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Trends in Susceptibility of *Escherichia coli* from Intra-Abdominal Infections to Ertapenem and Comparators in the United States According to Data from the SMART Program, 2009 to 2013

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Antimicrobial resistance in *Enterobacteriaceae*, including resistance to carbapenems, is increasing worldwide. However, using U.S. Study for Monitoring Antimicrobial Resistance Trends (SMART) data for 2009 to 2013, no statistically significant decreasing susceptibility trends were found overall for *Escherichia coli* isolates from patients with intra-abdominal infections. In the subset of isolates from community-associated infections, susceptibility to levofloxacin decreased significantly and the increasing rate of multidrug-resistant *E. coli* approached statistical significance. In 2013, ertapenem, imipenem, and amikacin showed the highest susceptibility rates (≥99%) and fluoroquinolones the lowest (<70%). The 10 non-ertapenem-susceptible isolates (0.3% of all *E. coli* isolates) encoded one or more carbapenemases, extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, or non-ESBL β-lactamases.

As *Enterobacteriaceae* producing extended-spectrum β-lactamases (ESBLs) spread, carbapenems are often considered the treatment of choice for intra-abdominal infections (IAIs) (1–3). However, reports of decreased susceptibility to carbapenems in *Enterobacteriaceae*, due to carbapenemases or porin deficiency combined with production of ESBLs or AmpC cephalosporinases, are mounting (4–7). Monitoring changes in the susceptibility of *Escherichia coli*, the most common IAI pathogen, is crucial for decision-making regarding empirical therapy, as well as for efforts to control the spread of ESBLs and carbapenemases. The Study for Monitoring Antimicrobial Resistance Trends (SMART) program has been monitoring IAIs for antimicrobial susceptibility, to assess worldwide trends, since 2002. This report examines trends in the activity of ertapenem and comparator agents against *E. coli* isolates collected over the past 5 years from patients with IAIs in the United States. Susceptibility is reported for agents recommended in the Surgical Infection Society and the Infectious Diseases Society of America guidelines for the diagnosis and management of complicated intra-abdominal infections (2).

(The results of this report were presented in part as an abstract at IDWeek 2014, Philadelphia, PA.)

Between 2009 and 2013, 29 hospitals in 17 states participated in the SMART program in the United States. A map of the participating states is presented in Fig. S1 in the supplemental material. Participating sites each collected up to 100 consecutive aerobic or facultatively anaerobic Gram-negative IAI pathogens per year. Only one isolate per species per patient was allowed. Of 7,907 IAI isolates, 2,897 (37%) were *E. coli*. Isolates were identified to the species level and were sent to a central laboratory (International Health Management Associates, Inc., Schaumburg, IL) for susceptibility testing and confirmation of identification. MICs and phenotypic ESBL status were determined by broth microdilution, following the Clinical and Laboratory Standards Institute (CLSI) guidelines, using custom dehydrated MicroScan panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA) (8, 9). MIC interpretive criteria followed 2014 CLSI guidelines (9). As in other studies, multidrug resistance (MDR) was defined as resistance to three or more drug classes (in this study, aminoglycosides, β-lactam/β-lactamase inhibitors, cephems, carbapenems, and quinolones) (10). An IAI was defined as hospital associated or community associated if cultured ≥48 or <48 h postadmission, respectively.

All non-ertapenem-susceptible and >70% of phenotypically ESBL-positive *E. coli* isolates were molecularly characterized for β-lactamase genes. According to the SMART protocol, 50% of phenotypically ESBL-positive *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* isolates from each site were to be randomly selected for molecular characterization. However, sometimes additional isolates were characterized for special analyses in support of publications, resulting in an overall final proportion of characterized ESBL-positive isolates that was greater than 50%. Genes encoding ESBLs (TEM, SHV, and CTX-M-type), carbapenemases (KPC, NDM, IMP, VIM, and OXA-48-type), and AmpC β-lactamases (CMY, DHA, FOX, MOX, ACC, MIR, and ACT) were detected using a combination of microarray (Check-MDR CT101; Check-Points B.V., Wageningen, the Netherlands), as described previously (11), and multiplex PCR assays, as described in the supplemental material. Detected genes were sequenced and compared to public databases available from the

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TABLE 1 Trends in susceptibility to ertapenem and comparators of *E. coli* isolates from IAIs in the United States in 2009 to 2013

Agent	Susceptibility rate (%)[a]														
	All[b]					Hospital-associated					Community-associated				
	2009 (n = 551)	2010 (n = 613)	2011 (n = 554)	2012 (n = 603)	2013 (n = 576)	2009 (n = 291)	2010 (n = 249)	2011 (n = 213)	2012 (n = 277)	2013 (n = 258)	2009 (n = 184)	2010 (n = 334)	2011 (n = 311)	2012 (n = 326)	2013 (n = 318)
ETP	99.8	99.5	99.6	99.7	99.7	99.7	99.6	100	99.6	99.2	100	99.7	99.4	99.7	100
IPM	99.8	99.5	99.6	99.7	99.8	99.7	99.6	100	99.6	99.6	100	99.4	99.4	99.7	100
FEP	93.8	93.1	91.2	94.2	91.0	93.5	91.2	91.1	93.1	89.9	95.7	95.2	91.3	95.1	91.8
CTX	90.2	90.2	89.0	91.9	88.9	89.7	88.4	87.8	91.7	88.4	93.5	92.8	90.4	92.0	89.3[c]
CRO	90.4	90.4	89.4	92.5	89.8	90.0	88.0	87.8	92.8	88.4	93.5	93.4	90.7	92.3	90.9
CAZ	92.4	91.7	90.8	94.4	91.5	91.4	90.4	89.2	95.0	89.9	95.7	93.7	92.6	93.9	92.8
FOX	90.9	90.7	91.2	93.4	91.7	91.1	89.6	91.6	94.6	91.1	94.6	93.1	91.0	92.3	92.1
TZP	92.6	93.5	94.0	95.9	94.3	91.4	90.4	94.4	94.6	93.0	93.5	96.4	95.2	96.9	95.3
CIP	70.2	71.5	69.7	72.8	68.2	70.8	63.5	68.1	72.2	68.2	71.7	78.4	71.4	73.3	68.2
LVX	71.5	72.3	70.2	73.0	68.6	72.2	64.7	68.5	72.6	69.0	72.3	79.0	72.0	73.3	68.2[d]
AMK	98.9	98.5	98.7	99.3	99.3	98.6	98.0	99.5	99.3	99.6	99.5	99.4	98.7	99.4	99.1

[a] Susceptibility rates of ≥90% are shaded gray. ETP, ertapenem; IPM, imipenem; FEP, cefepime; CTX, cefotaxime; CRO, ceftriaxone; CAZ, ceftazidime; FOX, cefoxitin; TZP, piperacillin-tazobactam; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin.

[b] Includes isolates from hospital-associated and community-associated IAIs, as well as isolates for which the time of collection postadmission was not reported.

[c] Statistically significant decrease in the susceptible proportion in the sensitivity analysis of the 12 continuously participating sites ($P < 0.05$).

[d] Statistically significant decrease in the susceptible proportion in the main analysis of all 29 sites ($P < 0.05$).

National Center for Biotechnology Information and the Lahey Clinic. Annual rates of genotypically ESBL-positive isolates were estimated by using as weights the yearly sampling fractions of phenotypically ESBL-positive isolates (i.e., the proportion of phenotypically ESBL-positive isolates that were molecularly characterized each year).

ESBL, MDR, and susceptibility rates were evaluated for linear trends with the Cochran-Armitage test, while trends in MICs were assessed using Pearson's correlations between logarithmically transformed MICs and calendar years. The main analyses included all 2,897 *E. coli* isolates from all 29 U.S. sites. Sensitivity analyses included only 1,856 isolates from the 12 sites in 9 states that participated in all 5 years. *P* values of <0.05 were considered statistically significant. Analyses were performed with XLSTAT v2011.1.05.

Of 2,897 *E. coli* isolates, 69% were from general hospital wards and 17% from intensive care units. Medical wards contributed 44% of isolates and surgical units 36%. Susceptibility, MIC, and prevalence results shown in the tables and figures are for the main analyses using all sites; the statistical test results of the sensitivity analyses are reported in the footnotes. Overall, activities were highest for amikacin, ertapenem, and imipenem, with susceptibility rates being consistently ≥98%; piperacillin-tazobactam and all cephalosporins except for cefotaxime and ceftriaxone demonstrated susceptibility rates of >90%, and the fluoroquinolones showed the lowest susceptibility rates, with rates falling below 70% in 2013 (Table 1). Susceptibility rates did not differ between hospital-associated and community-associated IAIs for amikacin, ertapenem, and imipenem, while small differences were observed for cephalosporins (on average, 1 to 3% lower for hospital-associated infections) and fluoroquinolones (on average, 4% lower). Susceptibility rates appeared fairly stable over the past 5 years, with no statistically significant trends in the main analysis except for a decreasing trend for levofloxacin susceptibility among isolates from community-associated IAIs ($P = 0.04$) (Table 1); however, this trend was not confirmed in the sensitivity analysis. Decreasing trends for ciprofloxacin and cefotaxime susceptibility among isolates from community-associated IAIs approached significance ($P < 0.1$) in the main analysis, and the latter was statistically significant in the sensitivity analysis (decreasing from 94% in 2009 to 87% in 2013; $P = 0.02$). Ertapenem activity also appeared remarkably stable when the MIC distribution was examined (Fig. 1), with no statistical evidence of a shift in MICs ($P > 0.05$). Furthermore, our data showed no increase in isolates with MICs of 0.25 or 0.5 μg/ml, which is important in light of reports of carbapenemases and other resistance mechanisms increasing carbapenem MICs in *Enterobacteriaceae* but leaving the isolates susceptible (ertapenem MICs of ≤0.5 μg/ml) (4).

Between 2009 and 2013, nine isolates were resistant to ertapenem and one exhibited intermediate resistance (total of 0.3% non-ertapenem-susceptible isolates), without evidence of an increasing trend. Molecular characterization of these 10 isolates revealed four KPC carbapenemase producers from New York and Pennsylvania (Table 2); although KPC is usually associated with *K. pneumoniae*, KPC-producing *E. coli* isolates were recently noted in the mid-Atlantic region (12). Another four isolates encoded CMY-2 or CTX-M-15 enzymes, which have been reported to cause increased carbapenem MICs in *E. coli* when expressed at high levels in combination with porin deficiency (13–16). The isolate encoding only CTX-M-71 was carbapenemase negative by

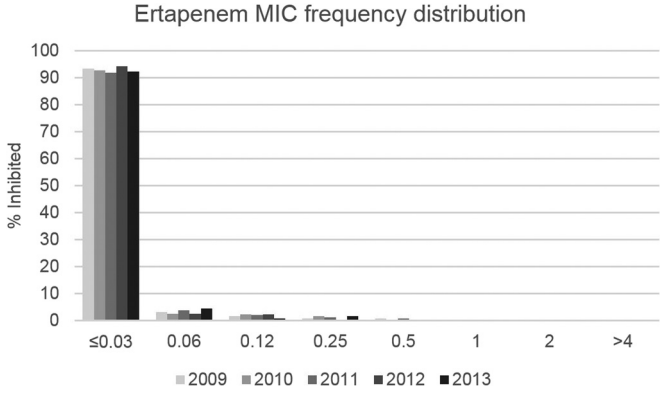

FIG 1 Frequency distribution of ertapenem MICs (in micrograms per milliliter) for *E. coli* isolates from IAIs in the United States in 2009 to 2013. No statistically significant trends in MICs were noted in the main or sensitivity analyses ($P > 0.05$). *E. coli* sample sizes were as follows: 2009, 551 isolates; 2010, 613 isolates; 2011, 554 isolates; 2012, 603 isolates; 2013, 576 isolates.

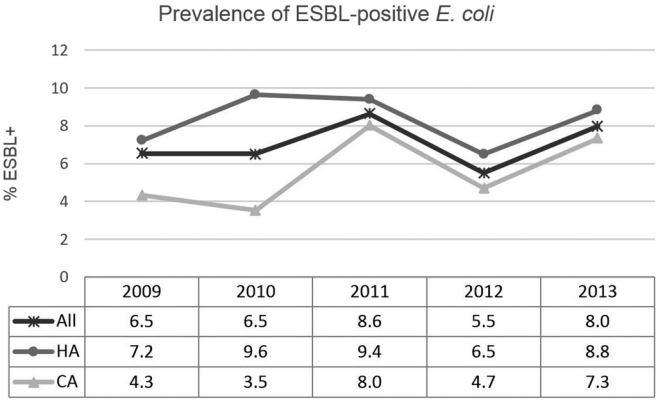

FIG 2 Trends in the prevalence of genotypically ESBL-positive isolates of *E. coli* from IAIs in the United States in 2009 to 2013. No statistically significant trends were noted in main (all 29 sites) or sensitivity (12 continuously participating sites) analyses (all $P > 0.05$). HA, hospital-associated; CA, community-associated. *E. coli* sample sizes (denominators) were as follows: all (including isolates from HA and CA IAIs, as well as isolates for which the time of collection postadmission was not reported), 2009, 551 isolates; 2010, 613 isolates; 2011, 554 isolates; 2012, 603 isolates; 2013, 576 isolates; HA, 2009, 291 isolates; 2010, 249 isolates; 2011, 213 isolates; 2012, 277 isolates; 2013, 258 isolates; CA, 2009, 184 isolates; 2010, 334 isolates; 2011, 311 isolates; 2012, 326 isolates; 2013, 318 isolates.

the CarbaNP test (17). CTX-M-71 was first observed in a *K. pneumoniae* isolate that was resistant to ertapenem and meropenem. The purified CTX-M-71 enzyme displayed only weak carbapenemase activity, suggesting that an additional nonenzymatic mechanism (e.g., porin deficiency) was required for the reduction in susceptibility (18). The last isolate encoded only non-ESBL TEM. That isolate displayed MICs of 2 μg/ml for ertapenem and 4 to 8 μg/ml for cefepime in multiple determinations, was susceptible to cefotaxime, ceftazidime, and imipenem, and was not susceptible to cefoxitin and piperacillin-tazobactam. This pattern is similar to that observed by Beceiro et al. for a non-ESBL TEM-1 expressed under the control of a promoter with elevated activity in a porin-deficient *E. coli* strain (19); however, in contrast to that case, the isolate in this study was not sensitive to the combination of cefepime and clavulanic acid (data not shown), suggesting that additional resistance mechanisms may be involved.

ESBL rates increased slightly from 6.5% in 2009 to 8.0% in 2013, with a faster increase among isolates from community-associated IAIs (from 4.3 to 7.3%), but none of these trends was statistically significant (Fig. 2). Multidrug-resistant (MDR) *E. coli* presented a similar pattern, with the rate more than doubling from 2009 to 2013 among community-associated infections (Fig. 3). This trend approached statistical significance in both the main analysis ($P = 0.10$) and the sensitivity analysis ($P = 0.07$). We cannot explain the decreases in the ESBL and MDR rates seen in 2012. Since these decreases were also found in the sensitivity analyses, they do not appear to be caused by sampling bias due to sites not participating every year. They are likely at least partly due to sampling variations common in surveillance studies, in which the characteristics of a population are estimated by examining a limited subset of that population. The finding underscores the importance of looking at longer-term trends, rather than placing undue significance on individual yearly estimates.

This study has limitations. The categorization of IAIs into hospital-associated and community-associated infections based on the length of time between hospital admission and specimen collection is imperfect, since patients may be transferred to a hospital from another health care facility. Nevertheless, publications on various infection types, regions, and time periods using this defi-

TABLE 2 MICs and β-lactamases found in 10 non-ertapenem-susceptible isolates from IAIs in the United States in 2009 to 2013

Year	State	Patient age (yr)	Type[a]	MIC (μg/ml)[b]									Molecular characteristics[c]			
				ETP	IPM	FEP	CTX	CAZ	FOX	TZP	CIP	AMK	OSBL	ESBL	AmpC	Carbapenemase
2009	Ohio	61	HA	>4	8	8	128	128	>16	64	≤0.25	≤4			CMY-2	
2010	California	2	CA	>4	>8	8	128	>128	>16	>64	0.5	≤4	TEM		CMY-2	
2010	California	46	NA	1	0.25	>32	>128	>128	>16	>64	>2	32		CTX-M-15		
2010	Pennsylvania	49	HA	>4	>8	>32	>128	>128	>16	>64	>2	≤4		SHV-12		KPC-2
2011	Pennsylvania	51	CA	>4	8	>32	>128	128	>16	>64	>2	≤4		SHV-12		KPC-2
2011	New York	56	CA	>4	4	>32	>128	>128	>16	>64	>2	>32	TEM	SHV-5		KPC-3
2012	California	55	HA	2	0.25	4	≤0.5	≤0.5	16	64	>2	16	TEM			
2012	Georgia	86	CA	>4	8	8	32	128	>16	64	>2	≤4	TEM		CMY-2	
2013	Michigan	67	HA	2	0.25	32	32	16	16	32	>2	16		CTX-M-71		
2013	New York	80	HA	>4	4	>32	>128	128	>16	>64	>2	≤4	TEM			KPC-3

[a] HA, hospital-associated (hospital stay of ≥48 h at the time of specimen collection); CA, community-associated (hospital stay of <48 h); NA, not available.
[b] ETP, ertapenem; IPM, imipenem; FEP, cefepime; CTX, cefotaxime; CAZ, ceftazidime; FOX, cefoxitin; TZP, piperacillin-tazobactam; CIP, ciprofloxacin; AMK, amikacin.
[c] OSBL, original-spectrum β-lactamase; ESBL, extended-spectrum β-lactamase; AmpC, plasmid-encoded class C β-lactamase.

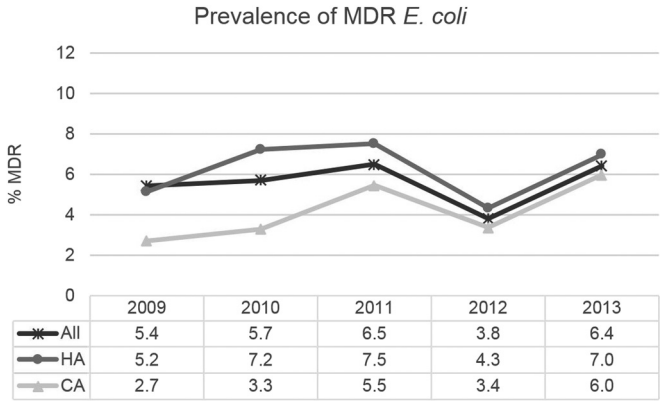

FIG 3 Trends in the prevalence of multidrug-resistant isolates of *E. coli* from IAIs in the United States in 2009 to 2013. No statistically significant trends were noted in main (all 29 sites) or sensitivity (12 continuously participating sites) analyses (all $P > 0.05$). MDR, multidrug-resistant; HA, hospital-associated; CA, community-associated. *E. coli* sample sizes (denominators) were as follows: all (including isolates from HA and CA IAIs, as well as isolates for which the time of collection postadmission was not reported), 2009, 551 isolates; 2010, 613 isolates; 2011, 554 isolates; 2012, 603 isolates; 2013, 576 isolates; HA, 2009, 291 isolates; 2010, 249 isolates; 2011, 213 isolates; 2012, 277 isolates; 2013, 258 isolates; CA, 2009, 184 isolates; 2010, 334 isolates; 2011, 311 isolates; 2012, 326 isolates; 2013, 318 isolates.

nition have consistently found higher susceptibility and lower ESBL rates for community-associated infections, thus helping to depict community trends (20–23). Another limitation common in longitudinal surveillance studies is that analyses are often negatively affected by changes in local sites from year to year. Therefore, sensitivity analyses were performed using only continuously participating sites. About one-third of the isolates had to be excluded, leading to smaller sample sizes and less power to find statistical significance. On the other hand, sensitivity analyses may make it easier to discern trends, as the "noise" and diluting effects of sites that enter and leave the study are reduced. The sensitivity analyses performed for this report corroborated the stability of susceptible rates found for most agents, as well as the stability of MICs for ertapenem, and they confirmed the weak statistical evidence of an increase in MDR rates in the community. The decreasing trends in susceptibility to levofloxacin and cefotaxime in the community were found only in either the main analysis or the sensitivity analysis. Both are plausible, considering the spread of *E. coli* ST131 (24) and the slight increase in ESBL rates, affecting cephalosporins and often being associated with coresistance to other drug classes.

Both globally and in North America, decreasing susceptibility to many drugs of *E. coli* isolates from IAIs was reported in several studies for the years leading up to 2009/2010 (25–27). In those studies, ertapenem, imipenem, and amikacin were the only tested agents without evidence of activity loss in North America. The current report found that, since 2009, resistance rates have stabilized for almost all drugs, and carbapenems have maintained their excellent activity, despite increasing reports of carbapenem resistance worldwide (4, 6). However, this report did find some evidence of increasing resistance among isolates from community-associated infections, including the decreasing trends in levofloxacin and cefotaxime susceptibility in the main and/or sensitivity analyses, which were statistically significant, the increasing trends in MDR rates, which approached significance, and the slight increase in ESBL-positive isolates, which, although not statistically significant, is worrisome considering other reports of the spread of ESBLs in the community (28, 29). Worldwide reports of increasing resistance and new resistance mechanisms, the mobility of plasmid-mediated resistance, and today's human mobility all combine to underscore the importance of remaining vigilant and continuing surveillance efforts. Surveillance is important at every level (global, national, and local), as resistance patterns and trends help inform empirical treatment decisions and support infection control efforts.

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