

# Epidemiology of Community-Associated Carbapenem-Resistant *Enterobacteriaceae* Identified through the Emerging Infections Program

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## BACKGROUND

- Carbapenem-resistant *Enterobacteriaceae* (CRE) are an emerging public health problem in the United States (U.S.) with acquisition mostly in the inpatient healthcare setting.
- Enterobacteriaceae* are common causes of infections in the community.
- Other drug-resistant *Enterobacteriaceae* (e.g. CTX-M *Escherichia coli*) cause community-associated (CA) infections.
- CRE as a cause of infections outside of healthcare has important public health implications.

## OBJECTIVES

- To describe the proportion of CRE identified through the Multi-site Gram-negative Surveillance Initiative (MuGSI) that have no identified healthcare risk factors (i.e. community-associated cases).
- To describe the epidemiological characteristics of MuGSI CRE among cases that were classified as community-associated after extensive medical record review.

## METHODS

- Between January 2012 and December 2013, 5 EIP sites (CO, GA, MN, NY and OR) identified cases of CRE in their surveillance catchment areas.
- A CRE case was defined as isolation of *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, or *Klebsiella oxytoca* from a culture of a normally sterile site or urine, that was carbapenem-nonsusceptible (excluding ertapenem) and resistant to all 3<sup>rd</sup> generation cephalosporins tested.
- For incident cases, defined as the first isolate of CRE from a patient in a 30-day period, data collectors reviewed inpatient and outpatient medical records that pertained to the positive culture. Information on known healthcare risk factors for the acquisition of CRE (hospital admission, long term care residence or chronic dialysis in the prior year and presence of indwelling devices in the 2 days prior to culture), patient demographics, types of infections associated with the positive culture, and documented comorbidities were collected. The Charlson Comorbidity Index (CCI) was calculated based on the comorbidities identified. For patients with urine cultures, data were gathered on method of urine collection, culture colony counts, and signs and symptoms.
- Cases were classified as community-associated (CA) CRE if:
  - No healthcare risk factors were identified during medical record review; and
  - The initial CRE-positive culture was collected within 3 days after hospital admission, if the patient was hospitalized.
- Cases were classified as healthcare-associated (HCA) CRE if:
  - Healthcare risk factors were identified during medical record review; or
  - The patient was hospitalized, and the initial CRE-positive culture was collected > 3 days after hospital admission.
- CA-CRE cases with positive urine cultures had the National Healthcare Safety Network (NHSN) Long Term Care Facility (LTCF) Component Symptomatic Urinary Tract Infection (SUTI) definitions applied to determine whether the positive urine cultures indicated colonization or infection.
- Eligible isolates were collected and sent to CDC for testing:
  - Antibiotic susceptibility testing (AST) testing by reference broth microdilution.
  - Carbapenemase testing by modified Hodge test (MHT) and polymerase chain reaction (PCR) for *K. pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM) and OXA-48-like carbapenemase.
  - Isolates determined to be metallo-β-lactamase (MBL) screen-positive and KPC- and NDM-negative were further tested using PCR for Verona integron-encoded metallo-β-lactamase (VIM) and IMP-type carbapenemases (IMP).
  - A subset of isolates were tested for extended-spectrum β-lactamase (ESBL) and plasmid AmpC using a nucleic acid-based microarray (Check-MDR CT101 kit; Check-Points, Wageningen, Netherlands).
- Analysis was conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). P values for comparisons of categorical variables were calculated using the chi-square test or the Fisher's Exact Test when cell sizes fell below 5. P values for comparisons of continuous variables were calculated using the Wilcoxon rank-sum test.

## RESULTS

### Carbapenem-Resistant *Enterobacteriaceae* Case Identification:

- 430 incident cases of CRE were identified.
- 414 (96%) could be classified as CA/HCA based on data available., representing 329 unique patients.
  - 43 (10%) classified as CA-CRE Cases
  - 371 (90%) classified as HCA-CRE Cases

**Table 3:** CRE Organism and Source among Community-Associated vs. Healthcare-Associated Cases, n=414

	CA-CRE Cases (n=43)	HCA-CRE Cases (n=371)	P-Value
<i>Enterobacteriaceae</i>			
<i>E. coli</i>	6 (14%)	48 (13%)	0.85
<i>E. cloacae</i>	6 (14%)	45 (12%)	0.73
<i>E. aerogenes</i>	17 (40%)	40 (11%)	<0.0001
<i>K. pneumoniae</i>	13 (30%)	235 (63%)	<0.0001
<i>K. oxytoca</i>	1 (2%)	3 (1%)	0.34
Culture Source*			
Urine	43 (100%)	314 (85%)	0.001
Blood	0	46 (12%)	
Pleural Fluid	0	1 (0.03%)	
Peritoneal Fluid	0	7 (2%)	
Joint	0	1 (0.03%)	
Other (body site, sterile fluid, tissue)	0	6 (2%)	

\*For 4 cases, patient was CRE culture-positive for both blood and urine at the time of initial culture.

**Table 5:** Outcomes of Hospitalized CRE Cases, n=270

	Hospitalized CA-CRE Cases (n=12)	Hospitalized HCA-CRE Cases (n=258)
Hospitalized at the time of, or in the 30 days after the date of culture <sup>^</sup>	12/43 (29%)	258/371 (68%)
Admitted to the ICU in the 7 days after the date of culture	0 (0%)	97 (36%)
Location discharged to:		
Private Residence	10 (83%)	92 (36%)
LTCF	2 (17%)	107 (41%)
LTACH	0 (0%)	22 (9%)
Unknown	0 (0%)	37 (14%)
Inpatient mortality*	0/12 (0%)	34/256 (13%)

<sup>^</sup> P-value <0.0001

\*2 cases had unknown or missing information for mortality

**Table 1:** Breakdown of Community-Associated and Healthcare-Associated CRE Cases by EIP Site

EIP Site	CA-CRE Cases, n=43	HCA-CRE Cases, n=371
CO	4/23 (17%)	19/23 (83%)
GA	15/298 (5%)	283/298 (95%)
MN	14/64 (22%)	50/64 (78%)
NY	6/16 (38%)	10/16 (62%)
OR	4/13 (31%)	9/13 (69%)

**Table 4:** Infectious syndromes reported among CRE cases, Community-Associated vs. Healthcare-Associated CRE, n=414

Infectious Syndrome	CA-CRE Cases (n=43)	HCA-CRE Cases (n=371)
No infectious syndrome reported	3 (7%)	52 (14%)
One infectious syndrome reported	39 (90%)	266 (72%)
Two or more infectious syndromes reported	0 (0%)	40 (11%)
Top 5 Infectious Syndromes Reported (multiple categories possible)		
Bacteremia	3 (7%)	2 (0.5%)
Phylonephritis	0 (0%)	10 (3%)
Pneumonia	0 (0%)	10 (3%)
Septic Shock	36 (83%)	246 (66%)
Urinary Tract Infection		
Unknown infectious syndromes	1 (2%)	13 (4%)

**Table 2:** Demographics of Community-Associated CRE Patients vs. Healthcare-Associated CRE Patients n=329

Characteristics	CA-CRE Patients (n=39)	HCA-CRE Patients (n=290)	P-Value
Sex (%Female)	28 (72%)	162 (56%)	0.06
Race/Ethnicity			
White	16 (41%)	110 (38%)	0.71
Black	9 (23%)	147 (51%)	0.001
Other	0 (0%)	10 (3%)	0.61
Unknown	14 (36%)	23 (8%)	<0.0001
Age, mean, median (range)	58, 63 (16-98)	62, 64 (9-100)	0.49
Comorbidities			<0.0001
None	16 (41%)	12 (4%)	
Any	23 (59%)	271 (93%)	
Unknown	0 (0%)	7 (3%)	
Charlson Comorbidity Index*			<0.0001
Mean	0.90	3.14	
Median	0.00	3.00	
Range	0-5	0-12	
Std Deviation	1.35	2.41	

\* 7 HCA cases had unknown underlying conditions and were not included.

### CA-CRE Isolate Results:

- 15 CA-CRE isolates tested at CDC for carbapenemases.
  - E. aerogenes*, n=8
  - E. cloacae*, n=3
  - E. coli*, n=2
  - K. pneumoniae*, n=2
- 1 *E. cloacae* and 1 *K. pneumoniae* were positive for KPC.

### Summary of Characteristics of CA-CRE Patients/Cases:

- Patients are younger and healthier:
  - Mean age 58 years (16-98)
  - 41% had no comorbidities reported
  - Mean Charlson Comorbidity Index: 0.90 (0-5)
- Cases have less severe disease:
  - No deaths among CA-CRE cases
  - 98% of cases had no (7%) or one (90%) infectious syndrome reported
- All CA-CRE cases were isolated from urine:
  - 83% had UTI reported in the medical record
  - 37% met one or more NHSN definitions for SUTI

## LIMITATIONS

- Medical records were reviewed only at the facility where the CRE culture was identified, therefore if a patient had a health care exposure outside of that facility, it could have been missed.
- Although this surveillance activity covers a population of 12.5 million people, it was not designed to be representative of the U.S. and therefore results might not be generalizable to all communities.

## CONCLUSIONS

- Retrospective in-depth medical record review among patients with CRE from geographically diverse EIP sites suggest that 10% do not have major healthcare exposures in the prior year that might explain CRE acquisition.
- CA-CRE cases were more commonly female (72% vs 56% of HCA), less commonly black (23% vs. 51% of HCA, p=0.001) and had fewer comorbidities (CCI 0.9 vs. 3.14 for HCA, p=<0.0001)
- Fewer CA-CRE cases were hospitalized (29% vs. 68% of HCA, p=<0.0001) and none died.
- Only two of the 15 CA-CRE isolates, tested at CDC, were positive for KPC carbapenemase.
- A more in-depth validation of this data is currently underway, including re-abstraction and an expanded medical record review of all cases initially identified as "CA".

## CONTACT INFO

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