Emerging Infections Program (EIP) Network Report Healthcare-Associated Infections Community Interface Multi-site Gram-negative Surveillance Initiative Carbapenem-Resistant Enterobacteriaceae (CRE) Surveillance, 2014

EIP Areas
Colorado (5 county Denver area); Georgia (8 county Atlanta area); Maryland (4 county Baltimore area); Minnesota (2 metro Twin Cities counties); New Mexico (1 county Albuquerque area); New York (1 county Rochester area); Oregon (3 county Portland area); and Tennessee (8 county Nashville area).
Tennessee was a new surveillance area in 2014.

Population
The surveillance areas represent 15,012,292 persons.
Source: National Center for Health Statistics bridged-race vintage 2014 postcensal file.

Case Definition
A CRE case was defined as isolation of *Escherichia coli*, *Enterobacter aerogenes* (now *Klebsiella aerogenes*), *Enterobacter cloacae* complex, *Klebsiella pneumoniae,* or *Klebsiella oxytoca* with the following criteria:

- Carbapenem-nonsusceptible (doripenem, imipenem, or meropenem) and resistant to all tested third generation cephalosporins (ceftriaxone, ceftazidime, or cefotaxime) using the 2014 Clinical and Laboratory Standards Institute clinical breakpoints (1);
- Isolated from either a normally sterile body site (e.g., blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body sites, or muscle) or urine;
- Identified in residents of the surveillance area in 2014.

Because the clinical breakpoint defining resistance to ertapenem in Enterobacteriaceae is lower than the clinical breakpoint for other carbapenems, ertapenem was excluded from this CRE definition to increase specificity for carbapenemase-producing CRE.

Methodology
Case finding was active, laboratory-based, and population-based. Clinical laboratories that serve residents of the surveillance area were routinely contacted for case identification through a query of minimum inhibitory concentration (MIC) values from automated testing instruments. When possible, the MIC values obtained directly from the automated testing instruments were used to determine if an isolate met the phenotypic case definition. An incident CRE case was defined as the first CRE isolate meeting the case definition from a patient during a 30-day period.

A standardized case report form was completed for each incident case through review of medical records. Inpatient and outpatient medical records were reviewed for information on patient demographics, clinical syndrome, outcome of illness, and relevant healthcare exposures.

A convenience sample of CRE isolates (N=221) was collected from EIP sites and submitted to CDC for additional testing including species confirmatory testing, antimicrobial susceptibility testing by reference broth microdilution with a metallo-β-lactamase (MBL) screen, screening for carbapenemase production using the Modified Hodge Test (MHT), polymerase chain reaction (PCR) screening for KPC, NDM, and OXA-48-like carbapenemase genes, and PCR testing for other carbapenemase genes (i.e., VIM) if MBL screen positive and negative for KPC, NDM, and OXA-48-like genes.

Incidence rates for CRE cases were calculated using the 2014 US Census estimates of the surveillance area population as the denominator. Assessment of vital status in patients admitted to a hospital occurred at the time of discharge from the acute care hospital. For patients in a long-term care facility, long-term acute care

facility, or in an outpatient dialysis center, vital status was assessed 30 days after culture collection. For all other patients, vital status was assessed using medical records from the healthcare facility encounter associated with the culture.

CRE surveillance data underwent regular data cleaning to ensure accuracy and completeness. Patients with complete case report form data as of 1/2/2020 were included in this analysis. Because data can be updated as needed, analyses of datasets generated on a different date may yield slightly different results.

Results

Table 1. Specimen Sources for Incident CRE Cases by Organism (N=529), 2014

CRE Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood %	Other Sterile Sites No.	Other Sterile Sites %
Enterobacter (*Klebsiella*) *aerogenes*	66	61	92.4	5	7.6	0	0
Enterobacter cloacae complex	70	57	81.4	7	10.0	6	8.6
Escherichia coli	117	109	93.2	6	5.1	2	1.7
Klebsiella pneumoniae	264	236	89.4	26	9.8	2	0.8
Klebsiella oxytoca	12	10	83.3	2	16.7	0	0
Total	529	473	89.4	46	8.7	10	1.9

[a]Category includes cases with both a positive blood and urine specimen.

Table 2a. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=221), 2014

Organism	Isolates Submitted to CDC	Carbapenemase-Producing No.[a, b]	%
Enterobacter (*Klebsiella*) *aerogenes*	35	2/35	5.7
Enterobacter cloacae complex	43	11/43	25.6
Escherichia coli	44	11/44	25.0
Klebsiella pneumoniae	96	81/96	84.4
Klebsiella oxytoca	3	2/3	66.7
Total	221	107/221	48.4

[a]Testing was performed by PCR.

[b]Carbapenemase-producing isolates were collected from urine (n=92/107; 86.0%), blood (n=14/107; 13.1%), and other sterile sites (n=1/107; 0.9%).

Table 2b. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=221), 2014 by Carbapenemase Gene

Organism	KPC No.	KPC %	NDM No.	NDM %	OXA-48-like No.	OXA-48-like %
Enterobacter (*Klebsiella*) *aerogenes*	2	5.7	0	0	0	0
Enterobacter cloacae complex	11	25.6	0	0	0	0
Escherichia coli	10	22.7	1	2.3	0	0
Klebsiella pneumoniae	79	82.3	1	1.0	1	1.0
Klebsiella oxytoca	2	66.7	0	0	0	0
Total	104	47.1	2	0.9	1	0.5

Table 2c. Confirmatory Antimicrobial Susceptibility Results of CRE Isolates Submitted to CDC

Organism	Carbapenem-resistant, No.[c]	Carbapenem-resistant %[c]	Difficult to Treat, No.[d]	Difficult to Treat %
Enterobacter (*Klebsiella*) *aerogenes*	9	25.7	0	0
Enterobacter cloacae complex	23	53.5	9	20.9
Escherichia coli	16	36.4	10	22.7
Klebsiella pneumoniae	83	86.5	69	71.9
Klebsiella oxytoca	2	66.7	0	0
Total	133	60.2	88	39.8

[c]Carbapenem resistance is defined as resistance to doripenem, ertapenem, imipenem, or meropenem, which differs from the surveillance case definition.
[d]Difficult to treat is defined as non-susceptibility to all first-line agents tested (i.e., carbapenems, extended-spectrum cephalosporins, fluoroquinolones, piperacillin-tazobactam, and aztreonam) (2).

Table 3. Incidence Rates for CRE Cases by Sex, Race, and Age (N=529), 2014

Sex	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
Female	329	4.28	4.25, 4.30
Male	200	2.73	2.71, 2.76

Race	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
Black or African American	188	5.75	5.69, 5.81
White	262	2.47	2.45, 2.49
Other[a]	21	1.84	1.67, 2.02
Unknown	58	N/A	N/A

Age group, years	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
0–18	12	0.32	0.27, 0.38
19–49	70	1.06	1.03, 1.09
50–64	145	5.06	4.99, 5.13
65–79	189	13.87	13.73, 14.01
≥80	113	25.05	24.62, 25.49
Invasive cases[b]	61	0.41	0.39, 0.42
All cases	529	3.52	3.51, 3.54

[a]Other race includes Asian and American Indian or Alaska Native.
[b]Invasive cases include cases with a sterile incident specimen source or an incident urine specimen with a subsequent non-incident sterile specimen collected on the date of incident specimen collection or in the 29 days after.

Table 4. Clinical Characteristics and Infection Types for Incident CRE Cases (N=529), 2014[a]

No. of Immunocompromised Cases	%
27	5.1

Infection types	No. of Cases	%
Urinary tract infection[c]	362	68.4
Bacteremia[d]	53	10.0
Septic shock	23	4.3
Pneumonia	12	2.3
Other infection types	21	4.0
None[e]	67	12.7
Unknown	48	9.1

[a] Patients could have more than one type of infections reported.
[b]Immunocompromised includes solid organ transplant recipients and patients with a documented diagnosis of AIDS or a hematologic malignancy.
[c]Among 362 cases with a documented urinary tract infection (UTI), 156 (43.1%) had signs and symptoms associated with a UTI documented in the medical record. Reported signs and symptoms included fever, dysuria, frequency, urgency, costovertebral angle pain or tenderness, and suprapubic tenderness
[d]Bacteremia includes cases with a positive blood specimen (incident or non-incident) or a documented diagnosis of sepsis, septicemia, bacteremia, or blood stream infection.
[e]No infection types reported.

Table 5. Patient Location Before, During, and After Incident Specimen Collection Among Incident CRE Cases (N=529), 2014

Residence before incident specimen collection	No. of Cases	%
Private residence or Homeless	222	42.0
Long-term care facility	166	31.4
Acute care hospital (inpatient)	100	18.9
Long-term acute care hospital	21	4.0
Unknown	20	3.8

Collection location	No. of Cases	%
Outpatient setting or emergency department	234	44.2
Acute care hospital	141	26.7
Long-term care facility	124	23.4
Long-term acute care hospital	22	4.2
Unknown	8	1.5

Hospitalized on the day of or in the 29 days after the date of incident specimen collection	No. of Cases	%
Hospitalized	288	54.4
Not hospitalized	218	41.2
Unknown	23	4.3

Discharge location among hospitalized patients (N=288)	No. of Cases	%
Long-term care facility	117	40.6
Private residence	112	38.9
Long-term acute care hospital	20	6.9
Died during hospitalization	34	11.8
Unknown	5	1.7

Table 6. Outcome of CRE Cases (N=529), 2014

Outcome	No. of Cases	%
ICU admission in the 6 days after the date of incident specimen collection	68	12.9
Died	31	5.9
Cases with a positive incident sterile site specimen (N=56)	10	17.9
Cases with a positive incident urine specimen (N=473)	21[a]	4.4

[a]None had a subsequent non-incident blood specimen collected on the date of incident specimen collection or in the 29 days after.

Table 7. Selected Characteristics of Incident CRE Cases (N=529), 2014[a]

Exposure	No. of Cases	%
Healthcare facility stay in the year before the date of incident specimen collection	399	75.4
Acute care hospital	337	63.7
Long-term care facility	245	46.3
Long-term acute care hospital	54	10.2
Surgery in the year before the date of incident specimen collection	132	25.0
In ICU in the 7 days before the date of incident specimen collection	36	6.8
Specimen collected ≥3 days after hospital admission	78	14.7
Chronic dialysis	41	7.8
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection	303	57.3
Urinary catheter	218	41.2
Central venous catheter	107	20.2
Other[b]	167	31.6
None of the above healthcare exposures[c]	56	10.6
International travel in the 2 weeks before the date of incident specimen collection	6	1.1

[a] Patients could have more than one prior healthcare risk factor reported.

[b]Other medical devices include: endotracheal or nasotracheal tube, tracheostomy, gastrostomy tube, nephrostomy tube, nasogastric tube.

[c]Defined as having no healthcare exposures in the year before specimen collection, no selected medical devices in place in the 2 days before specimen collection, and specimen collected before calendar day 3 after hospital admission if hospitalized.

Summary

The overall crude incidence rate of CRE in 2014 was 3.52 cases per 100,000 persons. The incidence rate increased with age, was higher in women than in men, and higher in persons of Black or African American race than in persons of other races. Most CRE were isolated from a urine source rather than from normally sterile body sites. Prior healthcare exposures were reported for most cases, with hospitalization in the prior year, presence of indwelling medical devices, and prior long-term care facility residency being the most common exposures. More than half of the cases required hospitalization, and overall crude mortality rate was 5.9%, with a higher mortality observed in cases with a sterile-site specimen source compared to those with a urine specimen source.

Among the 221 isolates submitted to CDC, about half were carbapenemase-producing. KPC was detected in all but three carbapenemase-producing isolates, NDM was detected in two isolates, and OXA-48-like carbapenemase was detected in one isolate.

References

1. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement*. CLSI document M100-S22 (ISBN 1-56238-786-3). Wayne, PA 2012.
2. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018 Nov 28;67(12):1803-14.

Citation

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