



# Prevalence of Invasive Infections Due to Carbapenem-Resistant *Enterobacteriaceae* among Adult Patients in U.S. Hospitals

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**ABSTRACT** This large-scale retrospective analysis ( $n = 60,551$ ) of the Premier inpatient database (1 January 2011 to 31 December 2014) found an overall prevalence of carbapenem-resistant *Enterobacteriaceae* strains of 2.3% (range, 0.9% to 5.8% by geographic region) among patients with infections due to *Enterobacteriaceae*. Ongoing monitoring and development of decision support tools/algorithms are needed for identification of high-risk patients.

**KEYWORDS** bacterial drug resistance, anti-infective agents, carbapenems, bacterial infections, urinary tract infections, intra-abdominal infections, bacterial pneumonia, bacteremia

Although the U.S. Centers for Disease Control and Prevention (CDC) identifies infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) as an urgent public health threat (1), limited data exist regarding the true prevalence of these infections among adult hospitalized patients. Existing surveillance programs potentially underestimate prevalence owing to limited site participation and clinical specimen availability. This study sought to quantify the prevalence of carbapenem resistance in invasive infections due to *Enterobacteriaceae* among adult hospitalized patients within 9 geographic regions across the United States.

(Preliminary results from this study were presented at the Society for Healthcare Epidemiology of America Spring 2015 Conference, 14–17 May, 2015, Orlando, FL.)

To accomplish the study objectives, a retrospective observational study was performed using hospital discharge data from approximately 178 U.S. health care facilities in the Premier research database with accessible microbiology results (see Appendix A in the supplemental material). In total, the Premier hospital database includes data from approximately 80 million admissions (>5 million added per year since 2011). Admissions data are provided by >500 participating acute care hospitals from across the United States and account for approximately 20% of all inpatient discharges in the nation (Premier Healthcare Database: Data that Informs and Performs, Premier, Inc., Charlotte, NC). The infective episode for a patient was included if all of the following criteria were met: (i) patient  $\geq 18$  years of age; (ii) inpatient discharge between 1 January 2011 and 31 December 2014; (iii) primary or secondary diagnosis at discharge using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), codes of complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), hospital-associated pneumonia (HAP), or bloodstream infection (BSI) (see Appendix B in the supplemental material); (iv) positive culture for an *Enterobacteriaceae* strain obtained from a site consistent with the infection type (see Appendix C in the supplemental material); (v) receipt of antibiotic treatment on day of *Enterobacteriaceae* culture collection or  $\leq 3$  days after index *Enterobacteriaceae* culture; and (vi) available susceptibility data for the index isolate.

Cohorts by infection type were not mutually exclusive; patients were allowed to

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contribute information to multiple cohorts. However, in any qualifying admission, a patient could contribute data to a given disease cohort only once. All infections observed in qualifying admissions were considered independent.

Because of changing susceptibility breakpoints during the study period, resistance was defined as nonsusceptibility to meropenem, imipenem, doripenem, or ertapenem. Carbapenem resistance rates were stratified by U.S. geographic region (9 CDC regions), hospital type and characteristics (teaching versus nonteaching, urban versus rural), hospital unit (intensive care unit [ICU] versus non-ICU), infection type (cUTI, cIAI, HAP, or BSI), and pathogen (*Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, or other [*Citrobacter* spp. and *Serratia* spp.]). All calculations were computed using SAS 9.3 (SAS Institute, Cary, NC).

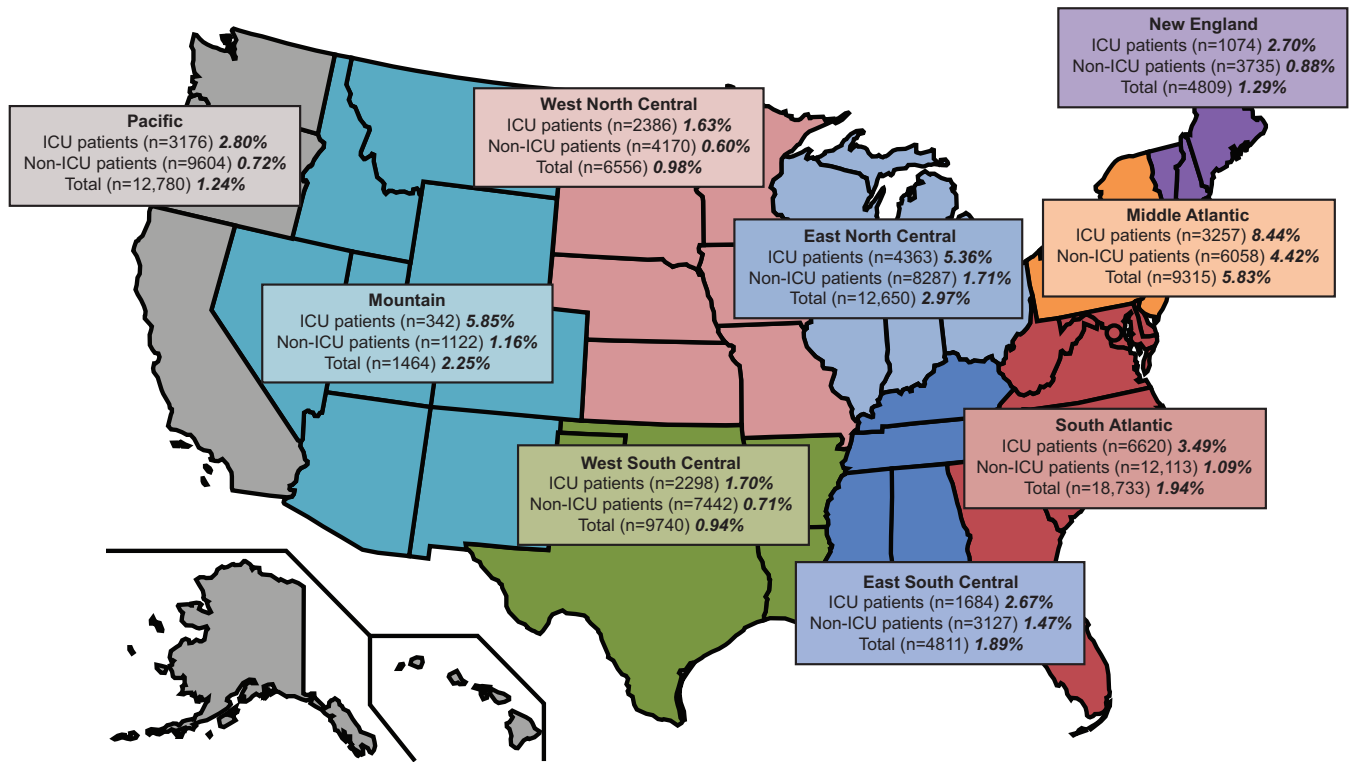
A total of 60,551 infective episodes met the study criteria. Overall resistance to carbapenem was 2.3% with substantial variation by geographic region (Fig. 1). The highest rates of CRE were observed in the Mid-Atlantic, East North Central, and Mountain areas, whereas the lowest rates were observed in the West North Central and West South Central areas. Prevalence of CRE was higher in ICUs than in non-ICUs across all geographic regions (Fig. 1A). Prevalence of CRE was also highest among patients with HAP relative to those with other infection types (Fig. 1B). Stratification by hospital type showed that resistance rates were higher in teaching than in nonteaching hospitals (3.2% versus 1.6%) and higher in urban than in rural hospitals (2.4% versus 0.8%). Rates also tended to be higher in larger hospitals, with rates of 1.0%, 2.3%, and 2.8%, respectively, for hospitals with 0 to 199, 200 to 499, and  $\geq 500$  beds.

Prevalence of CRE by geographic region, pathogen, and hospital unit are displayed in Table 1. In several regions, the prevalence of carbapenem resistance among patients with invasive infections due to *Klebsiella* spp. and *Enterobacter* spp. exceeded 5% and approached 10% (i.e., several with a prevalence of  $\geq 8\%$ ). In contrast, rates of carbapenem resistance among infections due to *E. coli* were less than 1% for all geographic regions except in the ICUs in the East South Central, Mid-Atlantic, and Mountain regions. Prevalence of CRE by infection type, pathogen, and hospital unit are shown in Table 2. Irrespective of infection type, the highest rates of carbapenem resistance were observed in patients in the ICU with an infection due to *Klebsiella* spp. or *Enterobacter* spp.

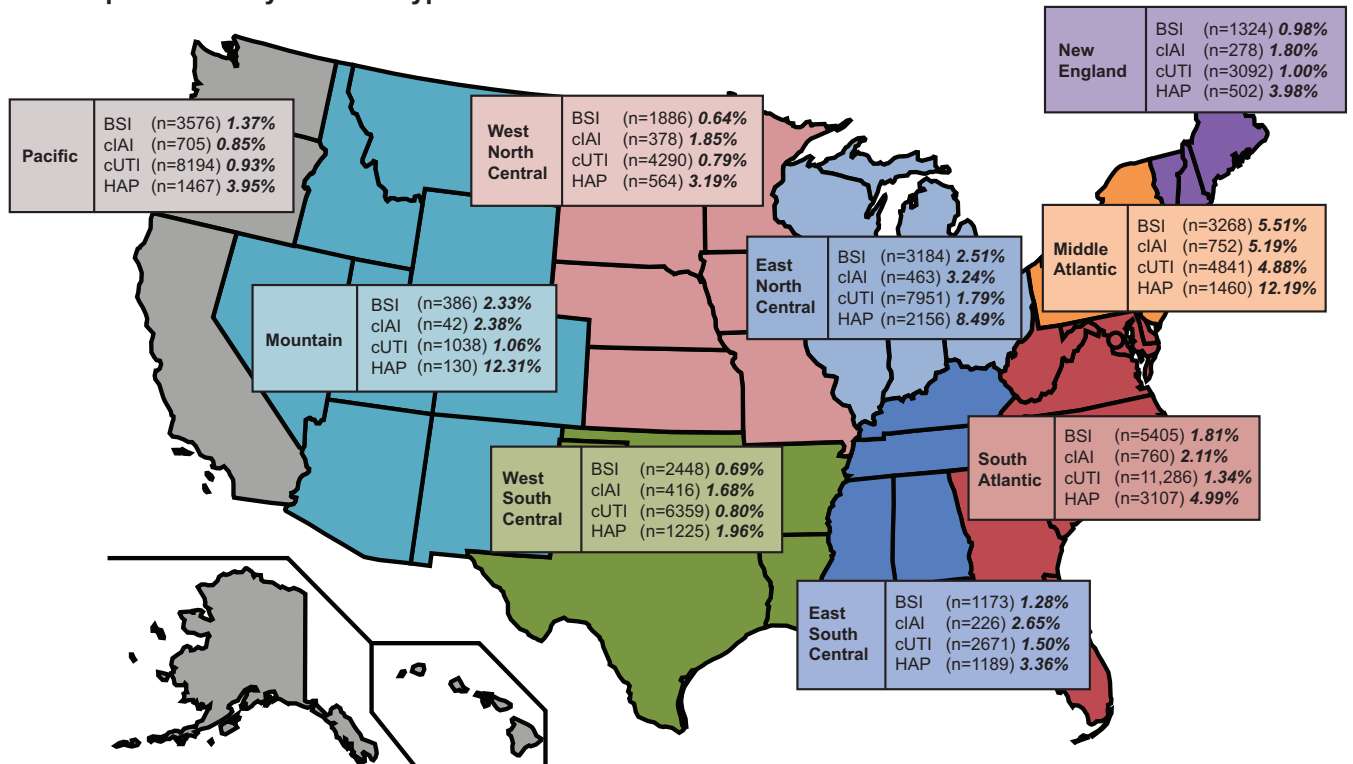
In light of our findings, the use of empirical carbapenems should be revisited in some hospitals located in areas of high CRE prevalence in patients with suspected or documented invasive infection due to *Klebsiella* spp. and *Enterobacter* spp., especially among those patients in the ICU and those with HAP. Although there are no definitive guidelines regarding empirical antibiotic selection for treatment of a suspected or documented infection due to *Enterobacteriaceae*, it is typically not advisable to select an antibiotic as empirical treatment once rates of resistance to that antibiotic exceed 20% (2). The rapid spread of CRE over the past 10 years across the United States also highlights the need for ongoing monitoring at the regional and hospital levels. Furthermore, the results suggest that institutions should proactively identify patient populations at greatest risk for carbapenem resistance and develop decision support tools/algorithms for identifying patients who are at high risk for CRE. This information will be important for clinicians to support selection of the most appropriate empirical treatment for patients within the first 48 to 72 h of infection onset before culture results are available.

Several limitations affect the interpretation of these findings. Because data were extracted from an electronic database, our findings may be limited by the accuracy of the coding of those data, including the accuracy of the microbiological data. However, Premier does link patient keys (unique identifiers) to microbiological specimens and specimen information, including isolated organisms and susceptibility data, to ensure accuracy within the database. In addition, Premier conducts a separate validation process to ensure that the data are entered into the database correctly. In addition to relying on ICD-9-CM coding, we also required culture data from sites appropriate for the ICD-9-CM code to minimize the impact of any coding errors. Nonetheless, data

**A. CRE prevalence by region: cUTI + cIAI + HAP + BSI**



**B. CRE prevalence by infection type**



**FIG 1** Prevalence of carbapenem resistance rates among hospitalized patients with infection due to *Enterobacteriaceae*, stratified by (A) geographic area (U.S. Centers for Disease Control and Prevention regions, combined cUTI, cIAI, HAP, and BSI) and hospital unit, 2011 to 2014, and (B) infection type. Rates are shown in bold italic type. BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant *Enterobacteriaceae*; cUTI, complicated urinary tract infection; HAP, hospital-associated pneumonia; ICU, intensive care unit.

**TABLE 1** Prevalence of carbapenem resistance rates among hospitalized patients with infection due to *Enterobacteriaceae*, stratified by geographic area (U.S. Centers for Disease Control and Prevention regions), pathogen, and hospital unit, 2011–2014

Geographic division	Hospital unit	<i>Klebsiella</i> spp.		<i>Enterobacter</i> spp.		<i>Escherichia coli</i>		<i>Citrobacter</i> spp.		<i>Serratia</i> spp.	
		No. of patients	% with CRE <sup>a</sup>	No. of patients	% with CRE	No. of patients	% with CRE	No. of patients	% with CRE	No. of patients	% with CRE
East North Central	ICU <sup>b</sup>	1,503	12.18	579	6.04	2,346	0.34	193	2.07	311	1.61
	Non-ICU	1,742	5.97	484	3.72	5,980	0.15	267	1.50	193	4.15
	Total	3,245	8.84	1,063	4.99	8,326	0.20	460	1.74	504	2.58
East South Central	ICU	554	3.97	242	4.55	935	1.18	59	5.08	126	2.38
	Non-ICU	701	3.99	254	3.94	2,123	0.19	82	1.22	120	2.50
	Total	1,255	3.98	496	4.23	3,058	0.49	141	2.84	246	2.44
Mid-Atlantic	ICU	1,250	14.96	502	14.34	1,656	1.15	185	3.24	238	4.62
	Non-ICU	1,395	14.48	434	8.53	4,183	0.65	218	0.92	160	1.88
	Total	2,645	14.71	936	11.65	5,839	0.79	403	1.99	398	3.52
Mountain	ICU	114	7.89	37	8.11	186	1.61	10	0.00	18	27.78
	Non-ICU	137	1.46	53	7.55	925	0.54	25	0.00	8	25.00
	Total	251	4.38	90	7.78	1,111	0.72	35	0.00	26	26.92
New England	ICU	312	1.92	161	6.83	568	0.88	66	1.52	109	5.50
	Non-ICU	726	1.24	317	3.15	2,583	0.39	175	1.14	95	3.16
	Total	1,038	1.45	478	4.39	3,151	0.48	241	1.24	204	4.41
Pacific	ICU	1,018	3.54	370	5.14	1,931	0.88	128	2.34	156	8.97
	Non-ICU	1,572	1.84	429	1.86	7,638	0.26	268	0.37	146	8.22
	Total	2,590	2.51	799	3.38	9,569	0.39	396	1.01	302	8.61
South Atlantic	ICU	2,410	4.73	930	8.82	3,412	0.59	263	3.04	411	2.68
	Non-ICU	2,489	2.61	732	4.10	8,701	0.29	357	0.56	302	3.64
	Total	4,899	3.65	1,662	6.74	12,113	0.37	620	1.61	713	3.09
West North Central	ICU	679	3.98	259	3.09	1,473	0.27	100	0.00	89	0.00
	Non-ICU	756	2.51	266	1.50	3,106	0.03	129	0.00	81	1.23
	Total	1,435	3.21	525	2.29	4,579	0.11	229	0.00	170	0.59
West South Central	ICU	702	2.56	250	3.20	1,431	0.42	103	2.91	108	4.63
	Non-ICU	1,202	1.41	360	2.50	5,844	0.29	199	3.52	140	2.86
	Total	1,904	1.84	610	2.79	7,275	0.32	302	3.31	248	3.63

<sup>a</sup>CRE, carbapenem-resistant *Enterobacteriaceae*.

<sup>b</sup>ICU, intensive care unit.

abstraction from medical records or prospective data collection would provide more accurate and comprehensive clinical data. Although resistance rates were stratified by region and hospital characteristics, these findings may not apply to every institution in a given region. In addition, the variations in resistance rates may in part be due to the small number of patients with CRE in certain regions. As such, local antibiograms and patient and disease characteristics should always drive empirical antibiotic selection. However, the data clearly highlight carbapenem resistance concerns among hospitalized patients with an invasive infection due to *Enterobacteriaceae*. Carbapenem resistance was defined as nonsusceptibility to  $\geq 1$  carbapenem only, as opposed to resistance to  $\geq 1$  carbapenem and nonsusceptibility to  $\geq 1$  relevant third-generation cephalosporin. Due to the changing Clinical and Laboratory Standards Institute and U.S. Food and Drug Administration definitions of carbapenem susceptibility over the study period, this study relied solely on nonsusceptibility to carbapenem. This study did not evaluate antibiotic resistance factors at a patient-specific level. Despite these limitations, the characterization of CRE trends at the regional level and by hospital characteristics provides information to support clinicians in empirical antibiotic selection.

The findings from this study underscore the urgent public health threat from infections caused by CRE, especially among patients with an invasive infection due to *Klebsiella* spp. or *Enterobacter* spp. in the Mid-Atlantic and surrounding regions. Rising rates of CRE necessitate ongoing monitoring at regional and hospital levels. Given the

**TABLE 2** Prevalence of carbapenem resistance rates among hospitalized patients with infection due to *Enterobacteriaceae*, stratified by infection type, pathogen, and hospital unit, 2011–2014

	Pathogen	Setting	No. of Patients	% with CRE <sup>a</sup>
Complicated urinary tract infection	<i>E. coli</i>	ICU <sup>b</sup>	5,835	0.51
	<i>E. coli</i>	Non-ICU	31,874	0.29
	<i>E. coli</i>	Total	37,709	0.32
	<i>Enterobacter</i> spp.	ICU	607	6.75
	<i>Enterobacter</i> spp.	Non-ICU	1,962	4.08
	<i>Enterobacter</i> spp.	Total	2,569	4.71
	<i>Klebsiella</i> spp.	ICU	2,292	7.20
	<i>Klebsiella</i> spp.	Non-ICU	6,737	4.72
	<i>Klebsiella</i> spp.	Total	9,029	5.35
	<i>Serratia</i> spp.	ICU	209	4.31
	<i>Serratia</i> spp.	Non-ICU	544	3.86
	<i>Serratia</i> spp.	Total	753	3.98
	<i>Citrobacter</i> spp.	ICU	394	2.54
	<i>Citrobacter</i> spp.	Non-ICU	1,296	1.00
<i>Citrobacter</i> spp.	Total	1,690	1.36	
Complicated intra-abdominal infection	<i>E. coli</i>	ICU	1,396	1.07
	<i>E. coli</i>	Non-ICU	1,589	0.19
	<i>E. coli</i>	Total	2,985	0.60
	<i>Enterobacter</i> spp.	ICU	315	10.16
	<i>Enterobacter</i> spp.	Non-ICU	155	4.52
	<i>Enterobacter</i> spp.	Total	470	8.30
	<i>Klebsiella</i> spp.	ICU	654	5.50
	<i>Klebsiella</i> spp.	Non-ICU	406	1.97
	<i>Klebsiella</i> spp.	Total	1,060	4.15
	<i>Serratia</i> spp.	ICU	41	2.44
	<i>Serratia</i> spp.	Non-ICU	21	4.76
	<i>Serratia</i> spp.	Total	62	3.23
	<i>Citrobacter</i> spp.	ICU	150	3.33
	<i>Citrobacter</i> spp.	Non-ICU	109	0.00
<i>Citrobacter</i> spp.	Total	259	1.93	
Hospital-associated pneumonia	<i>E. coli</i>	ICU	3,058	0.88
	<i>E. coli</i>	Non-ICU	1,223	0.74
	<i>E. coli</i>	Total	4,281	0.84
	<i>Enterobacter</i> spp.	ICU	1,868	8.40
	<i>Enterobacter</i> spp.	Non-ICU	458	4.37
	<i>Enterobacter</i> spp.	Total	2,326	7.61
	<i>Klebsiella</i> spp.	ICU	3,803	8.73
	<i>Klebsiella</i> spp.	Non-ICU	1,291	6.51
	<i>Klebsiella</i> spp.	Total	5,094	8.17
	<i>Serratia</i> spp.	ICU	1,067	4.22
	<i>Serratia</i> spp.	Non-ICU	389	5.40
	<i>Serratia</i> spp.	Total	1,456	4.53
	<i>Citrobacter</i> spp.	ICU	429	3.03
	<i>Citrobacter</i> spp.	Non-ICU	114	3.51
<i>Citrobacter</i> spp.	Total	543	3.13	
Bloodstream infection	<i>E. coli</i>	ICU	5,949	0.79
	<i>E. coli</i>	Non-ICU	9,426	0.27
	<i>E. coli</i>	Total	15,375	0.47
	<i>Enterobacter</i> spp.	ICU	934	7.17
	<i>Enterobacter</i> spp.	Non-ICU	909	3.19
	<i>Enterobacter</i> spp.	Total	1,843	5.21
	<i>Klebsiella</i> spp.	ICU	2,963	6.38
	<i>Klebsiella</i> spp.	Non-ICU	3,035	3.43
	<i>Klebsiella</i> spp.	Total	5,998	4.68
	<i>Serratia</i> spp.	ICU	434	4.15
	<i>Serratia</i> spp.	Non-ICU	364	1.92
	<i>Serratia</i> spp.	Total	798	3.13
	<i>Citrobacter</i> spp.	ICU	274	1.09
	<i>Citrobacter</i> spp.	Non-ICU	277	1.44
<i>Citrobacter</i> spp.	Total	551	1.27	

<sup>a</sup>CRE, carbapenem-resistant *Enterobacteriaceae*.<sup>b</sup>ICU, intensive care unit.

importance of initiating early appropriate therapy, the findings highlight the need for developing decision support tools to identify patients at high risk for CRE and should be considered alongside patient and hospital characteristics when selecting empirical treatment for patients before availability of culture results.

### SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.00228-17>.

**SUPPLEMENTAL FILE 1**, PDF file, 0.3 MB.

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