggest that comparison of NNIS data with other data sources will depend on the period examined. However, even if the period is controlled, other factors must be considered when comparing resistance rates for an antimicrobial-pathogen combination. For example, The Surveillance Network found that 3.9% of *E. coli* isolates recovered from North America in 2001 were resistant to third-generation cephalosporins [17]. For the same period, Streit et al. [18] found 11.3% of North American *E. coli* to be resistant to third-generation cephalosporins. Unfortunately, the definitions of resistance, the methods used to detect resistance, and the isolates selected to be tested differed making comparisons of data from these studies very difficult. However, The Surveillance Network has a more inclusive se-

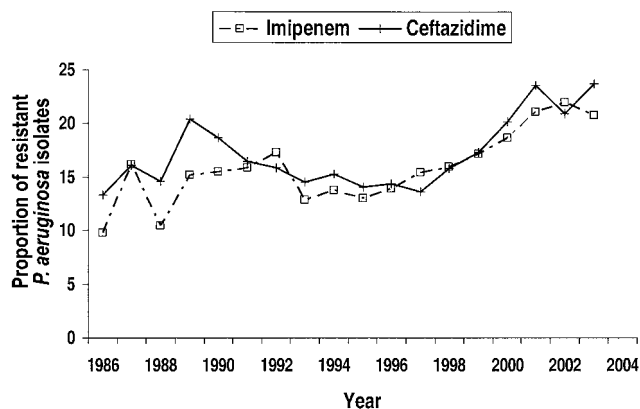


Figure 4. Results of intensive care unit surveillance revealing the proportions of *Pseudomonas aeruginosa* isolates that were resistant to imipenem and ceftazidime—National Nosocomial Infections Surveillance system, 1986–2003. In both instances, results of Cochran-Armitage χ^2 tests for trend were significant ($P < .001$).

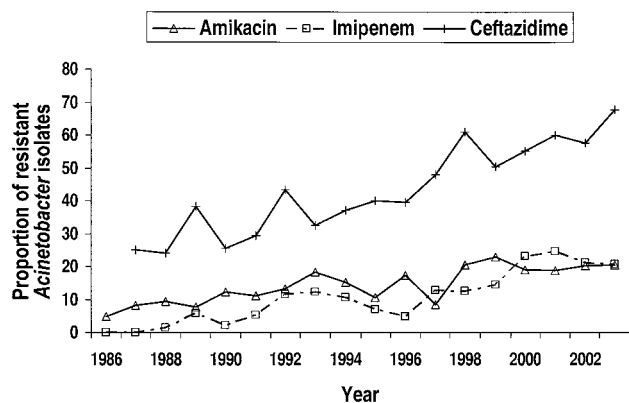


Figure 5. Results of intensive care unit surveillance revealing the proportions of *Acinetobacter* isolates that were resistant to amikacin, imipenem, and ceftazidime—National Nosocomial Infections Surveillance system, 1986–2003. In all instances, results of Cochran-Armitage χ^2 tests for trend were significant ($P < .001$).

lection of *E. coli* isolates from inpatient and outpatient cultures, which would tend to bias the resistance rates toward the more susceptible isolates.

The SENTRY system tests isolates from cultures of blood obtained from patients in the ICU, limiting the pool of tested isolates to patients with bacteremia. Because the NNIS data are from ICUs but include all isolates associated with hospital-acquired infections, not just BSIs, a 2001 *E. coli* resistance rate of 6.4% to third-generation cephalosporins is consistent with expectations, on the basis of the biased comparisons described. Similarly, for *K. pneumoniae*, 2001 resistance rates to third-generation cephalosporins were 11.2% for The Surveillance Network, 14.2% for NNIS ICU data, and 16.2% for SENTRY ICU bloodstream isolates.

Elsewhere, we reported on interhospital transmission of extended-spectrum, β -lactamase-producing (ESBL) *K. pneumoniae* in one region of the United States [19]. A rapid increase in the prevalence of this resistant strain was noted in one hospital in the region, and the strain quickly spread to other hospitals nearby. This is the source of the increase in 1991 shown in figure 3. Unfortunately, our data and data from The Surveillance Network and SENTRY support the existence of ESBL *K. pneumoniae* throughout the United States, with no one particular region responsible for the phenotype of resistance described in our earlier study [19].

Although the pathogens associated with hospital-acquired infections are similar worldwide, the rate of antimicrobial resistance among nosocomial pathogens is increasing for nearly all antimicrobial-pathogen combinations that have been examined, but these resistance rates differ markedly within and between countries [8, 20]. The rate of antimicrobial resistance is especially increasing among *Acinetobacter* species and *P. aeru-*

ginosa. We are currently analyzing NNIS data on a variety of antimicrobial-pathogen combinations in greater detail, with emphasis on resistance among *K. pneumoniae*, *Acinetobacter*, and *P. aeruginosa* strains. Antimicrobial resistance will continue to be a major objective of the CDC's National Healthcare Safety Network [21]. Gram-negative bacilli, such as *P. aeruginosa*, that are intrinsically resistant to antimicrobials and/or that have acquired antimicrobial resistance may contribute to the perception that the proportion of nosocomial bacilli that are gram negative is increasing [22]. However, the increase in the prevalence multidrug resistance may be the greatest concern for gram-negative bacilli associated with hospital-acquired infections. Many of these resistant isolates lack options for treatment and represent a serious public health concern.

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