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Trends in Antimicrobial Susceptibilities among *Enterobacteriaceae* Isolated from Hospitalized Patients in the United States from 1998 to 2001

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Longitudinal surveillance of *Enterobacteriaceae* for antimicrobial susceptibility is important because species of this family are among the most significant and prevalent human pathogens. To estimate rates of in vitro antimicrobial susceptibility among hospitalized patients in the United States, data from The Surveillance Network were studied for 14 agents tested against 10 species of *Enterobacteriaceae* (n = 384,279) isolated from intensive-care-unit (ICU) patients and non-ICU inpatients from 1998 to 2001. Cumulative susceptibility (percent) data for all species of *Enterobacteriaceae* isolated from ICU patients and non-ICU inpatients, respectively, were ranked as follows: ampicillin-sulbactam (45.5 and 57.2) ≪ ticarcillin-clavulanate (74.8 and 83.5) < trimethoprim-sulfamethoxazole (87.0 and 84.5) ≅ cefotaxime (82.9 and 92.6) = ceftazidime (82.3 and 91.0) = ceftriaxone (86.5 and 93.9) = piperacillin-tazobactam (83.5 and 90.5) < levofloxacin (89.3 and 90.6) = ciprofloxacin (91.0 and 91.7) < gentamicin (91.8 and 94.3) < cefepime (95.0 and 97.9) < amikacin (98.5 and 99.2) < imipenem (100 and 100) = meropenem (100 and 100). Of those agents studied only susceptibilities to ciprofloxacin (94 to 89%) and levofloxacin (93 to 89%) decreased in a stepwise manner from 1998 to 2001. Decreased fluoroquinolone susceptibility was most pronounced for *Escherichia coli*, *Proteus mirabilis*, and *Enterobacter cloacae*. For all species of *Enterobacteriaceae*, trimethoprim-sulfamethoxazole resistance was more commonly observed in isolates with a single-drug resistance phenotype while gentamicin and fluoroquinolone resistances were more common in isolates resistant to at least one additional class of antimicrobial agent. Ongoing surveillance of *Enterobacteriaceae* will be particularly important to monitor changes in fluoroquinolone susceptibility, as well as changes in the prevalence of isolates resistant to multiple classes of antimicrobial agents.

Members of the family *Enterobacteriaceae* are among the most important bacterial human pathogens. They comprise approximately 80% of gram-negative bacteria and 50% of all isolates identified in hospital laboratories in the United States (6). *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* spp., and *Serratia marcescens* account for the majority of *Enterobacteriaceae* isolated from clinical specimens. Risk factors for nosocomial gram-negative bacterial infections are widely known and include prior antimicrobial agent use, prolonged hospitalization, advanced age, severity of comorbid illnesses, immunosuppression associated with chemotherapy for malignancy and organ transplantation, invasive monitoring techniques (e.g., indwelling lines, catheters, and endotracheal tubes), and mechanical ventilation. Monitoring for antimicrobial resistance in species of *Enterobacteriaceae* in hospitalized patients is important because resistance has been reported elsewhere to be associated with increased patient morbidity and mortality, prolonged hospitalization, and increased hospital expenditures particularly for gram-negative bacteremia and ventilator-associated pneumonia (5, 19). Determining susceptibility patterns by location within the hospital (i.e., intensive-care units [ICUs] and non-ICU locations) may identify substantial differences that would be obscured if hospital-wide data were aggregated (7).

Antimicrobial resistance is increasing in many species of *Enterobacteriaceae* as well as in other gram-negative, gram-positive, and anaerobic bacteria. Current antimicrobial resistance issues for *Enterobacteriaceae* include the emergence and proliferation of extended-spectrum β-lactamases, β-lactamase-inhibitor-resistant TEM enzymes, stably derepressed and plasmid-encoded AmpC cephalosporinases, fluoroquinolone resistance, and the dissemination of multidrug-resistant (MDR) strains (3). MDR strains have arisen in a multitude of bacterial species including most species of *Enterobacteriaceae* and are of particular concern because of their potential for widespread dissemination, acquisition of additional resistance elements, and complications in therapeutic management of infected patients, particularly in seriously ill patients. Access to current antimicrobial susceptibility data is of importance to all healthcare providers but is of particular significance to physicians treating hospitalized patients. The present study was undertaken to determine the in vitro activities of 14 commonly tested antimicrobial agents against 10 of the most common, clinically relevant species of *Enterobacteriaceae* isolated from ICU patients and non-ICU inpatients in U.S. hospitals from 1998 to 2001.

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TABLE 1. In vitro antimicrobial agent susceptibilities of 10 species of *Enterobacteriaceae* reported by 126 clinical laboratories in the United States (cumulative 1998 to 2001 results)

Organism(s)	Antimicrobial agent	No. of isolate results		% Susceptible		% Intermediate		% Resistant	
		ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU
E. coli	Amikacin	7,101	82,309	99.2	99.6	0.4	0.2	0.4	0.2
	Ampicillin-sulbactam	9,883	86,372	58.4	59.7	18.2	20.1	23.4	20.2
	Cefepime	4,655	42,532	98.2	99.1	0.4	0.2	1.5	0.6
	Cefotaxime	5,499	54,404	96.8	96.8	0.9	0.6	2.3	0.6
	Ceftazidime	9,877	89,839	95.9	97.4	1.2	0.9	3.0	1.7
	Ceftriaxone	11,384	117,495	98.0	98.9	0.6	0.5	1.5	0.7
	Ciprofloxacin	12,520	125,671	93.5	94.4	0.2	0.1	6.3	5.5
	Gentamicin	15,199	158,512	93.8	95.8	0.6	0.4	5.6	3.8
	Imipenem	9,796	90,933	100	100	0	0	0	0
	Levofloxacin	6,752	86,968	89.2	92.3	0.2	0.3	10.6	7.4
	Meropenem	1,212	9,741	100	100	0	0	0	0
	Piperacillin-tazobactam	7,100	59,522	92.5	95.4	3.5	2.8	4.0	1.9
	Ticarcillin-clavulanate	6,209	60,328	79.8	83.7	11.5	10.0	8.8	6.2
	SXT	14,994	163,766	81.3	81.6	0.2	0.1	18.6	18.3
K. pneumoniae	Amikacin	5,748	32,107	98.1	98.7	0.8	0.4	1.1	0.8
	Ampicillin-sulbactam	7,538	36,257	69.9	75.0	14.8	12.5	15.3	12.4
	Cefepime	3,867	18,778	95.3	96.9	0.8	0.7	3.9	2.4
	Cefotaxime	4,412	20,970	92.8	95.8	2.6	2.0	4.6	2.2
	Ceftazidime	7,258	35,556	88.6	92.3	1.8	1.2	9.6	6.6
	Ceftriaxone	7,533	41,302	92.9	95.7	3.0	2.0	4.2	2.3
	Ciprofloxacin	8,489	44,267	91.3	93.0	1.4	1.1	7.3	5.9
	Gentamicin	10,260	55,921	91.7	94.7	1.0	0.9	7.3	4.4
	Imipenem	7,457	36,344	100	100	0	0	0	0
	Levofloxacin	4,560	31,015	91.2	93.3	2.1	1.6	6.7	5.1
	Meropenem	960	4,725	100	100	0	0	0	0
	Piperacillin-tazobactam	5,675	24,981	86.9	90.0	5.7	5.1	7.4	4.9
	Ticarcillin-clavulanate	5,060	23,530	83.8	87.4	4.4	4.1	11.8	8.6
	SXT	10,026	56,688	89.2	89.1	0.3	0.2	10.5	10.7
E. aerogenes	Amikacin	1,992	6,003	98.7	97.8	0.4	0.9	0.9	1.3
	Ampicillin-sulbactam	2,881	7,055	23.0	29.3	18.2	21.3	58.8	49.4
	Cefepime	1,319	3,723	88.7	98.2	0.9	0.8	10.4	1.0
	Cefotaxime	1,731	4,322	62.3	76.5	22.0	16.6	15.7	16.9
	Ceftazidime	2,866	7,422	58.8	71.2	6.6	6.0	34.6	22.9
	Ceftriaxone	2,921	8,197	68.0	77.9	20.2	15.9	11.8	6.2
	Ciprofloxacin	2,955	8,120	93.3	93.3	0.8	1.1	5.9	5.6
	Gentamicin	3,675	10,320	92.5	96.2	0.1	0.4	7.4	3.4
	Imipenem	2,794	7,257	100	100	0	0	0	0
	Levofloxacin	1,626	5,627	95.1	94.5	1.6	1.2	3.3	4.4
	Meropenem	435	941	99.5	100	0	0	0.5	0
	Piperacillin-tazobactam	1,818	4,593	67.5	73.6	23.6	17.5	8.9	8.9
	Ticarcillin-clavulanate	1,836	4,395	55.0	67.1	11.6	10.7	33.4	22.1
	SXT	3,530	10,365	96.1	94.8	0.2	0.2	3.7	5.0
E. cloacae	Amikacin	4,361	14,082	98.5	99.0	0.6	0.5	0.9	0.5
	Ampicillin-sulbactam	5,584	15,537	14.5	18.0	14.1	16.3	71.4	65.6
	Cefepime	3,078	8,929	91.1	94.6	3.0	1.6	5.9	3.8
	Cefotaxime	3,705	11,404	57.8	66.3	8.3	8.4	33.9	25.3
	Ceftazidime	5,872	17,522	59.4	67.5	3.5	3.6	37.0	28.9
	Ceftriaxone	6,012	18,629	63.1	69.7	8.1	7.3	28.9	23.0
	Ciprofloxacin	6,152	18,077	89.7	89.6	1.7	1.5	8.6	8.9
	Gentamicin	7,428	23,383	90.3	91.2	1.0	0.9	8.7	7.8
	Imipenem	5,844	16,894	100	100	0	0	0	0
	Levofloxacin	3,194	13,058	88.4	89.6	2.6	2.1	9.1	8.3
	Meropenem	800	2,453	100	100	0	0	0	0
	Piperacillin-tazobactam	4,174	10,806	64.6	70.8	13.6	10.3	21.8	18.9
	Ticarcillin-clavulanate	3,710	10,305	53.4	63.7	9.1	9.2	37.5	27.1
	SXT	7,120	23,332	88.4	87.9	0.1	0.2	11.6	12.0
C. freundii	Amikacin	933	5,379	97.7	98.0	0.5	0.4	1.7	1.6
	Ampicillin-sulbactam	1,118	6,015	37.5	53.8	7.4	9.7	55.1	36.5
	Cefepime	620	3,078	96.0	98.4	1.6	0.6	2.4	1.0
	Cefotaxime	685	3,525	54.6	72.9	21.2	15.3	24.2	11.8
	Ceftazidime	1,184	6,321	50.6	67.9	3.6	3.8	45.8	28.2
	Ceftazidime	1,184	6,321	50.6	67.9	3.6	3.8	45.8	28.2
	Ceftriaxone	1,227	7,348	55.8	72.4	16.4	11.9	27.8	15.7
	Ciprofloxacin	1,322	7,303	81.4	83.9	3.2	2.1	15.4	14.0
	Gentamicin	1,586	9,178	83.2	89.5	1.7	1.5	15.1	9.0

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TABLE 1—*Continued*

Organism(s)	Antimicrobial agent	No. of isolate results		% Susceptible		% Intermediate		% Resistant	
		ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU
	Imipenem	1,197	6,058	100	100	0	0	0	0
	Levofloxacin	731	5,075	80.6	84.1	5.1	2.4	14.4	13.5
	Meropenem	170	710	100	100	0	0	0	0
	Piperacillin-tazobactam	798	4,005	65.9	74.7	19.7	14.7	14.4	10.6
	Ticarcillin-clavulanate	788	3,641	41.4	65.7	3.7	4.3	54.9	30.0
	SXT	1,552	9,246	83.8	78.7	0.3	0.1	15.9	21.1
M. morganii	Amikacin	396	3.191	99.0	99.4	0.8	0.3	0.3	0.3
	Ampicillin-sulbactam	518	3,767	30.3	31.3	19.9	20.1	49.8	48.6
	Cefepime	256	1,909	96.5	97.9	0.4	0.7	3.1	1.4
	Cefotaxime	294	2,117	79.3	85.4	11.9	9.6	8.8	5.0
	Ceftazidime	519	3,750	77.5	79.6	6.0	5.3	16.6	15.1
	Ceftriaxone	552	4,485	92.8	92.2	5.1	5.9	2.2	1.9
	Ciprofloxacin	600	4,292	82.8	78.2	1.2	0.9	16.0	20.9
	Gentamicin	718	5,422	85.5	85.4	1.7	1.5	12.8	13.1
	Imipenem	512	3,529	100	100	0	0	0	0
	Levofloxacin	330	3,042	80.9	78.1	1.5	1.4	17.6	20.5
	Meropenem	75	535	100	100	0	0	0	0
	Piperacillin-tazobactam	402	2,587	92.3	92.7	3.0	2.7	4.7	4.5
	Ticarcillin-clavulanate	330	2,387	85.8	82.6	7.0	7.8	7.3	9.6
	SXT	697	5,442	81.1	77.3	0.1	0.1	18.8	22.7
P. mirabilis	Amikacin	1,693	16,648	99.2	99.4	0.4	0.3	0.4	0.3
	Ampicillin-sulbactam	1,991	16,446	91.0	91.9	4.8	4.2	4.2	3.9
	Cefepime	1,131	8,345	97.3	97.4	1.1	1.1	1.6	1.5
	Cefotaxime	1,164	10,785	99.4	99.3	0.3	0.3	0.3	0.3
	Ceftazidime	1,957	16,722	98.6	98.4	0.7	0.9	0.7	0.7
	Ceftriaxone	2,294	22,279	99.7	99.4	0.1	0.3	0.2	0.3
	Ciprofloxacin	2,407	22,381	90.0	86.4	1.0	0.9	9.1	12.6
	Gentamicin	2,957	28,885	92.5	92.0	0.7	1.5	6.7	6.6
	Imipenem	2,037	17,180	100	100	0	0	0	0
	Levofloxacin	1,387	16,413	87.7	84.0	0.8	1.6	11.5	14.4
	Meropenem	237	1,804	100	100	0	0	0	0
	Piperacillin-tazobactam	1,694	12,003	97.3	97.2	1.8	1.6	0.9	1.1
	Ticarcillin-clavulanate	1,305	12,036	99.6	99.6	0.3	0.3	0.1	0.1
	SXT	2,912	29,461	86.4	84.7	0.1	0.1	13.5	15.2
P. vulgaris	Amikacin	83	753	98.8	99.2	1.2	0	0	0.8
	Ampicillin-sulbactam	119	878	63.0	74.0	32.8	21.0	4.2	5.0
	Cefepime	45	442	97.8	98.0	0	0.7	2.2	1.4
	Cefotaxime	64	474	76.6	86.5	4.7	6.1	18.8	7.4
	Ceftazidime	122	892	97.5	97.8	1.6	1.2	0.8	1.0
	Ceftriaxone	133	1,071	75.9	73.6	12.8	16.6	11.3	9.8
	Ciprofloxacin	133	1,025	100	99.1	0	0.4	0	0.5
	Gentamicin	160	1,269	99.4	98.3	0.6	0.5	0	1.2
	Imipenem	116	811	100	99.4	0	0.6	0	0
	Levofloxacin	64	620	100	98.7	0	0.2	0	1.1
	Meropenem	14	105	100	100	0	0	0	0
	Piperacillin-tazobactam	86	597	98.8	97.3	1.2	2.0	0	0.7
	Ticarcillin-clavulanate	80	536	98.8	99.3	1.3	0.6	0	0.2
	SXT	158	1,279	97.5	95.2	0	0.1	2.5	4.8
Providencia spp.	Amikacin	229	2,161	97.4	99.1	1.7	0.6	0.9	0.3
	Ampicillin-sulbactam	267	2,172	17.6	22.6	34.8	44.2	47.6	33.2
	Cefepime	160	1,061	92.5	95.8	0.6	1.6	6.9	2.6
	Cefotaxime	167	1,398	92.8	94.3	6.0	4.4	1.2	1.2
	Ceftazidime	257	2,253	82.5	87.7	5.1	3.0	12.5	9.3
	Ceftriaxone	283	2,792	95.8	98.1	2.8	1.2	1.4	0.7
	Ciprofloxacin	303	2,564	38.9	47.1	2.0	3.0	59.1	49.9
	Gentamicin	356	3,382	74.7	72.4	6.7	7.7	18.5	19.8
	Imipenem	256	2,057	99.6	99.9	0.4	0.1	0	0
	Levofloxacin	176	1,963	34.1	45.6	4.5	6.1	61.4	48.3
	Meropenem	26	239	100	100	0	0	0	0
	Piperacillin-tazobactam	217	1,454	78.8	89.5	14.7	8.3	6.5	2.2
	Ticarcillin-clavulanate	170	1,458	98.8	97.3	0.6	1.6	0.6	1.1
	SXT	348	3,412	69.0	71.5	0.3	0.4	30.7	28.1
S. marcescens	Amikacin	2,703	8,112	96.8	98.4	0.6	0.7	2.6	0.9

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TABLE 1—*Continued*

Organism(s)	Antimicrobial agent	No. of isolate results		% Susceptible		% Intermediate		% Resistant	
		ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU
	Ampicillin-sulbactam	3,751	9,463	7.3	8.6	10.8	12.7	81.9	78.7
	Cefepime	1,917	5,191	95.4	97.2	0.8	0.9	3.9	2.0
	Cefotaxime	2,101	5,873	87.3	88.1	6.8	7.0	5.9	4.9
	Ceftazidime	3,579	9,922	90.6	90.2	1.8	2.1	7.6	7.7
	Ceftriaxone	3,734	10,595	91.1	91.8	4.8	4.8	4.0	3.5
	Ciprofloxacin	3,847	10,236	91.9	89.8	1.9	2.9	6.2	7.4
	Gentamicin	4,634	12,911	91.5	95.3	0.5	0.9	8.0	3.8
	Imipenem	3,684	9,435	100	100	0	0	0	0
	Levofloxacin	2,224	7,386	92.4	93.2	3.1	1.9	4.6	4.9
	Meropenem	505	1,483	100	100	0	0	0	0
	Piperacillin-tazobactam	2,684	6,534	87.9	88.9	6.3	5.9	5.7	5.2
	Ticarcillin-clavulanate	2,127	5,824	85.6	86.3	6.6	8.8	7.9	4.9
	SXT	4,496	12,932	95.7	95.0	0.1	0.3	4.2	4.6
Enterobacteriaceae	Amikacin	25,239	170,745	98.5	99.2	0.6	0.3	1.0	0.5
	Ampicillin-sulbactam	33,645	183,962	45.5	57.2	15.0	16.5	39.6	26.4
	Cefepime	17,048	93,988	95.0	97.9	1.1	0.6	3.9	1.5
	Cefotaxime	19,822	115,272	82.9	92.6	6.0	3.2	11.1	4.2
	Ceftazidime	33,491	190,199	82.3	91.0	2.4	1.7	15.2	7.4
	Ceftriaxone	36,073	234,193	86.5	93.9	5.0	2.6	8.6	3.5
	Ciprofloxacin	38,728	243,936	91.0	91.7	1.1	0.7	7.9	7.5
	Gentamicin	46,973	309,183	91.8	94.3	0.8	0.8	7.4	4.9
	Imipenem	33,693	190,498	100	100	0	0	0	0
	Levofloxacin	21,044	171,167	89.3	90.6	1.6	1.0	9.0	8.4
	Meropenem	4,434	22,736	100	100	0	0	0	0
	Piperacillin-tazobactam	24,648	127,082	83.5	90.5	8.0	4.9	8.5	4.6
	Ticarcillin-clavulanate	21,615	124,440	74.8	83.5	7.8	7.5	17.5	9.0
	SXT	45,833	315,923	87.0	84.5	0.2	0.1	12.8	15.4

MATERIALS AND METHODS

Antimicrobial susceptibility testing results. The Surveillance Network (TSN) Database-USA (Focus Technologies, Herndon, Va.) was used as the source of antimicrobial susceptibility testing results for this study. TSN electronically assimilates antimicrobial susceptibility testing and patient demographic data from a network of hospitals in the United States (23). The number of U.S. laboratories participating in TSN increased from 186 in 1998 to 232 in 1999, 258 in 2000, and 270 in 2001. Laboratories are included in TSN based on factors such as hospital bed size, patient population, geographic location, and antimicrobial susceptibility testing methods used (23). Susceptibility testing of patient isolates is conducted onsite by each participating laboratory as a part of their routine diagnostic testing. Only data generated by Food and Drug Administration-approved testing methods with MIC results interpreted according to NCCLS recommendations (17) are included in TSN. In addition, a series of quality-control filters (i.e., critical rule sets) are used to screen susceptibility test results for patterns indicative of testing error; suspect results are removed from the analyzable data set for laboratory confirmation.

The antimicrobial susceptibility testing results included in the present analysis were restricted to 126 U.S. laboratories that participated in TSN from 1998 to 2001 and that reported results for >100 isolates of *Enterobacteriaceae* per year from hospital inpatients. Isolates were restricted to the first isolate per patient, per bacterial species, per year. Data from ICU patients were analyzed separately and together with data from non-ICU hospital inpatients; data from patients in nursing facilities and hospital outpatients were excluded from the analysis. In TSN, all isolates are not tested with all antimicrobial agents, and variation can be observed for antimicrobial agents of the same class such as extended-spectrum cephalosporins (cefotaxime and ceftriaxone) and fluoroquinolones (ciprofloxacin and levofloxacin) for which similar in vitro activities have previously been demonstrated.

RESULTS

In vitro susceptibilities to 14 antimicrobial agents for clinical isolates of 10 common species of *Enterobacteriaceae* are depicted in Table 1. Cumulative 1998 to 2001 data are presented separately for isolates from patients in ICUs and for those from non-ICU inpatients. For all *Enterobacteriaceae*, susceptibility to all agents except trimethoprim-sulfamethoxazole (SXT) was greater for isolates from non-ICU inpatients than for isolates from ICU patients: differences exceeded 5% for ampicillin-sulbactam (11.7%), cefotaxime (9.7%), ticarcillin-clavulanate (8.7%), ceftazidime (8.7%), ceftriaxone (7.4%), and piperacillin-tazobactam (7.0%). Susceptibilities to ampicillin-sulbactam were lower than susceptibilities to any other agent for 9 of the 10 species of *Enterobacteriaceae* studied: *P. mirabilis* was the one exception for which susceptibilities were lower to ciprofloxacin, levofloxacin, and SXT than to ampicillin-sulbactam. For all isolates of *Enterobacteriaceae* studied, ampicillin-sulbactam susceptibilities among both ICU patients (45.5%) and non-ICU inpatients (57.2%) were >25% lower than for ticarcillin-clavulanate, the agent with the next lowest rate of susceptibility.

Essentially all isolates of *Enterobacteriaceae* studied were susceptible to the carbapenems, imipenem and meropenem. Three carbapenem-resistant isolates were identified, a resistance rate of 0.001% (3 of 235,042) (data not shown) for all *Enterobacteriaceae* tested with a carbapenem. Two of the three carbapenem-resistant isolates were *Enterobacter aerogenes*, and the remaining isolate was *E. coli*. Ceftazidime-nonsusceptible isolates were more common among ICU patients (4.2 and 11.4%) than among non-ICU inpatients (2.6 and 7.8%) for both *E. coli* and *K. pneumoniae*, respectively. Cefotaxime, ceftriaxone, and ceftazidime susceptibilities exceeded 90% for isolates of *Enterobacteriaceae* from non-ICU inpatients but were up to 10% lower (cefotaxime) among isolates from ICU patients.

Amikacin had higher susceptibilities against all species of

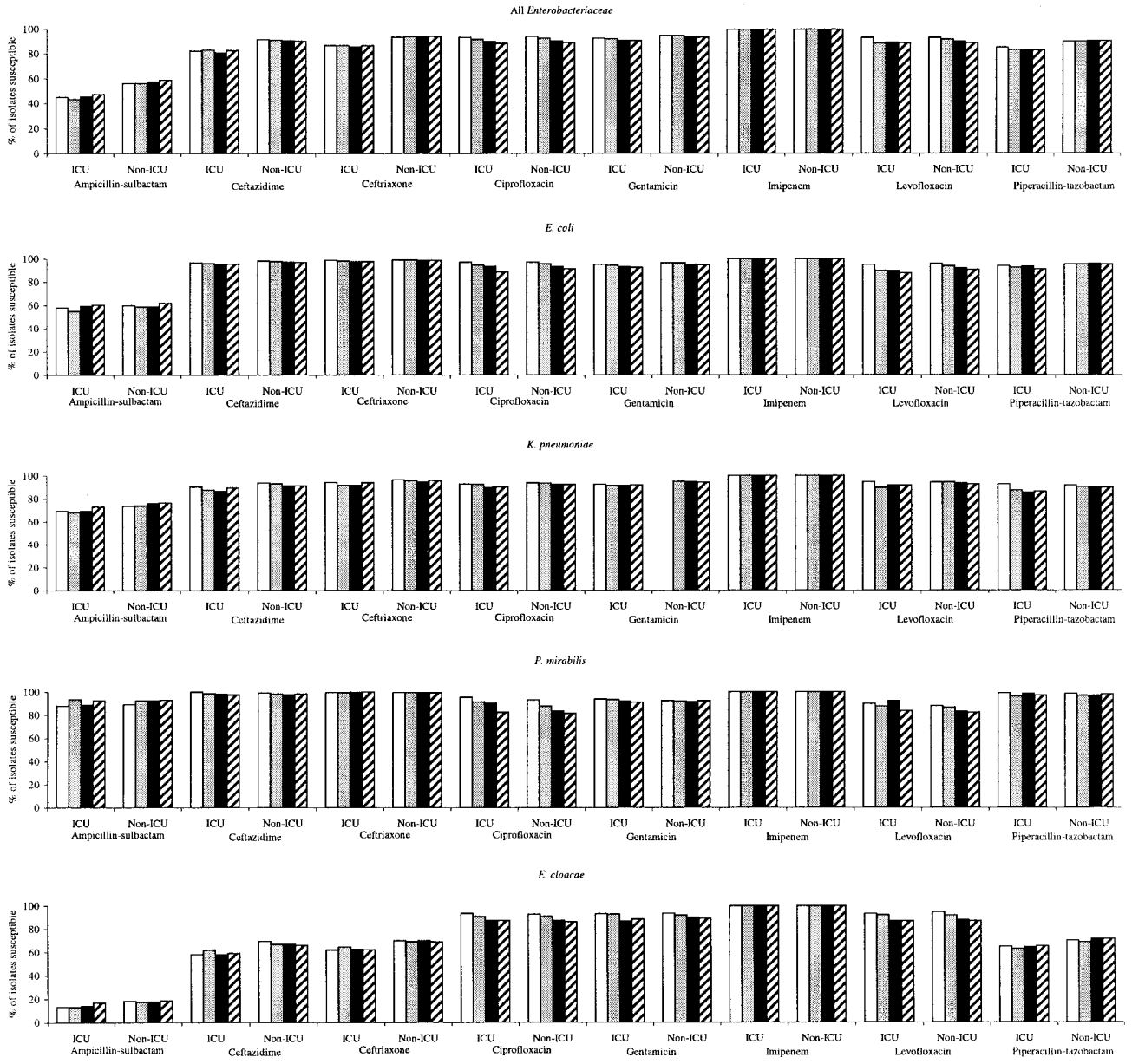

FIG. 1. Annual antimicrobial susceptibilities of *Enterobacteriaceae* from 1998 to 2001 for ICU patients and non-ICU inpatients. Open bars, 1998 data; lightly shaded bars, 1999 data; black bars, 2000 data; hatched bars, 2001 data.

Enterobacteriaceae than did gentamicin; the difference between the two aminoglycosides was greatest (>20%) for *Providencia* spp. Ciprofloxacin and levofloxacin demonstrated similar activities with 89.3 to 91.7% of *Enterobacteriaceae* isolates susceptible to fluoroquinolones for both ICU patients and non-ICU inpatients. Differences in susceptibility rates for isolates from ICUs and from non-ICU inpatients were similar (<3% difference) for amikacin (0.7%), ciprofloxacin (0.7%), levofloxacin (1.3%), gentamicin (2.5%), and cefepime (2.9%).

Figure 1 summarizes the susceptibilities to eight antimicrobial agents by year from 1998 to 2001 for all *Enterobacteriaceae* and, individually, for the four most commonly isolated species of *Enterobacteriaceae*. Rates of susceptibility for all *Enterobacteriaceae* from ICU and non-ICU inpatients demonstrated minor variations (<5%) between years for ampicillin-sulbactam, ceftazidime, ceftriaxone, and piperacillin-tazobactam but did not demonstrate a trend toward decreased susceptibility from 1998 to 2001. Imipenem susceptibility was 100% for all *Enterobacteriaceae* in all four years studied. Gentamicin susceptibility among all *Enterobacteriaceae* varied by <2% from 1998 to 2001; however, small stepwise decreases over time were observed for *Enterobacter cloacae* for isolates from both ICU patients (93.4 to 88.6%) and non-ICU inpatients (93.6 to 89.2%). Among all *Enterobacteriaceae*, susceptibilities declined in a stepwise manner for ciprofloxacin (94 to 89%) and levofloxacin (93 to 89%) from 1998 to 2001. The decline in fluoroquinolone activity was observed for all four species in Fig. 1

TABLE 2. Prevalence and composition of coresistance phenotypes[a] for 10 species of *Enterobacteriaceae* in 2001

Organism	No. of isolates	% of isolates pan-susceptible[b]	% of isolates resistant to one antimicrobial agent				% of isolates resistant to 2 antimicrobial agents	% of isolates resistant to 3 antimicrobial agents	% of isolates pan-resistant[c]	Most frequent coresistance phenotype(s) (% of total no. of isolates tested)
			Ceftazidime	Gentamicin	Levofloxacin	SXT				
E. coli	19,277	74.3	0.2	1.0	2.1	13.0	5.7	3.1	0.6	LVX, SXT (3.9); GEN, LVX, SXT (2.7)
K. pneumoniae	7,980	82.7	1.0	0.7	1.3	4.7	4.1	3.2	2.2	CTZ, GEN, LVX, SXT (2.2); CTZ, GEN, SXT (1.4)
E. aerogenes	1,727	73.4	15.6	0.4	1.3	1.0	6.0	1.8	0.6	CTZ, GEN (4.2); CTZ, GEN, SXT (0.8)
E. cloacae	4,153	62.7	16.4	0.7	1.0	2.2	5.8	6.6	4.7	CTZ, GEN, LVX, SXT (4.7); CTZ, GEN, SXT (3.4)
C. freundii	1,238	53.1	16.2	1.5	3.0	7.6	10.7	6.0	1.9	LVX, SXT (3.0); CTZ, SXT (2.4)
M. morganii	842	57.7	6.3	0.6	1.8	5.2	13.0	9.4	6.1	CTZ, GEN, LVX, SXT (6.1); LVX, SXT (6.0)
P. mirabilis	3,650	75.5	0.3	1.9	3.8	5.6	12.4	4.0	0.3	LVX, SXT (6.6); GEN, LVX, SXT (3.5)
P. vulgaris	170	88.2	1.2	1.8	0.6	8.2	1.2	0	0	GEN, SXT (1.2)
Providencia spp.	455	36.9	3.3	1.5	13.8	4.0	23.3	13.6	3.5	GEN, LVX, SXT (11.2); LVX, SXT (11.2)
S. marcescens	2,345	84.2	4.4	3.2	2.0	1.6	3.5	0.9	0.2	CTZ, GEN (1.2); GEN, LVX (0.7)

[a] Phenotypes were determined by using ceftazidime (CTZ), gentamicin (GEN), levofloxacin (LVX), and SXT susceptibility testing data.
[b] Pan-susceptible isolates were susceptible to ceftazidime, gentamicin, levofloxacin, and SXT.
[c] Pan-resistant isolates were resistant to ceftazidime, gentamicin, levofloxacin, and SXT.

but was more apparent for *E. coli*, *P. mirabilis*, and *E. cloacae* than for *K. pneumoniae*.

Table 2 summarizes the prevalence and composition of coresistance phenotypes of 10 species of *Enterobacteriaceae* for combined ICU and non-ICU inpatient isolates from 2001. Only isolates concurrently tested with ceftazidime, gentamicin, levofloxacin, and SXT (as representatives of different antimicrobial classes) were included in Table 2. Ampicillin-sulbactam was not included in this analysis, and data for ceftazidime, as the β-lactam class representative, cannot be used to estimate ampicillin-sulbactam activity. Pan-susceptible isolates (isolates susceptible to ceftazidime, gentamicin, levofloxacin, and SXT) were most common for *Proteus vulgaris* (88.2%), *S. marcescens* (84.2%), and *K. pneumoniae* (82.7%) and least common for *Morganella morganii* (57.7%) and *Providencia* spp. (36.9%). Coresistance phenotypes (isolates resistant to two or more of the drugs ceftazidime, gentamicin, levofloxacin, and SXT) most commonly involved resistance to a fluoroquinolone and SXT. SXT resistance was most common in *E. coli* (13.0%), and ceftazidime resistance was most common in *E. aerogenes* (15.6%), *E. cloacae* (16.4%), and *Citrobacter freundii* (16.2%). Among antimicrobial-resistant isolates, resistance to a single agent was more common than coresistance for *E. coli*, *E. aerogenes*, *E. cloacae*, *C. freundii*, *P. vulgaris*, and *S. marcescens* but not for *K. pneumoniae*, *M. morganii*, *P. mirabilis*, and *Providencia* spp. Ceftazidime and SXT resistance was more commonly observed in isolates with a single-drug resistance phenotype than in isolates with other resistances present. Gentamicin and levofloxacin resistance was more commonly associated with coresistance phenotypes than reported as a single resistance phenotype for all species of *Enterobacteriaceae* except *P. vulgaris*.

To show the observed relationship between fluoroquinolone susceptibility and susceptibility to other agents in greater detail, Fig. 2 depicts coresistance among fluoroquinolone-susceptible and fluoroquinolone-resistant isolates for ICU patients and non-ICU inpatients for all *Enterobacteriaceae* and individually for *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *E. cloacae*. As anticipated, resistance to levofloxacin was most strongly associated with lowered susceptibility to ciprofloxacin but was also associated with lowered susceptibility to ampicillin-sulbactam, ceftazidime, ceftriaxone, gentamicin, and piperacillin-tazobactam; associations were less evident (ampicillin-sulbactam, ceftazidime, and gentamicin) or essentially absent (ceftriaxone and piperacillin-tazobactam) for *P. mirabilis* compared with other species of *Enterobacteriaceae*. Differences in isolate susceptibilities between levofloxacin-susceptible and levofloxacin-resistant isolates were greatest for *E. cloacae*. Levofloxacin-susceptible isolates of *Enterobacteriaceae* were highly susceptible to antimicrobial agents of other classes.

The susceptibilities to ampicillin-sulbactam, piperacillin-tazobactam, cefepime, imipenem, gentamicin, and levofloxacin were also studied for ceftazidime-susceptible and ceftazidime-nonsusceptible (intermediate and resistant) isolates of *E. coli*, *K. pneumoniae*, and *E. cloacae* from combined ICU and non-ICU inpatients in 2001. For ceftazidime-susceptible and ceftazidime-nonsusceptible *E. coli* isolates, susceptibilities (percents) were as follows: ampicillin-sulbactam, 60.3 and 12.5; piperacillin-tazobactam, 95.8 and 65.8; cefepime, 99.8 and 72.4; imipenem, 100 and 100; gentamicin, 95.2 and 45.4; and levofloxacin, 91.4 and 26.8, respectively. For ceftazidime-susceptible and ceftazidime-nonsusceptible *K. pneumoniae*, susceptibilities (percents) were as follows: ampicillin-sulbactam, 80.1 and 6.5; piperacillin-tazobactam, 93.6 and 37.9; cefepime, 99.9 and 62.8; imipenem, 100 and 100; gentamicin, 97.6 and 36.3; and levofloxacin, 95.8 and 43.1, respectively. For ceftazi-

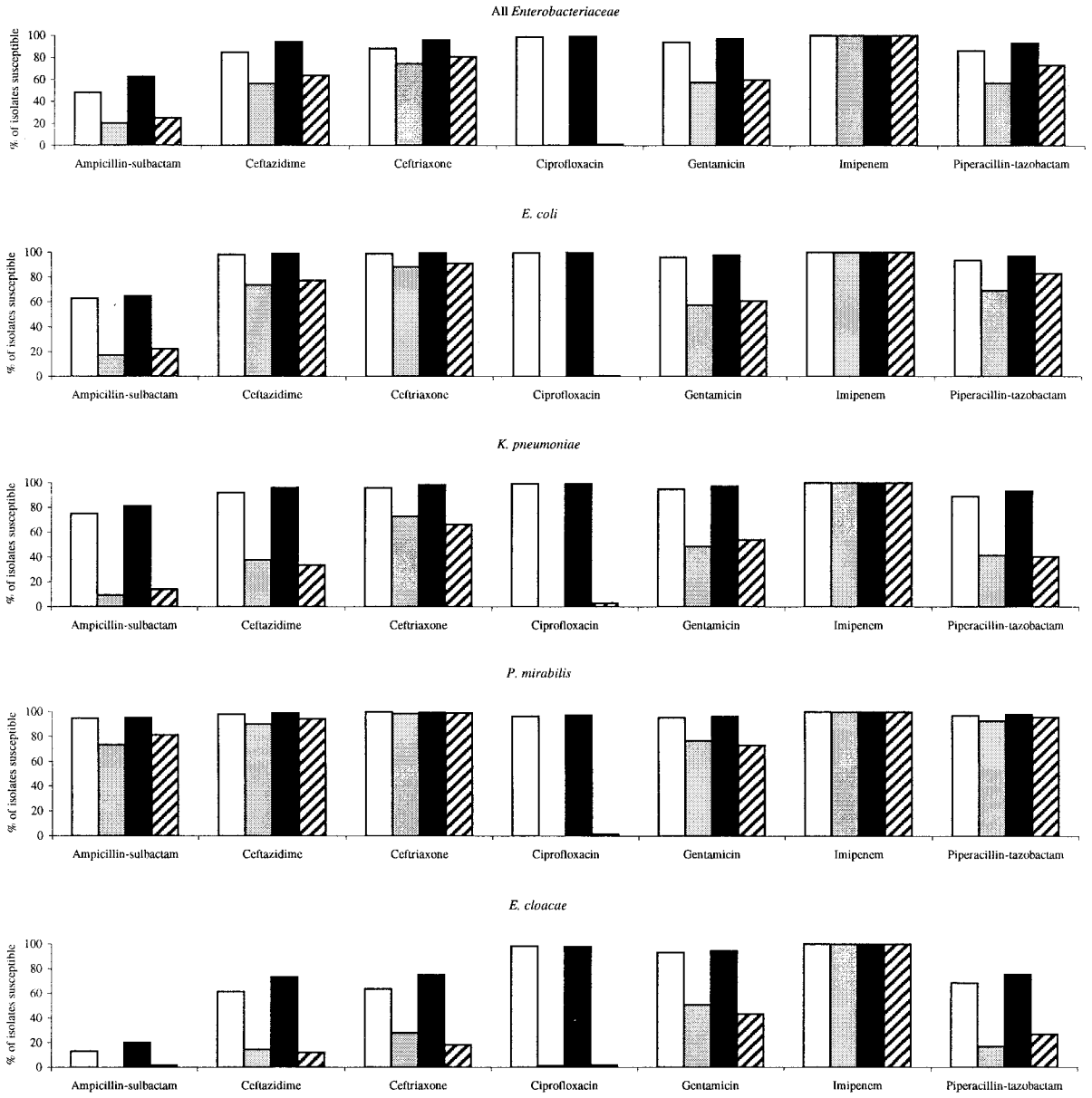

FIG. 2. Coresistance among fluoroquinolone-susceptible and fluoroquinolone-resistant isolates of *Enterobacteriaceae* in 2001 for ICU patients and non-ICU inpatients. Open bars, levofloxacin susceptible, ICU; lightly shaded bars, levofloxacin resistant, ICU; black bars, levofloxacin susceptible, non-ICU; hatched bars, levofloxacin resistant, non-ICU.

dime-susceptible and ceftazidime-nonsusceptible *E. cloacae*, susceptibilities (percents) were as follows: ampicillin-sulbactam, 27.6 and 0.5; piperacillin-tazobactam, 94.7 and 18.1; cefepime, 99.9 and 79.3; imipenem, 100 and 100; gentamicin, 97.6 and 70.2; and levofloxacin, 97.2 and 70.0, respectively.

Table 3 shows the susceptibility of *Enterobacteriaceae* to selected agents by patient age and specimen source for combined ICU and non-ICU inpatient isolates from 2001. Susceptibilities varied by <5% for patients aged <18 to >65 years for piperacillin-tazobactam, gentamicin, and SXT. Ceftazidime susceptibility was 6.4% lower among patients aged <18 years than among patients aged >65 years. Both ciprofloxacin and levofloxacin demonstrated differences of >10% for isolates from patients aged <18 years versus isolates from patients aged >65 years. Respiratory isolates were less susceptible to ceftazidime and piperacillin-tazobactam than were isolates from other sources. Isolates from all three specimen sources had similar susceptibilities to imipenem (100%), gentamicin (91.2 to 92.7%), ciprofloxacin (88.8 to 89.7%), and levofloxacin (88.9 to 89.7%). Isolates from respiratory sources were more susceptible to SXT than were isolates from blood and urine.

DISCUSSION

Antimicrobial resistance impedes effective treatment of patients with infections and is of particular concern for hospital-

TABLE 3. Susceptibility of *Enterobacteriaceae* to selected antimicrobial agents according to patient age and isolate specimen source in 2001

Patient age and specimen source	% of isolates susceptible to antimicrobial agent (no. of isolates tested)[a]						
	Ceftazidime	Imipenem	Piperacillin-tazobactam	Gentamicin	SXT	Ciprofloxacin	Levofloxacin
Age							
<18 yr	84.0 (6,812)	100 (5,705)	85.9 (4,840)	92.2 (9,227)	83.1 (9,194)	98.3 (7,254)	98.5 (6,595)
18–65 yr	89.5 (23,187)	100 (20,851)	89.5 (19,997)	93.6 (36,292)	83.8 (35,746)	89.5 (26,135)	90.3 (25,872)
>65 yr	90.4 (19,703)	100 (19,592)	90.7 (18,451)	93.3 (34,182)	84.3 (34,034)	87.0 (24,882)	86.3 (26,259)
Specimen source							
Blood	88.6 (5,002)	100 (4,921)	89.3 (4,554)	91.2 (6,252)	81.5 (6,068)	88.8 (4,928)	89.0 (4,383)
Respiratory	83.5 (10,130)	100 (9,150)	84.2 (9,154)	91.2 (12,481)	88.8 (12,069)	89.2 (8,934)	88.9 (8,510)
Urine	92.8 (27,526)	100 (25,607)	92.7 (22,179)	92.7 (25,607)	82.8 (51,441)	89.7 (38,644)	89.7 (40,171)

[a] Demographic and specimen source data were not available for all isolates.

ized patients. Given the prevalence and importance of *Enterobacteriaceae* as pathogens in hospitalized patients, the propensity for resistant organisms to move from patient to patient, and the mobility of resistance determinants (e.g., plasmids and transposons) between strains of the same and different species, routine surveillance of antimicrobial susceptibilities to all classes of clinically used agents is necessary. Surveillance assists in identifying and understanding trends in resistance; detecting the emergence of new resistance mechanisms; developing, implementing, and monitoring the impact of new empirical antimicrobial prescribing, infection control, and public health guidelines; and identifying outbreaks of resistant organisms. Only current surveillance data are beneficial in determining the best empirical regimens.

The present study provided a number of important observations regarding the susceptibility of *Enterobacteriaceae* to extended-spectrum cephalosporins, β-lactam–β-lactamase-inhibitor combinations, carbapenems, aminoglycosides, fluoroquinolones, and SXT. Rates of susceptibility to extended-spectrum cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) were steady for *Enterobacteriaceae* from 1998 to 2001 but were up to 10% lower for isolates from ICU patients than for those from non-ICU inpatients (Table 1 and Fig. 1). Ceftazidime-nonsusceptibility rates in isolates from ICU patients and non-ICU inpatients were 4.2 and 2.6% for *E. coli* and 11.4 and 7.8% for *K. pneumoniae*, respectively, and may serve as an estimate of the prevalence of extended-spectrum β-lactamases in these species (9). Differences in susceptibilities to the extended-spectrum cephalosporins of >5% for isolates from ICU patients and non-ICU inpatients were not observed for *E. coli*, *K. pneumoniae*, and *P. mirabilis* but did exist for *Enterobacter* spp. and other *Enterobacteriaceae* where susceptibilities were lower among ICU isolates than among isolates from non-ICU inpatients (Fig. 1). Similar observations as those made for extended-spectrum cephalosporins were also evident for β-lactam–β-lactamase-inhibitor combinations (ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) (Fig. 1 and Table 1). The in vitro susceptibility of *Enterobacteriaceae* to ampicillin-sulbactam, relative to the other agents tested, was limited for both ICU patients (45.5%) and non-ICU inpatients (57.2%).

Rates of susceptibility of *E. coli* to ampicillin-sulbactam observed in the present study (≤60%) were lower than previously reported in the United States (24) and suggest that this agent may not provide physicians and their patients with reliable therapy. The effectiveness of ampicillin-sulbactam in the treatment of *E. coli* infections is largely dependent on the inhibitory activity of sulbactam, as many isolates harbor the TEM-1 β-lactamase (13). However, sulbactam is a relatively weak inhibitor of TEM-1 (13), and resistance in *E. coli* can develop by hyperproduction of TEM-1, hyperproduction of chromosomal or plasmid-borne AmpC, and alteration of porin channels and less frequently by β-lactamase-inhibitor-resistant mutants of TEM.

Essentially all isolates in the present study were susceptible to carbapenems, including MDR isolates of *Enterobacteriaceae*. Carbapenems, such as imipenem, because of their resistance to hydrolysis by most β-lactamases, including those of groups 1, 2b, and 2be (4), are effective agents against a broad range of nosocomial pathogens including *Enterobacteriaceae*. β-Lactamases that hydrolyze carbapenems are still rare and not a global concern, but vigilant surveillance for these enzymes is important as some of the β-lactamases in this group possess the most extensive substrate hydrolysis profiles of all β-lactamases and plasmid-mediated carbapenem resistance has been reported previously (13, 15).

From 1998 to 2001 fluoroquinolone susceptibility showed the greatest relative decreases of all agents studied, perhaps reflecting the increased use of these agents for common infections such as those of the urinary and respiratory tracts or perhaps as supplements for the agricultural industry. Fluoroquinolone susceptibility was lower in adults than in children, reflecting the patterns of use of this class of agents. The widespread cumulative use of fluoroquinolones (ciprofloxacin and levofloxacin) may be accelerating the development of resistance to these agents and may be the driving force behind stepwise increases in resistance in *Enterobacteriaceae* and other bacterial species (2, 10, 14, 18, 21). Fluoroquinolone resistance was more commonly found as a component of coresistance phenotypes than as a single-agent resistance phenotype (Table 2 and Fig. 2) as has been reported by others (10, 11, 16, 20, 25). Fluoroquinolone-resistant species of *Enterobacteriaceae* were frequently also resistant to extended-spectrum cephalosporins, aminoglycosides, and SXT. The potential for commonly encountered gram-negative bacilli to acquire cross-resistance to several antimicrobial agents has been well documented (1, 10, 11, 25). The fact that fluoroquinolone resistance among gram-negative species is found predominantly among MDR isolates suggests that fluoroquinolone resistance will be maintained and perhaps accelerate even if other antimicrobials are used (8, 22). The apparent correlation between fluoroquinolone resistance and resistance to other classes of agents requires care-

ful monitoring, as such resistance profiles seriously limit the therapeutic options available to treat infections caused by these organisms and MDR isolates may pose greater public health problems than isolates that exhibit resistance to a single agent.

A previous report found that increases in fluoroquinolone resistance were significant only in isolates of *Enterobacteriaceae* from hospitalized patients outside the ICU and from hospital outpatients (7). The authors suggested that factors present outside ICUs such as excessive fluoroquinolone use or inadequate infection control practices may explain their observations. In the present study, fluoroquinolone susceptibilities for *Enterobacteriaceae* were similar (differing by <5%) for ICU patients and non-ICU inpatients (Table 1) with the exception of *Providencia* spp., which had lower fluoroquinolone susceptibility rates in isolates from ICU patients. It is notable that rates of resistance to ciprofloxacin and levofloxacin in Table 1 were generally higher (often only marginally higher) in isolates from ICU patients than in isolates from non-ICU inpatients.

Every species of *Enterobacteriaceae* in the present study demonstrated some percentage of isolates that were coresistant. Based on reports from individual institutions and from different countries, the prevalence and diversity of MDR phenotypes could substantially expand and become problematic (11); therefore, continued monitoring for these phenotypes in the United States is warranted. Multidrug resistance in gram-negative bacteria appears to be primarily the result of the acquisition of resistance genes by horizontal transfer (12); however, clonal spread is also important and is the most likely mechanism by which coresistant strains involving fluoroquinolone resistance spread. Strains of MDR *Enterobacteriaceae* have been isolated with increasing frequency in hospital settings and are having a significant impact on clinical practice and overall treatment costs (8, 12, 22).

In conclusion, because antimicrobial resistance patterns are continually evolving, surveillance studies will continue to be essential to ensure the provision of safe and effective empirical therapy. Clearly, the current prevalence of coresistant isolates among *Enterobacteriaceae* isolated in U.S. laboratories suggests that monitoring these phenotypes is important (Table 2). The results of this study confirm those of other investigators suggesting that rates of resistance to extended-spectrum cephalosporins, other β-lactams, and β-lactamase-inhibitor combinations among *Enterobacteriaceae* such as *Enterobacter* spp. and *C. freundii* are quite high and may be increasing. Essentially all *Enterobacteriaceae* isolated and tested in clinical laboratories from 1998 to 2001 remain susceptible to carbapenems. Ongoing surveillance of *Enterobacteriaceae* should focus particularly on the continued increases in fluoroquinolone resistance, as well as changes in the prevalence and composition of coresistance phenotypes.

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REFERENCES

1. **Acar, J. F., and F. W. Goldstein.** 1998. Consequences of increasing resistance to antimicrobial agents. Clin. Infect. Dis. **27**(Suppl. 1)**:**S125–S130.
2. **Blumberg, H. M., D. Rimland, D. J. Carroll, P. Terry, and I. K. Wachsmuth.** 1991. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*. J. Infect. Dis. **163:**1279–1285.
3. **Bradford, P. A.** 2001. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin. Microbiol. Rev. **14:**933–951.
4. **Bush, K., G. A. Jacoby, and A. A. Medeiros.** 1995. A functional classification scheme for β-lactamases and its correlation with molecular structure. Antimicrob. Agents Chemother. **39:**1211–1233.
5. **Cosgrove, S. E., K. S. Kaye, G. M. Eliopoulos, and Y. Carmeli.** 2002. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. Arch. Intern. Med. **162:**185–190.
6. **Eisenstein, B. I., and D. F. Zaleznik.** 2000. *Enterobacteriaceae*, p. 2294–2310. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases, 5th ed. Churchill Livingstone, Philadelphia, Pa.
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 (ICARE) Project Hospitals.** 2002. Temporal changes in prevalence of antimicrobial resistance in 23 U.S. hospitals. Emerg. Infect. Dis. **8:**697–701.
8. **Friedrich, L. V., R. L. White, and J. A. Bosso.** 1999. Impact of use of multiple antimicrobials on changes in susceptibility of gram-negative aerobes. Clin. Infect. Dis. **28:**1017–1024.
9. **Hadziyannis, E., M. Touhy, L. Thomas, G. W. Procop, J. A. Washington, and G. S. Hall.** 2000. Screening and confirmatory testing for extended spectrum β-lactamases (ESBL) in *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* clinical isolates. Diagn. Microbiol. Infect. Dis. **36:**113–117.
10. **Hooper, D. C.** 2001. Emerging mechanisms of fluoroquinolone resistance. Emerg. Infect. Dis. **7:**337–341.
11. **Jacobson, K., K. Rolston, L. Elting, B. LeBlanc, E. Whimby, and D. H. Ho.** 1999. Susceptibility surveillance among gram-negative bacilli at a cancer center. Chemotherapy **45:**325–334.
12. **Leverstein-van Hall, M. A., A. T. A. Box, H. E. M. Blok, A. Paauw, A. C. Fluit, and J. Verhouf.** 2002. Evidence of extensive interspecies transfer of integron-mediated antimicrobial resistance genes among multidrug-resistant *Enterobacteriaceae* in a clinical setting. J. Infect. Dis. **186:**49–56.
13. **Livermore, D. M.** 1995. β-Lactamases in laboratory and clinical resistance. Clin. Microbiol. Rev. **8:**557–584.
14. **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.
15. **Lucet, J. C., S. Chevret, D. Decre, D. Vaniak, A. Macrez, J. P. Bedos, M. Wolff, and B. Regnier.** 1996. Outbreak of multiply resistant *Enterobacteriaceae* in an intensive care unit: epidemiology and risk factors for acquisition. Clin. Infect. Dis. **22:**430–436.
16. **Meyer, K. S., C. Urban, J. A. Eagan, B. J. Berger, and J. J. Rahal.** 1993. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Ann. Intern. Med. **119:**353–358.
17. **National Committee for Clinical Laboratory Standards.** 2001. Performance standards for antimicrobial susceptibility testing; 11th informational supplement. Vol. 21, no. 1. M100-S11. National Committee for Clinical Laboratory Standards, Wayne, Pa.
18. **Pena, C., J. M. Albareda, R. Pallares, M. Pujol, F. Tubua, and J. Ariza.** 1995. Relationship between quinolone use and emergence of ciprofloxacin-resistant *Escherichia coli* in bloodstream infections. Antimicrob. Agents Chemother. **39:**520–524.
19. **Rello, J., M. Gallego, D. Mariscal, R. Sonora, and J. Valles.** 1997. The value of routine microbial investigation in ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **156:**196–200.
20. **Rice, L. B., S. H. Willey, G. A. Papanicolaou, A. A. Medeiros, G. M. Eliopoulos, R. C. Moellering, and G. A. Jacoby.** 1990. Outbreak of ceftazidime resistance caused by extended-spectrum β-lactamases at a Massachusetts chronic-care facility. Antimicrob. Agents Chemother. **34:**2193–2199.
21. **Richard, P., M. H. Delangle, F. Raffi, E. Espaze, and H. Richet.** 2001. Impact of fluoroquinolone administration on the emergence of fluoroquinolone-resistant Gram-negative bacilli from gastrointestinal flora. Clin. Infect. Dis. **32:**162–166.
22. **Sahm, D. F., I. A. Critchley, L. J. Kelly, J. A. Karlowsky, D. C. Mayfield, C. Thornsberry, Y. R. Mauriz, and J. Kahn.** 2001. Evaluation of current activities of fluoroquinolones against gram-negative bacilli using centralized in vitro testing and electronic surveillance. Antimicrob. Agents Chemother. **45:**267–274.
23. **Sahm, D. F., M. K. Marsilio, and G. Piazza.** 1999. Antimicrobial resistance in key bloodstream bacterial isolates: electronic surveillance with the surveillance network database—USA. Clin. Infect. Dis. **29:**259–263.
24. **Shungu, D. L., S. Ponticas, and C. J. Gill.** 1989. Comparative activity of cefoxitin, ampicillin/sulbactam, and imipenem against clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*. Clin. Ther. **11:**315–318.
25. **Weiner, J., J. P. Quinn, P. A. Bradford, R. V. Goering, C. Nathan, K. Bush, and R. A. Weinstein.** 1999. Multiple antibiotic-resistant *Klebsiella pneumoniae* and *Escherichia coli* in nursing homes. JAMA **281:**517–523.