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Carbapenem-Resistant enterobacterales in individuals with and without health care risk factors —Emerging infections program, United States, 2012-2015

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SUPPLEMENTARY MATERIALS

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Abstract

Background: Carbapenem-resistant Enterobacterales (CRE) are usually healthcare-associated but are also emerging in the community.

Methods: Active, population-based surveillance was conducted to identify case-patients with cultures positive for Enterobacterales not susceptible to a carbapenem (excluding ertapenem) and resistant to all third-generation cephalosporins tested at 8 US sites from January 2012 to December 2015. Medical records were used to classify cases as health care-associated, or as community-associated (CA) if a patient had no known health care risk factors and a culture was collected <3 days after hospital admission. Enterobacterales isolates from selected cases were submitted to CDC for whole genome sequencing.

Results: We identified 1499 CRE cases in 1194 case-patients; 149 cases (10%) in 139 case-patients were CA. The incidence of CRE cases per 100,000 population was 2.96 (95% CI: 2.81, 3.11) overall and 0.29 (95% CI: 0.25, 0.35) for CA-CRE. Most CA-CRE cases were in White persons (73%), females (84%) and identified from urine cultures (98%). Among the 12 sequenced CA-CRE isolates, 5 (42%) harbored a carbapenemase gene.

Conclusions: Ten percent of CRE cases were CA; some isolates from CA-CRE cases harbored carbapenemase genes. Continued CRE surveillance in the community is critical to monitor emergence outside of traditional health care settings.

Keywords

Carbapenems; Carbapenemase-producing enterobacterales; Community-associated disease; Healthcare-associated infections; Multi-drug resistant gram-negative organisms

BACKGROUND

Carbapenem-resistant Enterobacterales (CRE) are typically associated with health care settings and are the focus of targeted infection-control interventions because of CRE's capacity to cause difficult-to-treat infections and to spread rapidly.[1–4] Of particular concern are CRE that produce carbapenemases, enzymes that inactivate most or all β-lactam antibiotics and are frequently encoded on mobile genetic elements such as plasmids that can be transmitted between organisms, facilitating spread.[5] The burden of CRE infections might be increasing among persons without health care exposure, both in the United States and abroad; however, as most United States CRE surveillance is hospital-based, robust ascertainment of prior health care exposures in patients with CRE and epidemiologic descriptions of CRE among persons without health care exposures are limited.[6–9]

The Centers for Disease Control and Preventions' (CDC's) Emerging Infections Program (EIP) Health Care-Associated Infections–Community Interface Activity (HAIC) has conducted surveillance for CRE and other drug-resistant Gram-negative bacteria since 2012 through the Multi-site Gram-negative Surveillance Initiative (MuGSI). We analyzed MuGSI CRE surveillance data from 2012 to 2015 to compare the incidence and epidemiology of community-associated-CRE (CA-CRE) cases to CRE cases with health care risk factors, and to describe the molecular epidemiology of CRE isolated from CA-CRE cases.

METHODS

Surveillance catchment area

Laboratory and population-based surveillance was conducted at 8 EIP sites in 2012-2015. Participating sites as of 2015 included Atlanta, Georgia (8 counties; estimated population: 3,991,607); Minneapolis and St. Paul, Minnesota (2 counties; estimated population: 1,761,282); and Portland, Oregon (3 counties; estimated population; 1,766,135), Denver, Colorado (5 counties; estimated population: 2,694,886), Baltimore, Maryland (4 counties; estimated population: 1,934,018), Albuquerque, New Mexico (1 county; estimated population: 676,685), Rochester, New York (1 county; estimated population: 749,600), Nashville, Tennessee (8 counties; estimated population: 1,653,871).[10,11] The total population under surveillance in 2015 was approximately 15.2 million.[11]

Case definition and epidemiological classification

We defined a CRE case as the first isolation, in a 30-day period, from a catchment area resident, meeting the phenotypic case definition of carbapenem non-susceptible and third-generation cephalosporin-resistant *Klebsiella pneumoniae, K. oxytoca, K. aerogenes* (formerly *Enterobacter aerogenes), Enterobacter cloacae* complex, or *Escherichia coli* from a normally sterile body site or urine specimen. Antimicrobial resistance was defined according to the Clinical and Laboratory Standards Institute (CLSI) interpretive criteria.[12] Antimicrobial susceptibility testing results from the local clinical laboratory's primary testing method were used to identify isolates with carbapenem minimum inhibitory concentrations (MICs) ≥2 μg/mL to imipenem, meropenem, or doripenem (ertapenem was excluded) and with MICs indicating resistance to any third-generation cephalosporin tested (ceftazidime MIC ≥16 μg/mL; ceftriaxone or cefotaxime MIC ≥4 μg/mL).[12,13] Although this surveillance program is ongoing, the phenotypic case definition was changed in 2016, therefore our analysis is limited to data collected before 2016.[14]

A case was defined as health care-associated (HCA) if it occurred in a patient with any of the following risk factors: (1) collection of the case-defining culture on or after day 3 of admission to a short stay acute care hospital (ACH); (2) admission to an ACH or long-term acute care hospital (LTACH), residence in a long-term care facility (LTCF) (including nursing home, skilled nursing facility, inpatient hospice or physical rehabilitation facility), or inpatient or outpatient surgery in the year prior to the date of culture; (3) undergoing chronic dialysis at time of culture; or (4) presence of a urinary catheter or another type of indwelling device at the time of or in the 2 calendar days before the date of incident culture. Cases in patients without any of these health care risk factors were classified as CA.

Case identification and data collection

To identify cases, reports of CRE isolates were actively collected from clinical laboratories serving the catchment area. Catchment area residency was determined using the patient address that accompanied isolate submission. A standardized case report form was used to collect patient demographics, clinical characteristics, underlying conditions, health care exposures and outcomes, location of specimen collection, and types of infections associated with the case-defining specimen. All inpatient (ACH and LTACH) and LTCF medical

records from the year prior to the date of collection for the case-defining specimen were reviewed. In the outpatient setting, records from the 5 days prior to the date of collection for the case-defining specimen were reviewed; if no prior hospitalizations or surgeries were identified, then a full year of outpatient records was reviewed. Mortality was defined as death occurring within 30 days of the date of collection for the case-defining specimen, as documented in state death registries. A Charlson Comorbidity Index score (CCI) was calculated based on underlying conditions abstracted from the medical record.[15,16] If the case-defining CRE was isolated from a urine culture, additional information was collected to apply a standardized definition for urinary tract infection (UTI).[17] UTI was defined as a urine culture positive for $\geq 10^5$ CFU/ml of a single species of CRE in a patient who had any one of the following criteria: (1) documentation of a urinary catheter in place in the 2 days before the date of collection for the case-defining urine specimen, (2) documented signs or symptoms consistent with UTI during the 2 calendar days before through the 2 calendar days after the date of collection for the case-defining urine specimen, or (3) positive blood culture with the same CRE species within 30 days of the date of collection for the case-defining urine specimen.[17,18]

Analytic and statistical methods

Crude incidence rates were calculated by EIP site, year, and epidemiologic class using the annual case counts reported by each EIP site linked to the United States Census population for the areas under surveillance. These crude rates were expressed as the number of cases per 100,000 population, and 95% confidence intervals were calculated assuming a Poisson distribution.[19] Cases with missing values for race were imputed based on the distribution of known race among cases by age category, sex, EIP site, year of CRE specimen collection, and presence or absence of diabetes. Variables were selected for the imputation process to improve accuracy of the predicted race. Resulting imputed race categories were White, Black/African American, and other race which includes American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander. Due to small numbers all non-White race categories, even after imputation, were collapsed into a single category for analysis. We performed descriptive analyses of demographics at the patient level. Health care exposures, outcomes, and isolate antibiotic susceptibility were analyzed at the case level. Analysis was limited to case report forms determined to be complete as of March 13, 2018. *P*-values for comparisons of categorical variables were calculated using the χ^2test, or the Fisher's exact test for cell sizes less than 5. The Wilcoxon Rank Sum Test was used to test the difference between medians.[20] Data management and analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Isolate collection, submission and evaluation

A convenience sample of isolates was submitted for further evaluation at CDC; the methods for isolate collection evolved during the project period, and these changes are documented in the Supplementary Material.

Isolates received at the CDC underwent the following testing: species identification using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF Biotyper 3.1, Bruker Daltonics, Billerica, MA), antimicrobial susceptibility testing using

reference broth microdilution with a metallo-β-lactamase (MBL) screen; modified Hodge test to detect carbapenemase production (MHT; per CLSI the recommended phenotypic test for carbapenemase production at the time of isolate submission) and real-time polymerase chain reaction (PCR) testing for *bla*$_{KPC}$, *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ genes.[12,21,22] If a CRE isolate was determined to harbor a carbapenemase-producing gene, it was classified as carbapenemase-producing (CP). Additional real-time PCR testing was conducted for *bla*$_{VIM}$ if the isolate was MBL screen positive and *bla*$_{NDM}$ negative.[23] All isolates displaying a colistin MIC of ≥2 μg/mL were screened for plasmid-mediated colistin resistance genes (*mcr-1* and *mcr-2*) by real-time PCR.[24]

Whole genome sequencing was conducted on CA-CRE isolates that were confirmed carbapenem non-susceptible and third-generation cephalosporin-resistant using reference broth microdilution at the CDC. Sequencing was performed using an Illumina MiSeq System (San Diego, CA). Sequences were analyzed using the CDC laboratory's in-house QuAISAR-H pipeline (Quality, Assembly, species Identification, Sequence typing, Annotation, Resistance mechanism for Health care pathogens).[25] QuAISAR-H performs a variety of functions, including cleaning, trimming, and assembling sequence data from each isolate. QuAISAR-H identified antibiotic resistance (AR) genes, including carbapenemase genes, beta-lactamase genes, and plasmid-mediated colistin resistance (*mcr*) genes, using a combined database of acquired antimicrobial resistance (AR) genes from ResFinder, ARG-ANNOT, and AMRFinderPlus; genes with 95% Identity and 100% Coverage threshold were reported.[26–28] Multilocus sequence type (MLST) was determined using the publicly available schemes curated by pubMLST.[29,30] Whole genome sequence analyses were performed using the specified AR genes databases, listed above, current through December 27, 2019. All reported isolate results, generated at the CDC, are final as of August 7, 2020.

RESULTS

Cases and crude incidence rates

From January 1, 2012, through December 31, 2015, we identified a total of 1,585 incident cases. Among these, 1,499 cases in 1,194 case-patients are included in this analysis because the cases had complete medical record review, required for ascertainment of epidemiologic class. Among the cases, 1,350 (90%) were HCA-CRE and 149 (10%) were CA-CRE. The overall crude incidence of CRE across all the sites during the 4-year period was 2.96 (95% CI: 2.81, 3.11) cases per 100,000 population (Table 1). The crude incidence rates varied by EIP site, year, and epidemiological class (Table 1). Sites with the highest overall crude incidence of HCA-CRE, Maryland and Georgia, differed in epidmiological class from those with the highest overall crude incidence of CA-CRE, New Mexico and New York (Table 1).

Organism, culture source and infection syndrome

K. pneumoniae was the most frequent organism among all cases (n = 800, 53%), followed by *E. coli* (n = 275, 18%). Overall, a higher proportion of HCA-CRE were *K. pneumoniae* compared to CA-CRE (772/1350 [58%] vs 28/149 [19%], respectively; $P < .001$), and a higher proportion of CA-CRE were *E. coli* compared to HCA-CRE (61/149 [40%] vs 214/1350 [16%], respectively; $P < .001$); however, at 2 sites, Minnesota and Oregon,

the same organism predominated among both CA-CRE and HCA-CRE; in Minnesota, *K. aerogenes* (CA-CRE: 55%, HCA-CRE: 40%, overall: 42%), and in Oregon, *E. cloacae* complex (CA-CRE: 18%, HCA-CRE: 21%, overall: 20%).

Urine was the most common culture source among all CRE cases (n = 1,305, 87%) and was the source of 98% of all CA-CRE cases compared to 86% of HCA-CRE cases ($P <$ .001). The most common infection syndrome associated with all cases, as documented in the medical record, was UTI (n = 1,024). Clinically documented UTIs were more commonly identified among CA-CRE cases than HCA-CRE cases (83% vs 67%, $P <$ .001, Table 2). When applying a standardized UTI definition to cases where the isolate was from urine, 113 (9%) met the definition; the proportion of cases that met the UTI definition was similar among CA-CRE cases and HCA-CRE cases (16/146 [11%] vs 97/1159 [8%], $P =$ .27).

Demographics and clinical characteristics of case-patients

Among the 1,194 case-patients, the 139 CA-CRE case-patients were similar in age to the 1055 HCA-CRE case-patients (CA-CRE: median 64 years, interquartile range [IQR] 45-80; HCA-CRE: median 67 years, IQR 56-77; $P =$ .098), but were more likely to be female (CA-CRE: 117/139 [84%]; HCA-CRE: 613/1055 [58%]; $P <$ .001), of White race (CA-CRE: 102/139 [73%]; HCA-CRE: 539/1055 [51%,]; $P <$ .001), and to have fewer comorbid conditions (CA-CRE: median 1 [assessed among 139 patients], IQR 0-2; HCA-CRE: median 3 [assessed among 1052 case-patients], IQR 1-4; $P <$ .001) (Table S1 Supplementary Material).

Comorbid conditions could be assessed in 1,191 of the case-patients (see Table S1, Supplementary Material). Common comorbidities among CA-CRE and HCA-CRE case-patients included: diabetes (CA-CRE: 34/139 [24%]; HCA-CRE: 479/1052 [46%], $P <$.001), urinary tract problems/abnormalities (CA-CRE: 22/139 [16%]; HCA-CRE: 219/1052 [21%], $P =$ .17), neurological conditions (including quadriplegia) (CA-CRE: 15/139 [11%]; HCA-CRE: 292/1052 [28%], $P <$ .001,), and dementia (CA-CRE: 13/139 [9%]; HCA-CRE: 240/1,052 [23%], $P <$ .001). The proportion of CA-CRE case-patients without documentation of an underlying medical condition (n = 51, 37%) was greater when compared to HCA patients (n = 36, 3%, $P <$ .001).

Risk factors for infection and outcomes of cases

Culture sources, infection syndromes, and outcomes among cases are presented in Table 2. Overall, 15 cases occurred in 14 case-patients who had medical record notation of travel outside of the contiguous United States, Hawaii and/or Alaska in the 2 months before culture collection: these included 2 of 149 (1%) CA-CRE cases and 13 of 1350 (1%) HCA-CRE cases (Supplemental Material).

Antimicrobial susceptibility testing of incident case isolates at local clinical laboratories

Local clinical laboratory testing results for 12 non-carbapenem antibiotics are presented in Table 3. Among the 1,473 isolates that underwent testing for one or more common agents to treat UTI (ciprofloxacin, levofloxacin, ampicillin, nitrofurantoin, and trimethoprim-

sulfamethoxazole), 664 (45%) were susceptible to at least one. This included 120 (81%) of 148 CA-CRE cases compared to 544 (41%) of 1325 HCA-CRE cases ($P < .001$).

Characterization of isolates from community-associated CRE cases

Overall, 64 (43%) isolates from CA-CRE cases were submitted to the CDC for further characterization, from Minnesota (n = 18, 28%), New Mexico (n = 16, 24%), Colorado (n = 9, 14%), New York (n = 6, 9%), Oregon (n = 6, 9%), Tennessee (n = 4, 6%), Georgia (n = 3, 5%), and Maryland (n = 2, 3%). Isolates were *E. coli* (n = 26, 41%), *K. aerogenes* (n = 18, 28%), *E. cloacae* complex (n = 14, 22%), and *K. pneumoniae* (n = 6, 9%). Five (8%) isolates had a carbapenemase identified by PCR: 3 KPC-*K. pneumoniae*, 1 KPC-*E. cloacae* complex, and 1 NDM-*E. coli*. Among the 64 isolates, 15 (23%) were MHT positive using ertapenem (*K. aerogenes* [n = 8], *E. cloacae* complex [n = 3], *K. pneumoniae* [n = 3], and *E. coli* [n = 1]) and 13 (20%) were MHT positive using meropenem (*K. aerogenes* [n = 6], *K. pneumoniae* [n = 3], *E. cloacae* complex [n = 3], and *E. coli* [n = 1]). Nine isolates had a colistin MIC ≥2 μg/ml and underwent PCR testing for *mcr*-1; all tested negative. Twelve CA-CRE isolates underwent WGS at CDC; 5 of 12 (42%) were CP positive and all sequenced isolates had unique MLST (Table 4).

Epidemiology of carbapenemase-producing CA-CRE cases

Among the 12 CA-CRE cases with isolates that underwent WGS at CDC, 5 cases, representing 4 unique case-patients, harbored isolates that were CP. Of the CP-CA-CRE cases, 3 (60%) were from female patients, 4 (80%) were from individuals of White race, and the median case-patient age was 73 years (mean: 68, range: 52-84). Three cases had a documented urinary tract problem or abnormality, such as neurogenic bladder. The median CCI for the CP-CA-CRE cases was similar to the non-CP-CA-CRE cases (2 vs 1, respectively). Four CP-CA-CRE isolates (80%) were cultured from specimens collected in the outpatient setting, and one was collected in an emergency room; 2 (40%) cases were hospitalized. Three cases had documented diagnosis of UTI only, one had a bloodstream infection (BSI) only, and 1 patient had both a UTI and a BSI.

DISCUSSION

Through population- and laboratory-based surveillance in 8 United States metropolitan areas during 2012-2015, we observed that 10% of CRE cases were CA, occurring in patients without known health care risk factors. We observed variation in HCA- and CA-CRE cases by geographic site, organism distribution, and case-patient demographics and risk factors. The twelve CA-CRE isolates that underwent molecular characterization at CDC had diverse MLSTs, and at least 1 carbapenemase gene was identified in 5 isolates.

Consistent with the current understanding of CRE epidemiology in the United States, we observed that a minority of CRE cases occurred in individuals without recent health care exposures.[9] The 10% of cases that were CA-CRE is near the upper boundary of the 5.6%-10.8% range identified among the 4 studies conducted in the United States and described in a scoping review of international studies assessing CRE in the community.[9] A voluntary statewide surveillance program in Michigan (September 2012-February 2013),

which defined community-onset CRE based on where the specimen was collected (ie, collected in the outpatient setting or within the first 3 days of hospitalization), was the source of the upper boundary published by Kelly et al.[9,31] Our program's estimate of CA-CRE incidence is likely near the upper boundary because it was based on active laboratory- and population-based surveillance that included commercial outpatient laboratories, rather than hospital-based cohorts that formed the population for 2 studies with lower estimates.[9,32,33] Additionally, our surveillance system encompasses diverse geographies and included some areas with a high proportion of overall cases that were CA-CRE.

Compared to HCA-CRE, CA-CRE identified in our surveillance were more likely to be *E. coli*, and cases were more likely to occur in female persons of White race with few documented underlying conditions. Our finding of *E. coli* as the most common cause of CA-CRE UTIs, and that the CA-CRE UTIs occured primarily in women, is consistent with published literature on community-acquired UTIs.[34,35] Females outpatient settings who present with signs and symptoms of a UTI are likely treated empirically.[36,37] Our findings underscore the importance of using local epidemiology and patient risk factors (eg, age and sex) for decisions about testing and treatment.[37] Fifty percent of females will develop a UTI at some point in their lifetime, regardless of their degree of exposure to the health care setting.[34,35,38] Risk factors that predispose patients to UTIs include diabetes, neurological conditions that affect the urinary tract, and urinary tract problems or abnormalities, were frequently identified among our CA-CRE cases.[34,35,37,38] Additionally, menopause results in changes to the urobiome, putting post-menopausal females at higher risk for the development of a UTI.[38]

These data allow us to hypothesize that there could exist observed racial differences among patients with CA-CRE relative to HCA-CRE; these results were unexpected and merit further investigation. These differences may be due to unmeasured differences in health status, health care seeking behaviors, or provider laboratory test ordering practices. Unfortunately, due to small numbers we were not able to further assess differences among persons for whom race was reported to be non-White. Understanding racial and ethnic differences among patients who acquire multidrug-resistant organisms is complex, and the limited literature demonstrates a variety of causes for disparities. An analysis of patients with community-associated invasive methicillin-resistant *Staphylococcus aureus*, conducted within the EIP, found that patients of Black race had higher incidence of disease than patients of White race.[39] These differences were explained by socioeconomic characteristics as measured at the census tract level (eg, household income, proportion of expensive homes in a neighborhood, educational level, being in a medically underserved area).[39] A review of studies addressing racial and ethnic disparities among patients with health care-associated *Clostridioides difficile* infection found predominance among patients of White race, and authors theorized that access to health care and thus antibiotics could be the reason for this difference.[40] In an EIP study of CA-*Clostridioides difficile* infections (CA-CDI), communities with lower socioeconomic status, as measured at the census tract level, were found to have higher incidence of CA-CDI.[41] Lastly, the Department of Veterans Affaris demonstrated that among a retrospective cohort of patients with CRE, more persons

of White race were identified; however, among the subset with CP-CRE, patients were significantly more likely to be of African American or Black race.[42]

A carbapenemase gene was identified in 5 of the 12 CA-CRE isolates that underwent whole genome sequencing at the CDC, KPC being the most commonly identified gene (n = 4). In the United States, acquisition of CRE harboring carbapenemase enzymes is commonly linked to inpatient health care exposures, and among the carbapenemase KPC is the gene most commonly identified.[2,43,44] This has been demonstrated in an earlier description of this surveillance system where all carbapenemase enzymes identified were KPC, and through national data where KPC was identified in 85% of tested isolates.[44,45] However, isolated cases of CP-CRE in persons without health care exposures have previously been reported in the United States, including in Colorado, where 6 NDM-producing CRE were identified in individuals without health care exposure in 2014-2016; cases were noted to have prior antibiotic use, international travel (without hospitalization) and/or exposure to family members with frequent health care exposures.[43,46] Internationally, isolation of CP-CRE from persons without health care exposure has been documented.[9,47] These findings suggest the importance of case investigations of United States CA-CP-CRE that include patient interviews to characterize risk factors that might not be well-documented in the medical record and to inform prevention efforts for CP-CRE transmission that could be occurring outside of health care settings traditionally associated with CRE acquisition.

The limitations of this surveillance program have previously been described.[18,45] These data describe cases that were collected from 2012 to 2015, and the epidemiology of CRE in the population under surveillance may have since changed, so findings may not reflect the current epidemiology of CRE; we have some indication that CA-CRE in this population has increased.[7] Organisms that were not susceptible to ertapenem, but were susceptible to other carbapenems, were not included in our definition of CRE, as the current CDC CRE definition that includes ertapenem and excludes the third generation cephalosporins was not implemented until 2016.[45,46,48] Additionally, our cases are based on the reported phenotype generated by the ATI used by participating clinical laboratories. These instruments are known to overcall carbapenem resistance, therefore our estimates of CRE could be inflated for both CA and HCA cases.[49–51] Our rates of CA cases could have been underestimated because large private laboratories that mostly serve the outpatient setting did not participate uniformly across all sites.[18,45] Although the 15 million-person population under surveillance is large, the data demonstrate considerable heterogeneity by geographic region, and therefore caution should be used in extrapolating to other regions.[18,45] Our isolate collection is a convenience sample, and only about 10% of all cases that could have an isolate submitted, did. Additionally, isolate collection methods changed during the surveillance period. Despite this, case characteristics were similar between those with isolates that were eligible for shipment and those submitted to the CDC. Finally, data were retrospectively abstracted from medical records, and the quality and completeness of such records can vary between health care system and facility types, resulting in differences in reporting of some data elements. Despite expanded review of medical records for potential CA-CRE cases, it is possible that some health care exposures were missed, resulting in misclassification of HCA cases as CA.[45]

We used active, laboratory and population-based surveillance to compare the incidence and epidemiology of CA and HCA-CRE in the United States. Although the overall proportion of CRE in patients without health care risk factors was low, there was substantial site variation. Continued monitoring of CRE in the community is critical to inform prevention efforts, which are currently primarily targeted at health care settings, and understand populations at risk for CA-CRE infections.[2,52] Continued population-based surveillance of resistant gram-negative bacteria will further describe the intersection between health care and community settings and changes in the epidemiology of CA-CRE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Included authors have nothing to disclose.

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Table 1

Carbapenem-resistant Enterobacterales (CRE) crude incidence, by Emerging Infections Program site and epidemiological classification, 2012-2015, n = 1499

EIP Site	Crude incidence rates per 100,000 population (95% confidence cnterval)									
	2012		2013		2014		2015		Overall	
	CA	HCA	CA	HCA	CA	HCA	CA	HCA	CA	HCA
CO			0.12 (0.02, 0.34)	0.93 (0.60, 1.38)	0.04 (0.00, 0.21)	0.61 (0.35, 0.99)	0.33 (0.15, 0.63)	0.93 (0.60, 1.37)	0.16 (0.09, 0.28)	0.82 (0.63, 1.05)
GA	0.21 (0.09, 0.41)	4.16 (3.54, 4.86)	0.13 (0.04, 0.30)	4.11 (3.50, 4.81)	0.20 (0.09, 0.40)	3.90 (3.30, 4.57)	0.13 (0.04, 0.29)	3.43 (2.88, 4.06)	0.17 (0.11, 0.24)	3.90 (3.59, 4.22)
MD			0.05 (0.00, 0.29)	4.43 (3.54, 5.48)	0.52 (0.25, 0.95)	7.68 (6.49, 9.02)	0.31 (0.11, 0.68)	6.67 (5.57, 7.93)	0.29 (0.17, 0.47)	6.27 (5.64, 6.94)
MN	0.29 (0.10, 0.68)	1.53 (1.00, 2.23)	0.35 (0.13, 0.76)	1.85 (1.27, 2.62)	0.23 (0.06, 0.59)	2.18 (1.54, 2.99)	0.40 (0.16, 0.82)	2.55 (1.86, 2.42)	0.32 (0.20, 0.48)	2.03 (1.71, 2.40)
NM			0.00 (0.00, 0.44)	1.33 (0.61, 2.53)	2.66 (1.58, 4.21)	4.29 (2.87, 6.17)	1.48 (0.71, 2.72)	3.10 (1.92, 4.74)	1.38 (0.92, 2.00)	2.91 (2.22, 3.76)
NY			0.93 (0.38, 1.92)	2.53 (1.53, 3.96)	1.33 (0.64, 2.45)	4.80 (3.36, 6.65)	0.80 (0.29, 1.74)	1.73 (0.92, 2.97)	1.02 (0.65, 1.53)	3.02 (2.35, 3.83)
OR	0.12 (0.01, 0.43)	0.24 (0.06, 0.61)	0.23 (0.06, 0.60)	0.47 (0.20, 0.92)	0.00 (0.00, 0.17)	0.52 (0.24, 0.98)	0.28 (0.09, 0.66)	0.17 (0.04, 0.50)	0.16 (0.08, 0.29)	0.35 (0.22, 0.52)
TN					0.31 (0.10, 0.72)	0.68 (0.34, 1.22)	0.24 (0.07, 0.62)	0.73 (0.37, 1.27)	0.27 (0.13, 0.52)	0.70 (0.45, 1.05)
Overall	0.21 (0.12, 0.34)	2.62 (2.26, 3.02)	0.20 (0.13, 0.29)	2.54 (2.28, 2.83)	0.37 (0.28, 0.48)	2.93 (2.66, 3.22)	0.34 (0.26, 0.45)	2.53 (2.28, 2.79)	0.29 (0.25, 0.35)	2.66 (2.52, 2.81)

CA, community-associated; HCA, health care-associated.

Table 2

Organism type, culture source, infection syndrome, and outcomes among Carbapenem-resistant Enterobacterales (CRE) cases at Emerging Infections Program sites, by epidemiological class, 2012-2015, n = 1499

	Number of cases (%)			*P* value
	All, n = 1499	**CA, n = 149**	**HCA, n = 1350**	
Organism type				
Klebsiella pneumoniae	800 (53.4)	28 (18.8)	772 (57.2)	.0008[††]
Escherichia coli	275 (18.3)	61 (40.9)	214 (15.9)	.1142
Enterobacter cloacae	208 (13.9)	27 (18.1)	181 (13.4)	<.0001
Klebsiella aerogenes	191 (12.7)	32 (21.5)	159 (11.8)	.5039
Klebsiella oxytoca	25 (1.7)	1 (0.7)	21 (1.8)	<.0001
Culture Source				
Urine	1305 (87.1)	146 (97.9)	1159 (85.9)	<.0001[§]
Blood[*]	162 (10.8)	3 (2.0)	159 (11.8)	
Other normally sterile site[†]	32 (2.1)	0 (0.0)	32 (2.4)	
Selected Infection Syndromes[‡]				
Urinary Tract Infection	1024 (63.7)	123 (82.6)	901 (66.7)	<.0001
Bacteremia/Sepsis	197 (13.1)	4 (2.7)	193 (14.3)	<.0001
Septic Shock	64 (4.3)	0 (0.0)	64 (4.7)	.0020
Pneumonia	34 (2.3)	0 (0.0)	34 (2.5)	.0425
Pyelonephritis	23 (1.5)	4 (2.7)	19 (1.4)	.2769
Vascular Graft Infection	1 (0.1)	1 (0.7)	0 (0.0)	.0994
No infection syndrome documented	218 (14.5)	19 (12.8)	199 (14.7)	.5134
Outcomes				
Hospitalized at the time of, or within 30 days after, the date of incident culture[**]	908/1490 (61.0)	29/149 (19.5)	879/1341 (65.6)	<.0001
Admission to an intensive care unit on the day of, or within 7 days after, initial culture	316/908 (34.8)	2/29 (6.9)	314/879 (35.7)	.0006
Died within 30 days of date of incident culture	167/1499 (11.1)	4/149 (2.7)	163/1350 (12.1)	.0002
Among cases with a sterile site culture	58/167 (34.7)	0/4 (0.0)	58/163 (35.6)	.2992
Among cases with a urine culture	109/167 (65.3)	4/4 (100.0)	105/163 (64.4)	

CA, community-associated; HCA, health care-associated.

[*] 16 HCA cases in which CRE was isolated from both blood and urine on the date of initial culture are included in the blood culture source category.

[†] Other normally sterile sites include internal body sites, bone, joint, peritoneal fluid and pleural fluid.

[‡] Infection syndromes described in the table are limited to those associated with CA cases for the purpose of comparison between CA and HCA cases. Additional infection syndromes were reported among HCA cases.

[§] Cases from urine compared to cases from normally sterile sites.

[**] Nine HCA cases had unknown hospital admission at the time of medical record review.

[††] P-values for pair-wise comparison by epidemiologic class of proportion of cases that were each organism.

Table 3

Antimicrobial susceptibility of Carbapenem-resistant Enterobacterales (CRE) isolates at local clinical laboratories, by epidemiological classification, 2012-2015, n = 1499

Antimicrobial agent	Number susceptible/ Total number tested (%)			*P*-value
	All, n = 1499	CA, n = 149	HCA, n = 1350	
Aminoglycosides				
Any tested	1253/1473 (85.1)	141/146 (96.6)	1112/1327 (83.8)	<.0001
Amikacin	875/1286 (68.0)	112/118 (94.9)	763/1168 (65.3)	<.0001
Gentamicin	973/1462 (66.6)	129/145 (89.0)	844/1317 (64.1)	<.0001
Tobramycin	534/1325 (39.9)	88/113 (77.9)	436/1212 (36.0)	<.0001
Fluoroquinolones				
Any tested	454/1465 (31.0)	102/145 (70.3)	352/1320 (26.7)	<.0001
Ciprofloxacin	391/1314 (29.8)	98/142 (69.0)	293/1172 (25.0)	<.0001
Levofloxacin	328/1133 (29.0)	63/98 (64.3)	265/1035 (25.4)	<.0001
Other antimicrobials				
Ampicillin	34/1295 (2.6)	22/121 (18.2)	12/1174 (1.0)	<.0001
Aztreonam	87/1161 (7.5)	35/105 (33.3)	52/1056 (4.9)	<.0001
Colistin *	194/222 (87.4)	2/2 (100.0)	192/220 (87.3)	.5894
Piperacillin-tazobactam	208/1397 (14.9)	57/138 (41.3)	151/1259 (12.0)	<.0001
Nitrofurantoin	90/377 (23.9)	23/39 (59.0)	67/338 (19.8)	<.0001
Tigecycline *	188/657 (28.6)	11/28 (39.3)	177/629 (28.1)	.2017
Trimethoprim-sulfamethoxazole	463/1456 (31.8)	80/144 (55.6)	383/1312 (29.2)	<.0001

CA, community-associated; HCA, health care-associated.

* EUCAST Version 8.0 clinical breakpoints were applied for colistin and tigecycline (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf).

Table 4

Multilocus sequence types, beta-lactamase genes identified, and antimicrobial resistance profiles of community-associated Carbapenem-resistant Enterobacterales isolates that underwent whole genome sequencing analysis at CDC, 2012-2015, n = 12

Organism type*	Carbapenemase gene variants	MLST	Non-carbapenemase beta-lactamase gene variants	Antimicrobial resistance profile‡
Enterobacter cloacae complex (n = 6)	None	Novel†	ACT-70	AMC, AMP, ATM, CFZ, FOX, TZP
	None	108	ACT-55	AMP, ATM, CFZ, FOX, TZP§
	KPC-3	171	ACT-45, OXA-9, SHV-12, TEM-1A	AMC, AMP, ATM, CFZ, FEP, FOX, CIP, LVX, TZP, SXT, TOB
	None	45	TEM-1B	AMC, AMP, ATM, CFZ, FOX, CST, TZP, PMB, SXT
	None	365	None	AMC, AMP, ATM, CFZ, FOX, CST, TZP, PMB
	None	125	ACT-28	AMC, AMP, ATM, CFZ, FOX, CST, TZP, PMB
Escherichia coli (n = 3)	NDM-1	5498	TEM-1A	AMP, CFZ, FEP, FOX, CIP, GEN, LVX, TZP, TET, SXT, TOB§
	None	167	CTX-M-15, OXA-1	AMP, ATM, CFZ, FEP, FOX, CIP, GEN, LVX, TET, SXT
	None	131	CTX-M-15, OXA-1, TEM-1B	AMC, AMP, ATM, CFZ, FEP, FOX, CIP, LVX, TZP, SXT, TOB
Klebsiella pneumoniae (n = 3)	KPC-3	258	SHV-11	AMC, AMP, ATM, CFZ, CIP, LVX, TZP, SXT, TOB
	KPC-3	1737	LEN-17	AMC, AMP, ATM, CFZ, FEP, CIP, LVX, TZP, SXT, TOB
	KPC-3	485	SHV-27	AMC, AMP, ATM, CFZ, FEP, CIP, LVX, TZP, SXT

*None of the identified community-associated- *K. aerogenes* isolates that were sequenced met the phenotypic case definition after testing at CDC.

†Novel: This MLST sequence type is not in the Pasteur MLST database.

§Isolate not tested against amoxicillin-clavulanic acid.

‡Antimicrobials reported if the isolate tested resistant based on reference broth microdilution testing performed at CDC. Isolates were tested against the following unless noted: AMK, amikacin; AMC, amoxicillin-clavulanic acid; AMP, ampicillin; ATM, aztreonam; CFZ, cefazolin; FEP, cefepime; CTX, cefotaxime; CAZ, ceftazidime; FOX, cefoxitin; CRO, ceftriaxone; CIP, ciprofloxacin; CST, colistin; DOR, doripenem; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; PMB, polymyxin B; TET, tetracycline; TGC, tigecycline; SXT, trimethoprim-sulfamethoxazole; TOB, tobramycin. Interpretations are based on the 2019 Clinical and Laboratory Standards Institute; CLSI, interpretative criteria. Performance standards for antimicrobial susceptibility testing: twenty-ninth informational supplement, M100-S29. Wayne [PA]: The Institute; 2019).