JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2007, p. 3352–3359 Vol. 45, No. 10
0095-1137/07/$08.00+0 doi:10.1128/JCM.01284-07

Antimicrobial Resistance among Gram-Negative Bacilli Causing Infections in Intensive Care Unit Patients in the United States between 1993 and 2004▽

Shawn R. Lockhart,[1]* Murray A. Abramson,[2] Susan E. Beekmann,[1] Gale Gallagher,[2] Stefan Riedel,[1] Daniel J. Diekema,[1] John P. Quinn,[3] and Gary V. Doern[1]

University of Iowa Hospital and Clinics, Division of Clinical Microbiology, Iowa City, Iowa[1]; Merck and Co., Inc., Merck Research Laboratories, Upper Gwynedd, Pennsylvania[2]; and Cook County Hospital, Division of Infectious Diseases, Chicago, Illinois[3]

Received 26 June 2007/Returned for modification 6 August 2007/Accepted 10 August 2007

During the 12-year period from 1993 to 2004, antimicrobial susceptibility profiles of 74,394 gram-negative bacillus isolates recovered from intensive care unit (ICU) patients in United States hospitals were determined by participating hospitals and collected in a central location. MICs for 12 different agents were determined using a standardized broth microdilution method. The 11 organisms most frequently isolated were *Pseudomonas aeruginosa* (22.2%), *Escherichia coli* (18.8%), *Klebsiella pneumoniae* (14.2%), *Enterobacter cloacae* (9.1%), *Acinetobacter* spp. (6.2%), *Serratia marcescens* (5.5%), *Enterobacter aerogenes* (4.4%), *Stenotrophomonas maltophilia* (4.3%), *Proteus mirabilis* (4.0%), *Klebsiella oxytoca* (2.7%), and *Citrobacter freundii* (2.0%). Specimen sources included the lower respiratory tract (52.1%), urine (17.3%), and blood (14.2%). Rates of resistance to many of the antibiotics tested remained stable during the 12-year study period. Carbapenems were the most active drugs tested against most of the bacterial species. *E. coli* and *P. mirabilis* remained susceptible to most of the drugs tested. Mean rates of resistance to 9 of the 12 drugs tested increased with *Acinetobacter* spp. Rates of resistance to ciprofloxacin increased over the study period for most species. Ceftazidime was the only agent to which a number of species (*Acinetobacter* spp., *C. freundii*, *E. aerogenes*, *K. pneumoniae*, *P. aeruginosa*, and *S. marcescens*) became more susceptible. The prevalence of multidrug resistance, defined as resistance to at least one extended-spectrum cephalosporin, one aminoglycoside, and ciprofloxacin, increased substantially among ICU isolates of *Acinetobacter* spp., *P. aeruginosa*, *K. pneumoniae*, and *E. cloacae*.

Gram-negative bacilli (GNB) are a common cause of sepsis, pneumonia, urinary tract infections, and postsurgical infections in patients in acute care hospitals (14, 24). Antimicrobial resistance among GNB is increasing worldwide (21). This is a major public health problem and a cause for both substantial morbidity and mortality among hospitalized patients. A direct correlation has been shown between resistance of GNB and patient mortality, cost of patient care, and length of stay in the hospital (3, 22, 26, 28). The problem of GNB resistance is of particular concern in the intensive care unit (ICU) setting.

The most important determinant in the successful management of infections in patients in the ICU is prompt institution of effective empirical antimicrobial therapy; inappropriate empirical therapy affects both patient mortality rates and patient time spent in the ICU (12, 17). Optimizing empirical therapy requires knowledge of likely antimicrobial resistance patterns. With the aim of tracking resistance rates among GNB as the causes of infection in patients in U.S. ICUs, Merck Research Laboratories (Merck & Co., Upper Gwynedd, PA) established a multicenter laboratory-based surveillance program in 1993. Two previous reports from this investigation were published in 1996 and 2003 (13, 20). The current report describes the in vitro activity of 12 agents versus more than 74,000 GNB isolates recovered from ICU patients in multiple U.S. hospitals during the 12-year period from 1993 to 2004.

MATERIALS AND METHODS

Participating centers performed antimicrobial susceptibility testing with 100 consecutive nonduplicate aerobic GNB per study year collected from ICU patients with infections. Attempts were made to distribute enrolled hospitals evenly throughout the country according to average population and to represent both large and small academic institutions and community hospitals. The number of hospitals enrolled changed from year to year throughout the study. Over the 12-year period of this study, the participating centers numbered between 42 and 99, with an average of 70 per year, and represented 43 states and the District of Columbia. Careful consideration was given to the hospitals enrolled to ensure an even geographic distribution and to avoid potential skewing of the surveillance data.

Only isolates of presumed clinical significance, as determined by the individual hospitals, were included. Only the first isolate of a particular species per patient over the entire collection period was acceptable. Organisms were identified using the conventional methods employed at each hospital. Standardized susceptibility testing was performed by broth microdilution using commercially prepared microtiter panels specifically manufactured for this study (Microscan MKD MIC; Dade International Microscan, Sacramento, CA). This testing was performed in the clinical microbiology laboratories of participating institutions, and the results were maintained with a computerized database at Merck Research Laboratories. Categorization of susceptibility test results as susceptible, intermediate, or resistant was accomplished using the interpretive criteria of the Clinical and Laboratory Standards Institute (CLSI [2]). Antimicrobials tested included ampicillin, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanate, cefotaxime, ceftriaxone, ceftazidime, cefepime, imipenem, ertapenem, aztreonam, tobramycin, gentamicin, amikacin, and ciprofloxacin. Quality control testing was performed at each hospital by using the following quality

* Corresponding author. Mailing address: University of Iowa Hospitals and Clinics, Department of Pathology–6008 BT GH, 200 Hawkins Drive, Iowa City, IA 52242-1009. Phone: (319) 356-2104. Fax: (319) 356-4916. E-mail: shawn-lockhart@uiowa.edu.
▽ Published ahead of print on 22 August 2007.

control strains: *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, and *Klebsiella pneumoniae* ATCC 700603.

For purposes of analysis, data were grouped into four 3-year blocks: 1993 to 1995, 1996 to 1998, 1999 to 2001, and 2002 to 2004. For each 3-year block, the MICs at which 50% (MIC_{50}) and 90% (MIC_{90}) and the percentages of intermediate and resistant values for each major GNB species group were calculated.

Fluoroquinolone usage data in the U.S. (prescriptions per month) were obtained from the IMS Health NSP database for the years 1999 to 2004 and were expressed as patient days of therapy (PDOT) for each of these years. Fluoroquinolone usage levels and fluoroquinolone resistance rates for each year of the study were compared using SAS version 9.1.3 software.

RESULTS

Organisms characterized. The mean number of isolates characterized by each hospital per year was 91 (range, 11 to 458). A total of 74,394 isolates were characterized between 1993 and 2004 (Table 1). The organisms most frequently isolated were *P. aeruginosa* (22.2%), *E. coli* (18.8%), *K. pneumoniae* (14.2%), *Enterobacter cloacae* (9.1%), *Acinetobacter* spp. (6.2%), *Serratia marcescens* (5.5%), *Enterobacter aerogenes* (4.4%), *Stenotrophomonas maltophilia* (4.3%), *Proteus mirabilis* (4.0%), *Klebsiella oxytoca* (2.7%) and *Citrobacter freundii* (2.0%). These 11 species accounted for 93.4% of the total number of isolates. The respiratory tract (52.1%), urine (17.3%), and blood cultures (14.2%) were the sources of ca. 84% of isolates. *P. aeruginosa* was the organism most frequently isolated in the respiratory tract (26.9%), while *E. coli* was most frequently isolated from both urine (42.4%) and blood (23.9%). Respiratory tract specimens were the most common sources of isolates for each of the species listed in Table 1, with the exception of *E. coli*, for which urine isolates were predominant.

Antimicrobial susceptibility. The antimicrobials tested and the percentages of isolates determined to be intermediate and resistant are listed in Table 2. Because resistance rates remained relatively constant over the 12-year period of this survey, only results for the most recent 3-year period, 2002 to 2004, are represented in Table 2. Furthermore, data were provided for 10 of the 11 most frequently isolated species. Since the CLSI provides limited interpretive breakpoints for *S. maltophilia*, this species was not included in Table 2.

Imipenem was consistently the most active agent among those tested. Eighty-two percent of *P. aeruginosa* and 88% of *Acinetobacter* spp. were susceptible to imipenem. Among the members of the family *Enterobacteriaceae* tested, more than 98% were susceptible to imipenem. Ertapenem was also nearly uniformly active against the *Enterobacteriaceae* with 95% of isolates susceptible. Among *Acinetobacter* spp. isolates, 77.2% were susceptible to ceftazidime and 71.1% were susceptible to amikacin. Ceftazidime and amikacin were also among the agents most active against *P. aeruginosa*. Ceftazidime, ceftriaxone, cefepime, piperacillin-tazobactam, imipenem, ertapenem, aztreonam, tobramycin, and amikacin all remained very active against *E. coli*, with mean resistance rates below 5%. Piperacillin (10.5%) and ciprofloxacin (15%) were the least active of the agents tested versus *P. mirabilis.*

Ampicillin-sulbactam, in general, had the highest resistance rates among all of the agents tested. Exceptions included piperacillin, which had higher resistance rates with *K. pneumoniae* and *K. oxytoca* and *Acinetobacter* spp., which had higher resistance rates to all of the β-lactam class antibiotics tested except ceftazidime, compared to that of ampicillin-sulbactam.

Changes in antimicrobial susceptibility. In general, resistance profiles remained relatively stable over the course of this study for most organism-antimicrobial combinations. Table 3 lists those combinations for which there was a discernible change over time. The data in Table 3 were predicated for all isolates of a species regardless of specimen type. The trends depicted in Table 3 were also observed when this analysis was restricted to bloodstream isolates.

As seen in Table 3, resistance rates with *Acinetobacter* spp. have increased over the 12-year period of this study, with 9 of the 12 antibiotics tested (i.e., ampicillin-sulbactam, ceftriaxone, cefepime, piperacillin, piperacillin-tazobactam, imipenem, tobramycin, amikacin, and ciprofloxacin). Interestingly, ceftazidime resistance rates with *Acinetobacter* spp. dropped from 23.9% to 14.6% over the study period. There was also a notable decline in ceftazidime resistance for *C. freundii*, *E. aerogenes*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, and *S. marcescens*.

Ciprofloxacin resistance rates increased with several species. The most dramatic change was observed for *Acinetobacter* spp., for which the percentage of susceptible strains dropped from 61.5% to 35.2% over the period of the study. Decreases in the percentage of isolates susceptible to ciprofloxacin were also seen with *P. aeruginosa* (83.2% to 66.3%), *E. coli* (98.9% to 82.5%), *C. freundii* (88% to 73.9%), *P. mirabilis* (96.4% to 82.9%), *E. cloacae* (93.5% to 85.9%), and *K. pneumoniae* (89% to 81.8%). Although piperacillin susceptibility decreased with *Acinetobacter* spp., it increased with both *E. aerogenes* (65.5% to 77.9%) and *K. pneumoniae* (34.3% to 54.3%).

Rates of resistance to tobramycin increased with a number of species. Over the 12-year study period, tobramycin resistance rates more than doubled with *P. aeruginosa*, *E. coli*, *C. freundii*, and *Acinetobacter* spp. Changes in imipenem resistance rates were species dependent. Resistance rates increased with both *P. aeruginosa* and *Acinetobacter* spp. but decreased with both *S. marcescens* and *P. mirabilis* to the extent that both species were nearly uniformly susceptible during the last study period. The activity profiles of both aztreonam and piperacillin-tazobactam remained nearly constant during the period of this survey. Only *C. freundii* showed an increase in resistance to ertapenem during the study period.

The trend toward multidrug resistance. Multidrug resistance was monitored for a number of species in the first year (1993) and the last year (2004) of the study period (Table 4). Multidrug resistance was defined as resistance to one or more of the extended-spectrum cephalosporins (ceftazidime, ceftriaxone, or cefotaxime), one of two aminoglycosides (amikacin or tobramycin), and ciprofloxacin. There was a greater than fourfold increase in multidrug resistance rates with *Acinetobacter* spp. during the study period and a more than fivefold increase in multidrug resistance with *P. aeruginosa*. Approximate twofold increases in multidrug resistance rates were seen with *C. freundii*, *E. cloacae*, and *K. pneumoniae*. Whereas not a single multidrug-resistant isolate was seen among 724 *E. coli* isolates from 1993, 2% of the 800 *E. coli* isolates from 2004 were multidrug resistant.

Antimicrobial usage data for fluoroquinolones. Annual usage levels of fluoroquinolones increased substantially over the

TABLE 1. Isolates characterized between 1993 and 2004

Organisms most frequently isolated	Total no. isolated (n = 74,394)	No. of isolates															
		1993–1995				1996–1998				1999–2001				2002–2004			
		Respiratory tract	Urine	Blood-stream infection	Other sources[c]	Respiratory tract	Urine	Blood-stream infection	Other sources	Respiratory tract	Urine	Blood-stream infection	Other sources	Respiratory tract	Urine	Blood-stream infection	Other sources
Pseudomonas aeruginosa	16,482	1,887	366	266	488	3,094	569	458	755	3,144	591	528	786	2,287	387	387	489
Escherichia coli	13,961	803	946	415	595	946	1,560	662	792	917	1,799	911	741	684	1,147	546	497
Klebsiella pneumoniae	10,571	996	354	300	350	1,571	506	490	486	1,527	612	642	481	1,121	442	407	286
Enterobacter cloacae	6,779	796	139	232	304	1,162	125	276	406	1,017	183	350	349	783	138	282	237
Acinetobacter spp.[a]	4,642	548	62	128	125	927	45	193	157	858	57	212	153	786	57	208	126
Serratia marcescens	4,112	453	60	74	88	910	41	169	132	844	68	192	164	621	54	133	109
Enterobacter aerogenes	3,307	523	77	86	111	726	85	82	141	614	85	102	112	360	58	62	83
Proteus mirabilis	3,011	272	138	68	134	354	269	102	190	326	248	173	176	216	149	91	105
Klebsiella oxytoca	2,018	240	72	44	89	316	70	78	90	294	82	106	87	234	55	88	73
Citrobacter freundii	1,483	153	59	48	100	212	97	47	116	163	97	59	98	83	75	32	44
All other species[b]	8,028	966	182	159	320	1,654	250	225	435	1,423	225	284	359	931	171	193	251

[a] Includes *Acinetobacter baumannii*, *Acinetobacter* spp. nosocomial (NOS), *Acinetobacter calcoaceticus*, *Acinetobacter anitratus*, *Acinetobacter lwoffii*, and *Acinetobacter junii*.

[b] Other species (number of isolates) include *Achromobacter* group VD (1), *Actinobacillus actinomycetemcomitans* (1), *Actinobacillus ureae* (1), *Aeromonas caviae* (2), *Aeromonas hydrophila* (79), *Aeromonas schubertii* (1), *Aeromonas sobria* (6), nosocomial (NOS) *Aeromonas* spp. (13), *Agrobacterium tumefaciens* (5), *Alcaligenes denitrificans* (1), *Alcaligenes faecalis* (27), *Alcaligenes odorans* (3), NOS *Alcaligenes* spp. (29), *Alcaligenes xylosoxidans* (335), *Bacteroides vulgatus* (1), *Bordetella bronchiseptica* (10), *Budvicia aquatica* (1), *Brevundimonas vesicularis* (3), *Burkholderia cepacia* (195), *Burkholderia gladioli* (3), *Burkholderia picketii* (1), NOS *Burkholderia* spp. (1), *Campylobacter jejuni* (1), NOS *Capnocytophaga* spp. (1), *Cedecea davisae* (5), NOS *Cedecea* spp. (3), *Chromobacterium violaceum* (3), *Chryseobacterium gleum* (4), *Chryseobacterium indologenes* (7), *Chryseobacterium meningosepti* (15), NOS *Chryseobacterium* spp. (5), *Chryseomonas luteola* (7), *Citrobacter amalonaticus* (96), *Citrobacter braakii* (34), *Citrobacter farmeri* (1), *Citrobacter indologenes* (2), *Citrobacter koseri* (734), NOS *Citrobacter* spp. (71), *Citrobacter youngae* (7), *Citrobacter werkmanii* (1), *Comamonas acidovorans* (13), NOS *Comamonas* spp. (3), *Comamonas testosteroni* (1), *Edwardsiella tarda* (3), *Enterobacter amnigenus* (23), *Enterobacter asburiae* (45), *Enterobacter cancerogenus* (33), *Enterobacter gergoviae* (32), *Enterobacter hormachei* (4), *Enterobacter intermedius* (12), *Enterobacter sakazakii* (65), NOS *Enterobacter* spp. (200), *Escherichia fergusonii* (11), *Escherichia hermanii* (7), NOS *Escherichia* spp. (2), *Escherichia vulneris* (3), *Flavimonas oryzihabitans* (14), *Flavobacterium breve* (3), *Flavobacterium indologenes* (18), *Flavobacterium meningosepticum* (33), *Flavobacterium odoratum* (6), NOS *Flavobacterium* spp. (23), NOS *Fusobacterium* spp. (1), *Haemophilus influenzae* (6), *Haemophilus parainfluenzae* (1), NOS *Haemophilus* spp. (1), *Hafnia alvei* (102), *Klebsiella ornithinolytica* (27), NOS *Klebsiella* spp. (65), *Klebsiella terrigena* (2), *Kluyvera ascorbate* (8), NOS *Kluyvera* spp. (9), *Leclercia adecarboxylata* (6), NOS *Leminorella* spp. (1), *Moraxella catarrhalis* (14), *Moraxella osloensis* (1), *Moraxella phenylpyruvica* (1), NOS *Moraxella* spp. (5), *Morganella morganii* (744), *Ochrobacterium anthropi* (6), *Pantoea agglomerans* (133), NOS *Pantoea* spp. (2), *Pasteurella multocida* (12), NOS *Pasteurella* spp. (1), *Plesiomonas shigelloides* (4), *Proteus penneri* (30), NOS *Proteus* spp. (14), *Proteus vulgaris* (191), *Providencia alcalifaciens* (1), *Providencia rettgeri* (81), *Providencia rustigianii* (1), NOS *Providencia* spp. (3), *Providencia stuartii* (319), *Pseudomonas alcaligenes* (7), *Pseudomonas fluorescens* (181), *Pseudomonas mendocina* (8), *Pseudomonas paucimobilis* (4), *Pseudomonas pseudoalcaligenes* (1), *Pseudomonas putida* (48), NOS *Pseudomonas* spp. (81), *Pseudomonas stutzeri* (45), *Rahnella aquatilis* (3), *Ralstonia picketii* (8), NOS *Roseomonas* spp. (1), *Salmonella choleraesuis* (3), *Salmonella enteritidis* (20), *Salmonella hadar* (1), *Salmonella montevideo* (1), NOS *Salmonella* spp. (46), *Salmonella enterica* serovar Typhimurium (6), *Serratia ficaria* (1), *Serratia fonticola* (23), *Serratia liquefaciens* (91), *Serratia odorans* (5), *Serratia odorifera* (20), *Serratia plymuthica* (14), *Serratia rubidaea* (18), NOS *Serratia* spp. (54), *Shewanella putrefaciens* (6), *Shigella sonnei* (4), NOS *Shigella* spp. (2), NOS *Sphingobacterium* spp. (1), *Sphingomonas paucimobilis* (4), *Stenotrophomonas maltophilia* (3,217), *Vibrio fluvialis* (1), *Vibrio vulnificus* (3), and *Yersinia enterocolitica* (4).

[c] Including abdomen, abscess, aorta, appendix, aspirate, bile, bone, bowel, biliary, colon, cerebral spinal fluid, drainage, eye, gastrointestinal, graft, gall bladder, kidney, liver, mandible, nasal cavities, mouth, pancreas, pelvis, perineum, peritoneum, pericardium, spleen, throat, unknown, and wound.

TABLE 2. Resistance rates for the 10 most frequently isolated GNB from 2002 to 2004[a]

GNB and source	% of isolates (%I/%R)											
	Ampicillin-sulbactam	Ceftriaxone	Ceftazidime	Cefepime	Piperacillin	Piperacillin-tazobactam	Imipenem	Ertapenem	Aztreonam	Tobramycin	Amikacin	Ciprofloxacin
P. aeruginosa												
Respiratory tract		34.9/48.6	6.5/4.6	14.6/13.0	NA/15.9	NA/13.7	3.5/14.9		15.7/18.5	1.8/13.5	6.9/3.5	5.7/27.4
Urine		35.4/48.1	4.1/3.1	16.0/12.9	NA/11.8	NA/14.0	3.1/13.4		17.1/17.3	2.1/17.8	7.8/4.7	2.1/41.9
Bloodstream infection		42.9/41.3	5.9/5.4	15.3/8.8	NA/18.9	NA/10.9	5.9/14.7		12.4/15.0	1.3/15.8	6.0/3.9	3.1/28.4
All		35.9/48.0	6.3/4.5	14.5/12.5	NA/16.0	NA/13.2	3.8/14.5		15.1/17.8	1.8/13.7	6.9/3.5	4.8/28.9
E. coli												
Respiratory tract	13.9/32.3	1.9/5.0	1.3/1.9	0.9/3.5	5.0/35.0	2.9/6.6	0/0	0.3/0.9	0.9/6.0	3.4/8.9	1.5/1.2	0.4/18.6
Urine	12.7/25.9	1.7/3.1	0.9/1.1	0.5/1.8	3.8/33.8	2.3/3.8	0.2/0.3	0.2/1.0	1.0/4.1	2.9/6.0	0.4/0.4	0.2/16.3
Bloodstream infection	14.1/35.4	2.8/2.9	0.9/1.8	0.4/1.8	5.6/41.9	4.0/3.9	0/0	0.6/0.6	1.8/3.5	3.5/7.1	0.7/1.3	0.2/16.3
All	13.5/30.0	2.1/4.6	1.2/1.6	0.5/2.5	4.3/36.3	2.8/4.8	0.1/0.2	0.4/0.9	1.2/4.6	3.3/7.1	0.7/0.9	0.2/17.3
K. pneumoniae												
Respiratory tract	8.2/22.9	4.8/11.7	0.7/4.1	2.1/8.1	19.9/24.9	4.3/11.8	0.7/0.7	0.2/3.5	1.1/15.7	2.2/15.2	5.4/3.4	1.6/16.8
Urine	8.6/21.3	4.3/10.4	1.4/2.9	1.6/6.6	16.2/31.8	5.0/7.5	0.5/0.2	0/2.0	1.1/13.1	2.3/13.6	3.4/2.3	1.1/16.1
Bloodstream infection	7.6/26.8	4.7/13.8	1.0/4.7	1.5/9.3	13.7/36.7	3.7/13.0	1.5/1.5	0.3/5.2	0.7/16.7	3.9/17.0	5.7/3.7	1.5/18.2
All	8.2/23.6	4.7/11.8	0.8/3.8	1.8/8.1	17.0/28.7	4.0/11.8	1.0/0.7	0.2/3.7	0.9/15.6	2.5/15.1	5.1/3.1	1.4/16.8
E. cloacae												
Respiratory tract	19.0/61.6	8.6/26.1	2.6/11.0	4.0/9.3	5.2/31.7	11.6/14.6	0.6/0.4	2.0/2.7	4.7/27.5	2.9/10.6	1.7/1.4	2.2/12.0
Urine	20.3/50.7	8.7/36.2	2.2/12.3	5.8/11.6	10.9/34.8	13.1/20.3	0/0	1.5/2.9	13.0/23.2	2.9/13.8	2.2/2.2	2.9/14.5
Bloodstream infection	16.7/62.4	10.3/30.1	3.6/13.5	2.8/16.0	6.9/46.0	13.1/17.7	0/0	3.6/0.7	5.0/33.7	2.5/13.1	1.8/2.1	1.4/12.1
All	18.5/62.5	8.9/28.7	2.7/11.7	4.0/10.8	6.1/35.1	12.6/16.2	0.4/0.3	2.3/2.3	5.0/30.1	3.1/11.1	1.6/1.5	1.7/12.4
Acinetobacter spp.												
Respiratory tract	7.6/31.6	16.4/53.2	7.4/13.4	13.7/46.6	11.4/50.4	16.9/35.8	6.4/4.8		22.8/60.6	4.6/28.5	5.2/21.9	1.4/61.5
Urine	10.5/29.8	17.5/68.4	10.5/22.8	17.5/54.4	11.1/66.7	26.3/33.3	1.8/8.8		14.0/75.4	3.5/36.8	5.3/31.6	0/74.5
Bloodstream infection	7.7/39.4	15.4/56.7	10.6/15.9	15.4/51.4	6.1/54.6	17.3/38.9	9.1/4.3		16.4/67.3	3.9/33.3	2.9/26.9	0.5/63.5
All	8.1/33.2	16.2/56.2	8.2/14.6	14.2/49.0	10.9/52.4	17.9/36.9	6.9/5.2		20.7/63.9	5.2/30.3	5.0/23.9	1.0/63.8
S. marcescens												
Respiratory tract	12.7/81.0	5.6/4.7	2.1/2.3	1.5/4.4	7.1/9.0	5.3/6.8	0.2/0.5	1.0/1.3	2.1/7.6	4.7/6.4	0.6/0.3	3.7/6.6
Urine	14.8/72.2	7.4/7.4	3.7/3.7	1.9/5.6	9.5/23.8	3.7/5.6	0/1.9	0/3.7	1.9/13.0	9.3/16.7	5.6/3.7	3.7/11.1
Bloodstream infection	18.8/76.7	6.0/2.3	2.3/0	2.3/2.3	2.5/15.0	6.0/9.0	0/1.5	0.8/0	3.0/7.5	6.8/9.8	1.5/2.3	3.8/1.5
All	14.0/79.6	5.7/4.5	2.2/1.9	1.4/4.0	6.6/10.9	5.5/7.2	0.1/0.7	0.8/1.3	2.5/17.8	5.8/7.1	1.1/0.8	3.7/6.1
E. aerogenes												
Respiratory tract	25.6/34.4	13.6/2.8	4.2/3.6	1.1/0.8	9.4/6.8	9.2/2.2	0.6/0	0.6/2.5	7.2/4.7	0.6/0.8	0.6/0.3	0.6/1.9
Urine	20.7/42.0	10.3/6.9	8.6/5.2	0/3.5	11.8/17.7	12.1/5.2	1.7/0	0/1.7	6.9/10.4	0/5.2	0/3.5	3.5/8.6
Bloodstream infection	19.4/48.4	25.8/1.6	11.3/4.8	0/0	21.1/15.8	17.7/3.2	0/0	0/0	12.9/8.1	1.6/0	0/0	1.6/4.8
All	22.9/38.9	15.6/4.3	5.9/4.6	1.2/1.5	11.3/10.8	11.4/3.4	1.1/0	0.4/2.8	8.4/7.1	0.7/1.8	1.2/0.5	1.1/3.5
P. mirabilis												
Respiratory tract	6.0/2.8	6.0/2.8	0.5/0.5	1.4/0.9	1.4/8.1	0.9/0.5	0.5/0	0/0.9	0/2.3	3.2/2.3	0.9/0.5	0.9/13.4
Urine	7.4/8.7	0/0.7	8.6/5.2	1.3/1.3	5.0/15.0	0/1.5	0/0	0/0.7	0/2.7	4.0/3.4	0.7/0	3.4/19.5
Bloodstream infection	6.7/7.7	1.1/0	0/1.1	0/2.2	0/14.7	1.1/1.1	1.1/0	0/1.1	0/1.1	3.3/4.4	0/0	3.3/12.1
All	7.5/5.3	1.2/0.4	0.5/0.5	0.9/1.4	2.1/10.5	0.7/0.7	0.7/0	0/0.7	0/2.1	3.0/3.6	0.5/0.2	2.1/15.0
K. oxytoca												
Respiratory tract	22.2/12.4	3.9/4.3	1.3/0.4	1.3/2.1	41.2/24.7	3.4/6.4	0/0	0/1.3	0.4/7.7	1.3/4.7	0/0.4	0.4/3.9
Urine	21.8/29.1	5.5/14.6	1.8/3.6	1.8/5.5	20.0/40.0	0/18.2	0/0	0/0	1.8/23.6	5.5/12.7	0/0	1.8/10.9
Bloodstream infection	19.3/25.0	6.8/8.0	0/1.1	1.1/0	10.0/40.0	4.6/10.2	0/0	0/1.1	2.3/13.6	5.7/6.8	2.3/0	2.3/4.6
All	19.8/17.6	4.9/6.0	0.9/1.1	1.1/2.0	32.9/27.0	3.3/8.7	0/0	0/1.1	0.9/11.3	2.9/6.0	0.4/0.4	0.9/6.0
C. freundii												
Respiratory tract	10.8/57.8	20.5/30.1	1.2/14.5	2.4/6.0	6.7/36.7	21.7/16.9	0/0	1.2/3.6	9.6/36.1	1.2/27.7	4.8/9.6	7.2/24.21
Urine	13.3/48.0	14.7/28.0	6.7/6.7	4.0/12.0	4.6/22.7	14.7/13.3	0/0	0/4.0	5.3/32.0	1.3/21.3	4.0/4.0	1.3/20.0
Bloodstream infection	12.5/43.8	12.5/15.6	3.1/15.6	0/0	7.7/46.2	9.4/9.4	0/0	0/3.1	9.4/28.1	6.3/28.1	3.1/0	3.1/18.8
All	12.8/53.4	18.8/25.2	3.9/15.0	2.6/6.8	10.5/37.2	15.4/13.7	0/0	0.4/3.9	9.0/31.6	3.9/23.1	4.7/5.1	4.7/21.4

[a] I, intermediate; R, resistant. NA, not available.

period of this study. For example, in 1999, there were 11,267 PDOT in the U.S.; in 2004, there were 18,898 PDOT. When fluoroquinolone resistance rates were compared to levels of fluoroquinolone usage, several statistically significant associations were elucidated (Table 5). The three strongest associations were observed with fluoroquinolone resistance in *E. coli* and both total fluoroquinolone use and use of levofloxacin and fluoroquinolone resistance in *P. aeruginosa* and total fluoro-

TABLE 3. Trends in antimicrobial resistance among various GNB between 1993 and 2004[a]

Organism	Antimicrobial	% of isolates (%I/%R)				Trend[b]
		1993–1995	1996–1998	1999–2001	2002–2004	
Pseudomonas aeruginosa	Ceftazidime	5.6/9.9	5.6/12	5.2/14.2	6.3/4.5	↓
	Imipenem	4.5/10.6	3.5/11.1	3.6/13.7	3.8/14.5	↑
	Tobramycin	0.9/7.8	1.5/9.6	0.4/13.3	1.8/13.7	↑
	Ciprofloxacin	5.6/11.2	5.7/17.6	5.4/25.1	4.8/28.9	↑
Escherichia coli	Ampicillin-sulbactam	10/22.9	10.8/26.4	10.3/28.6	13.5/30	↑
	Ceftriaxone	0.8/1	1.3/2.3	1.6/2.7	2.1/4.6	↑
	Tobramycin	0.9/1.5	0.1/2.9	1/4.6	3.3/7.1	↑
	Ciprofloxacin	0.2/0.9	0.4/3.9	0.4/8.3	0.2/17.3	↑
Klebsiella pneumoniae	Ceftazidime	0.6/12.7	1.4/13.5	1/10.8	0.8/3.8	↓
	Piperacillin	27.4/38.3	22.3/36.9	22.1/37.4	17/28.7	↓
	Ciprofloxacin	3.1/7.9	3.4/9.7	1.8/10.5	1.4/16.8	↑
Enterobacter cloacae	Ceftazidime	3.9/36	4.2/33.8	3.6/30.4	2.7/11.7	↓
	Ciprofloxacin	2.5/5	2.9/7.6	2.1/10.9	1.7/12.4	↑
Acinetobacter spp.	Ampicillin-sulbactam	6/18.2	9.3/22	7.5/25.5	8.1/33.2	↑
	Ceftriaxone	25/30.1	21.3/43	16.3/51.7	16.2/56.2	↑
	Ceftazidime	10.1/23.9	8.7/36.8	8/45.2	8.2/14.6	↓
	Cefepime		13.7/31.6	15.5/37.7	14.2/49	↑
	Piperacillin	18.9/31.4	16.4/40.3	14.8/49.1	10.9/52.4	↑
	Piperacillin-tazobactam		22.4/18.4	20.1/26.7	17.9/36.9	↑
	Imipenem	2.1/2	4.4/2.1	6.6/5.6	6.9/5.2	↑
	Tobramycin	7.8/13	7/24.5	5.8/30.4	5.2/30.3	↑
	Amikacin	3.7/5.7	3.9/13.4	4.1/19.2	5/23.9	↑
	Ciprofloxacin	2.6/35.9	3/49.4	1.9/57.1	1/63.8	↑
Serratia marcescens	Ceftazidime	1.8/8.4	3.5/11.6	2.5/10.7	2.2/1.9	↓
	Imipenem	2.8/3.6	1.5/1.8	0.7/1.3	0.1/0.7	↓
Enterobacter aerogenes	Ceftazidime	6.3/23.8	3/24.7	3.5/22.7	5.9/4.6	↓
	Piperacillin	12.5/22	15.8/17.1	11.5/19.5	11.3/10.8	↓
Proteus mirabilis	Imipenem	7.7/3.4	2.8/1.2	1.1/1.2	0.7/0	↓
	Ciprofloxacin	0.3/3.3	2.1/7.8	0.1/13.1	2.1/15	↑
Klebsiella oxytoca	Cefepime		0.9/3.4	1.9/5.1	1.1/2	↓
Citrobacter freundii	Ceftazidime	1.9/43.6	1.5/47	3.1/38.9	3.9/15	↓
	Ertapenem			1.4/1.7	0.4/3.9	↑
	Tobramycin	2.2/10.8	5.3/12.7	3.4/12.7	3.9/23.1	↑
	Ciprofloxacin	2.8/9.2	4.7/14.4	3.4/14.9	4.7/21.4	↑

[a] I, intermediate; R, resistant.
[b] Increase (↑) or decrease (↓) in resistance in the 12-year study period.

quinolone use. In general, when levofloxacin was examined individually, its use was more strongly associated with fluoroquinolone resistance than the use of ciprofloxacin, gatifloxacin, or moxifloxacin.

TABLE 4. Longitudinal increase in multidrug resistance

Organism	1993		2004	
	No. of MDR isolates/total no. of isolates[a]	% of MDR isolates	No. of MDR isolates/total no. of isolates	% of MDR isolates
Pseudomonas aeruginosa	13/769	1.7	93/1,004	9.3
Escherichia coli	0/724	0	16/808	2.0
Klebsiella pneumoniae	26/513	5.1	84/633	13.3
Enterobacter cloacae	13/397	3.3	24/406	5.9
Acinetobacter spp.	19/285	6.7	101/338	29.9
Enterobacter aerogenes	6/213	2.8	0/154	0
Proteus mirabilis	1/174	0.6	1/142	0.7
Citrobacter freundii	5/95	5.3	7/63	11.1

[a] Multidrug resistances is defined here as being resistant to one or more extended-generation cephalosporins (ceftazidime, ceftriaxone, or cefotaxime), one or more aminoglycosides (amikacin or tobramycin), and the fluoroquinolone ciprofloxacin. MDR, multidrug resistant.

DISCUSSION

We assessed trends in the development of antimicrobial resistance among GNB recovered from ICU patients with infections in U.S. hospitals between 1993 and 2004. Surprisingly, antimicrobial resistance rates remained relatively constant for the majority of the organism-antimicrobial combinations examined in this study. In general, carbapenems continue to be the most active agents versus GNB in U.S. ICUs. For example, imipenem resistance rates with the *Enterobacteriaceae* remained at levels of 1% or less throughout the 12-year period of this survey. These observations are consistent with the results of other recent surveillance studies from U.S. hospitals (5, 8, 27, 29).

Rhomberg and Jones (27) reported that despite consistent carbapenem susceptibility rates, "MIC creep" was occurring with carbapenems versus selected GNB, especially in the New York City area. Most of this change was thought to be the result of carbapenemase-producing strains of *K. pneumoniae.* With the exception of *Acinetobacter* spp., imipenem MIC_{50} values for the isolates characterized in our study either remained the same between 1993 and 2004 or decreased twofold (e.g., *E. aerogenes*, *P. aeruginosa*, and *S. marcescens*, for which

TABLE 5. Fluoroquinolones usage levels between 1999 and 2004 and antimicrobial resistance among GNB between 1999 and 2004[a]

Organism	R^2 values for fluoroquinolone resistance compared to that of antimicrobials shown				
	J01M	Levofloxacin	Ciprofloxacin	Gatifloxacin	Moxifloxacin
P. aeruginosa	0.7352	0.6624	0.1806	0.6473	0.1588
E. coli	0.7552	0.7262	0.5846	0.5099	0.6468
K. pneumoniae	0.5544	0.6193	0.6135	0.1816	0.07451
E. cloacae	0.5048	0.5852	0.0968	0.2224	0.0173
Acinetobacter spp.	0.5844	0.6724	0.6602	0.1976	0.6711
S. marcescens	0.1758	0.1212	0.4336	0.2023	0.566
E. aerogenes	0.0914	−0.0338	−0.1401	0.3243	−0.1359
P. mirabilis	0.0556	0.1484	0.0879	−0.1876	0.2782
K. oxytoca	−0.0721	−0.1682	−0.0307	0.0415	0.2849
C. freundii	0.4462	0.2455	0.1463	0.6528	0.3016

[a] Adjusted linear regression values comparing antimicrobial usage levels of fluoroquinolones in the United States between 1999 and 2004 and rates of antimicrobial resistance among GNB between 1999 and 2004. J01M, antimicrobial class of fluoroquinolones.

MIC_{50} values decreased from ≥2 μg/ml in 1993 to 1996 to ≥1 μg/ml in 2001 to 2004). In other words, carbapenem "MIC creep" was not observed for the current study. Because of the large number of hospitals involved in this study, our low rates of carbapenem resistance likely reflect the average rate of resistance nationwide and would not be influenced by regions, such as New York City, where carbapenem resistance rates might be considerably higher.

Amikacin was broadly active against the *Enterobacteriaceae* and *P. aeruginosa* in our study, but 24% of *Acinetobacter* spp. were noted to be nonsusceptible. These observations are similar to those of Neuhauser et al. (20); however, as opposed to their study, which reported essentially comparable activity profiles for amikacin and imipenem, we noted superior activity with imipenem versus amikacin for all study isolates except *P. aeruginosa*, where the reverse was true.

One of the most important observations from our study was the consistent downward trend in ciprofloxacin activity versus GNB from patients in U.S. ICUs over the period from 1993 to 2004. This was noted with 7 of the 10 organisms surveyed. *E. coli* went from almost universal susceptibility in 1993 (i.e., 0.9% resistance) to 17.3% resistance in 2004. Although ciprofloxacin resistance with *E. coli* has been reported previously (8, 11, 19, 27), the high resistance rates noted at the end of our study are truly alarming. This trend was not as apparent in a previous analysis of the 1994-to-2000 data set (20).

Fluoroquinolone resistance has been observed frequently for extended-spectrum β-lactamase-producing strains of *E. coli* and *K. pneumoniae* (18). Given the manner in which isolates were characterized in our study, we were are not able to reliably assess extended-spectrum β-lactamase production; however, we observed only a twofold increase in ciprofloxacin resistance rates for *K. pneumoniae* isolates between that of the first 3-year period of this study and the last (i.e., 7.9% to 16.8%). When the data from 2004 alone were analyzed, little correlation between ciprofloxacin resistance and multidrug resistance was observed for *E. coli*, i.e., only 16% of ciprofloxacin-resistant isolates were also found to be multidrug resistant. Among other *Enterobacteriaceae* species, there was a twofold increase in ciprofloxacin resistance with *C. freundii* and *E. cloacae* and a fourfold increase with *P. mirabilis*. *Acinetobacter* spp. (64%) and *P. aeruginosa* (29%) strains exhibited the highest levels of ciprofloxacin resistance. These rates are similar to those reported in the MYSTIC study between 2002 and 2004 from a worldwide collection of isolates (29).

Several studies have linked fluoroquinolone resistance to fluoroquinolone usage (16, 20). As reported previously, overall fluoroquinolone usage is strongly linked to the emergence of fluoroquinolone resistance among GNB, and once established, resistance rates increase with increased usage. This relationship was also apparent in our study. Of particular interest, however, was the seemingly disproportionate effect of individual fluoroquinolones as drivers of resistance. Specifically, levofloxacin usage was much more strongly associated with fluoroquinolone resistance than the usage of ciprofloxacin, gatifloxacin, or moxifloxacin. With respect to potency versus GNB, ciprofloxacin is more potent than levofloxacin, and gatifloxacin and moxifloxacin are less potent still. Intuitively, the use of less potent agents within an antimicrobial family would seemingly be more likely to promote resistance than the use of more potent agents. It may also be that when the potency of specific agents drops to low enough levels, selective pressure also diminishes.

The increasing prevalence of multidrug-resistant GNB in U.S. ICUs is also disturbing. D'Agata previously noted a substantial increase in multidrug resistance among GNB in one tertiary care hospital between 1994 and 2000 (4). In that study, the most common profile was resistance to an aminoglycoside, an extended-spectrum cephalosporin, and to ciprofloxacin. We employed the same definition of multidrug resistance and observed a substantial increase in multidrug resistance over the 12-year study period of our survey with *C. freundii*, *E. cloacae*, and *K. pneumoniae*. While the overall percentage of multidrug-resistant *E. coli* isolates in 2004 was small (2%), it represented a significant increase over that of 1993 when no such isolates were recovered. This trend toward increasing rates of multidrug-resistant GNB has also been observed for several other studies of more limited scope than ours (9, 15, 23, 25, 31).

We noted a surprising trend toward increasing susceptibility to ceftazidime with *Acinetobacter* species, *C. freundii*, *E. aerogenes*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, and *S. marcescens*. We could find no other reports of a similar trend in the literature. Friedland and colleagues (8) noted that between 1995 and 2000, ceftazidime resistance of *Enterobacter* spp. had stabilized and had only slightly increased for *K. pneumoniae* and *E. coli*. Fridkin et al. (7) reported similar results over a

shorter time frame (1996 to 1999) in the ICARE surveillance study. In the NNIS surveillance study (10), ceftazidime resistance of *Acinetobacter* spp. and of *P. aeruginosa* was noted to increase over the same period of time examined in our study. We are uncertain of the reason for this discrepancy since both the NNIS study and our investigation were predicated on GNB isolates from patients in the ICU. One important difference between these two studies is that the NNIS program is based on passive reporting of susceptibility test results from participating laboratories. As a result, the data were generally derived from various different automated susceptibility test systems which happen to be in place in the routine clinical microbiology laboratories of participating centers. In contrast, the data in our study were based on the performance of reference standard broth microdilution MIC determinations that had been subjected to rigorous quality controls. If ceftazidime resistance is indeed becoming less common, it may reflect diminished usage of this relatively older extended-spectrum cephalosporin in favor of more recently introduced and more potent parenteral β-lactam agents. Several recent studies have demonstrated that decreased use of ceftazidime results in decreased ceftazidime resistance among GNB in the hospital setting (1, 6, 30).

Our investigation has certain limitations. Although an attempt was made to restrict testing to GNB of clinical significance, in some cases, especially with isolates from the respiratory tract and urine specimens, it was impossible to know that this objective was achieved. We do not believe, however, that this was a major shortcoming, since resistance rates calculated from isolates recovered exclusively from blood cultures were essentially identical to rates derived from isolates from other sites. Second, patient demographic information, such as age, gender, primary source of infection, and individual antibiotic histories, was not available to us, and as a result, no analysis could be performed that could take these important factors into account. Third, test isolates were not routinely available to us for ancillary molecular characterization of either resistance determinants or clonal relationships. Finally, antimicrobial usage data were available only as patient days of therapy based on prescriptions for the entire country. No regional or individual hospital data for antimicrobial consumption were available for analysis. Not withstanding these shortcomings, it is believed that this study provides a unique, objective, and systematic view of the scope and magnitude of the problem of antimicrobial resistance among GNB in ICU patients today in the United States. The longitudinal length of this study and the sheer number of isolates analyzed by a single methodology give a unique look at the magnitude and scope of the current trend in drug resistance among GNB. We were able to show that while drug resistance has become a serious problem with some antibiotics, especially ciprofloxacin, the rates of resistance toward other antibiotics have remained stable for more than a decade.

REFERENCES

1. **Bamberger, D. M., and S. L. Dahl.** 1992. Impact of voluntary vs. enforced compliance of third-generation cephalosporin use in a teaching hospital. Arch. Intern. Med. **152:**554–557.
2. **Clinical and Laboratory Standards Institute.** 2006. Performance standards for antimicrobial susceptibility testing; 16th informational supplement document M100–S16. CLSI/NCCLS M100-S15. Clinical and Laboratory Standards Institute, Wayne, PA.
3. **Cosgrove, S. E.** 2006. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin. Infect. Dis. **42**(Suppl. 2)**:**S82–S89.
4. **D'Agata, E. M.** 2004. Rapidly rising prevalence of nosocomial multidrug-resistant, Gram-negative bacilli: a 9-year surveillance study. Infect. Control Hosp. Epidemiol. **25:**842–846.
5. **Diekema, D. J., M. A. Pfaller, R. N. Jones, G. V. Doern, P. L. Winokur, A. C. Gales, H. S. Sader, K. Kugler, and M. Beach.** 1999. Survey of bloodstream infections due to gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin. Infect. Dis. **29:**595–607.
6. **Empey, K. M., R. P. Rapp, and M. E. Evans.** 2002. The effect of an antimicrobial formulary change on hospital resistance patterns. Pharmacotherapy **22:**81–87.
7. **Fridkin, S. K., H. A. Hill, N. V. Volkova, J. R. Edwards, R. M. Lawton, R. P. Gaynes, J. E. McGowan, Jr., and the Intensive Care Antimicrobial Resistance Epidemiology Project Hospitals.** 2002. Temporal changes in prevalence of antimicrobial resistance in 23 U.S. hospitals. Emerg. Infect. Dis. **8:**697–701.
8. **Friedland, I., L. Stinson, M. Ikaiddi, S. Harm, and G. L. Woods.** 2003. Resistance in Enterobacteriaceae: results of a multicenter surveillance study, 1995–2000. Infect. Control Hosp. Epidemiol. **24:**607–612.
9. **Gales, A. C., R. N. Jones, J. Turnidge, R. Rennie, and R. Ramphal.** 2001. Characterization of *Pseudomonas aeruginosa* isolates: occurrence rates, antimicrobial susceptibility patterns, and molecular typing in the global SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin. Infect. Dis. **32**(Suppl. 2)**:**S146–S155.
10. **Gaynes, R., J. R. Edwards, and National Nosocomial Infections Surveillance System.** 2005. Overview of nosocomial infections caused by gram-negative bacilli. Clin. Infect. Dis. **41:**848–854.
11. **Goettsch, W., W. van Pelt, N. Nagelkerke, M. G. Hendrix, A. G. Buiting, P. L. Petit, L. J. Sabbe, A. J. van Griethuysen, and A. J. de Neeling.** 2000. Increasing resistance to fluoroquinolones in *Escherichia coli* from urinary tract infections in the Netherlands. J. Antimicrob. Chemother. **46:**223–228.
12. **Ibrahim, E. H., G. Sherman, S. Ward, V. J. Fraser, and M. H. Kollef.** 2000. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **118:**146–155.
13. **Itokazu, G. S., J. P. Quinn, C. Bell-Dixon, F. M. Kahan, and R. A. Weinstein.** 1996. Antimicrobial resistance rates among aerobic gram-negative bacilli recovered from patients in intensive care units: evaluation of a national postmarketing surveillance program. Clin. Infect. Dis. **23:**779–784.
14. **Jarvis, W. R., J. R. Edwards, D. H. Culver, J. M. Hughes, T. Horan, T. G. Emori, S. Banerjee, J. Tolson, T. Henderson, R. P. Gaynes, et al.** 1991 Nosocomial infection rates in adult and pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Am. J. Med. **91:**185S–191S.
15. **Karlowsky, J. A., M. E. Jones, C. Thornsberry, I. R. Friedland, and D. F. Sahm.** 2003. Trends in antimicrobial susceptibilities among *Enterobacteriaceae* isolated from hospitalized patients in the United States from 1998 to 2001. Antimicrob. Agents Chemother. **47:**1672–1680.
16. **Kern, W. V., K. Klose, A. S. Jellen-Ritter, M. Oethinger, J. Bohnert, P. Kern, S. Reuter, H. von Baum, and R. Marre.** 2005. Fluoroquinolone resistance of *Escherichia coli* at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. Eur. J. Clin. Microbiol. Infect. Dis. **24:**111–118.
17. **Kollef, M. H., G. Sherman, S. Ward, and V. J. Fraser.** 1999. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest **115:**462–474.
18. **Lautenbach, E., B. L. Strom, W. B. Bilker, J. B. Patel, P. H. Edelstein, and N. O. Fishman.** 2001. Epidemiological investigation of fluoroquinolone resistance in infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Clin. Infect. Dis. **33:**1288–1294.
19. **Livermore, D. M., D. James, M. Reacher, C. Graham, T. Nichols, P. Stephens, A. P. Johnson, and R. C. George.** 2002. Trends in fluoroquinolone (ciprofloxacin) resistance in Enterobacteriaceae from bacteremias, England and Wales, 1990–1999. Emerg. Infect. Dis. **8:**473–478.
20. **Neuhauser, M. M., R. A. Weinstein, R. Rydman, L. H. Danziger, G. Karam, and J. P. Quinn.** 2003. Antibiotic resistance among gram-negative bacilli in U.S. intensive care units: implications for fluoroquinolone use. JAMA **289:**885–888.
21. **NNIS System.** 2003. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2003, issued August 2003. Am. J. Infect. Control **31:**481–498.
22. **Paladino, J. A., J. L. Sunderlin, C. S. Price, and J. J. Schentag.** 2002. Economic consequences of antimicrobial resistance. Surg. Infect. **3:**259–267.
23. **Paterson, D. L.** 2006. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. Clin. Infect. Dis. **43**(Suppl. 2)**:**S43–S48.
24. **Pfaller, M. A., R. N. Jones, G. V. Doern, and K. Kugler.** 1998. Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY an-

timicrobial surveillance program (United States and Canada, 1997). Antimicrob. Agents Chemother. **42:**1762–1770.
25. **Pop-Vicas, A. E., and E. M. D'Agata.** 2005. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin. Infect. Dis. **40:**1792–1798.
26. **Raymond, D. P., S. J. Pelletier, T. D. Crabtree, H. L. Evans, T. L. Pruett, and R. G. Sawyer.** 2003. Impact of antibiotic-resistant Gram-negative bacilli infections on outcome in hospitalized patients. Crit. Care Med. **31:**1035–1041.
27. **Rhomberg, P. R., and R. N. Jones.** 2007. Contemporary activity of meropenem and comparator broad-spectrum agents: MYSTIC program report from the United States component (2005). Diagn. Microbiol. Infect. Dis. **57:**207–215.
28. **Tumbarello, M., T. Spanu, M. Sanguinetti, R. Citton, E. Montuori, F. Leone, G. Fadda, and R. Cauda.** 2006. Bloodstream infections caused by extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae*: risk factors, molecular epidemiology, and clinical outcome. Antimicrob. Agents Chemother. **50:**498–504.
29. **Unal, S., and J. A. Garcia-Rodriguez.** 2005. Activity of meropenem and comparators against *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolated in the MYSTIC Program, 2002–2004. Diagn. Microbiol. Infect. Dis. **53:**265–271.
30. **Urban, C., N. Mariano, N. Rahman, A. M. Queenan, D. Montenegro, K. Bush, and J. J. Rahal.** 2000. Detection of multiresistant ceftazidime-susceptible *Klebsiella pneumoniae* isolates lacking TEM-26 after class restriction of cephalosporins. Microb. Drug Resist. **6:**297–303.
31. **Wisplinghoff, H., M. B. Edmond, M. A. Pfaller, R. N. Jones, R. P. Wenzel, and H. Seifert.** 2000. Nosocomial bloodstream infections caused by *Acinetobacter* species in United States hospitals: clinical features, molecular epidemiology, and antimicrobial susceptibility. Clin. Infect. Dis. **31:**690–697.