Emerging Infections Program (EIP) Network Report
Healthcare-Associated Infections Community Interface Activity
Multi-site Gram-negative Surveillance Initiative
Carbapenem-Resistant Enterobacterales(CRE) Surveillance, 2018

Case Definition:

A carbapenem-resistant Enterobacterales (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-resistant (doripenem, imipenem, meropenem, or ertapenem) using the current Clinical and Laboratory Standards Institute clinical breakpoints (1);
- Isolated from 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 2018.

Surveillance Catchment Areas:

California (3 county San Francisco area), Colorado (5 county Denver area); Connecticut (statewide); Georgia (8 county Atlanta area); Maryland (4 county Baltimore area); Minnesota (2 county Minneapolis – St. Paul area); New Mexico (1 county Albuquerque area); New York (1 county Rochester area); Oregon (3 county Portland area); and Tennessee (8 county Nashville area).

Population:

The CRE surveillance area represents 22,922,812 persons.
Source: National Center for Health Statistics bridged-race vintage 2018 file.

Methods:

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=733) was collected from 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 Carbapenem Inactivation Method (mCIM), real-time polymerase chain reaction (PCR) screening for carbapenemase-encoding genes, including bla_{KPC}, bla_{NDM}, and $bla_{\text{OXA-48-like}}$ genes, and PCR testing for other carbapenemase genes (i.e., bla_{VIM}) if MBL screen positive and negative for bla_{KPC}, bla_{NDM}, and $bla_{\text{OXA-48-like}}$ genes.

Incidence rates for incident CRE cases were calculated using the 2018 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 2/2/2022 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 CRE Cases by Organism, 2018 (N=1227)

Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood[a] %	Other Sterile Sites No.	Other Sterile Sites %
Enterobacter cloacae complex	546	480	87.9	38	7.0	28	5.1
Escherichia coli	237	215	90.7	13	5.5	9	3.8
Klebsiella pneumoniae	332	272	81.9	43	13.0	17	5.1
Klebsiella aerogenes	92	85	92.4	5	5.4	2	2.2
Klebsiella oxytoca	20	16	80.0	2	10.0	2	10.0
Total	**1227**	**1068**	**87.0**	**101**	**8.2**	**58**	**4.7**

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

Table 2. Incidence Rates of CRE Cases by Sex, Race and Age, 2018 (N=1227)

Sex	No. of Cases	%	Incidence Rate[a]
Female	752	61.3	6.42
Male	474	38.6	4.23
Unknown	1	0.1	-

Race	No. of Cases	%	Incidence Rate[a]
White	713	58.1	4.49
Black or African American	285	23.2	6.55
Other[b]	49	4.0	1.83
Unknown	180	14.7	-

Age groups, years	No. of Cases	%	Incidence Rate[a]
0–18	36	2.9	0.68
19–49	151	12.3	1.52
50–64	247	20.1	5.62
65–79	433	35.4	17.29
≥80	360	29.3	46.15
Invasive cases[c]	166	13.5	0.72
All cases	1227	100.0	5.35

[a] Cases per 100,000 population for EIP areas (crude rates)

[b] Other race includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported

[c] 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 3. CRE Cases by Race and Ethnicity, 2018 (N=1227)

Characteristics	No. of Cases	%
Hispanic, any race	85	6.9
Not known to be Hispanic[a] – White[b]	679	55.3
Not known to be Hispanic[a] – Black or African American[c]	281	22.9
Not known to be Hispanic[a] – Asian[d]	41	3.3
Not known to be Hispanic – Other or multiple races[e]	12	1.0
Not known to be Hispanic[a,f]– Unknown race	129	10.5

[a] Records either indicated ethnicity was non-Hispanic, or ethnicity was not known

[b] 82 CRE cases with unknown ethnicity

[c] 18 CRE cases with unknown ethnicity

[d] 2 CRE cases with unknown ethnicity

[e] American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported; 1 CRE case with unknown ethnicity

[f] Of cases with unknown race, 111 CRE cases had unknown ethnicity

Table 4. Selected Characteristics of CRE Cases, 2018 (N=1227)

Location of patient on the 3rd calendar day before incident specimen collection	No. of Cases	%
Private residence	724	59.0
Long-term care facility	249	20.3
Acute-care hospital (inpatient)	198	16.1
Long-term acute care hospital	19	1.5
Homeless/incarcerated/other location	5	0.4
Unknown	32	2.6

Location of incident specimen collection	No. of Cases	%
Outpatient setting or emergency department	748	61.0
Acute care hospital	281	22.9
Long-term care facility	156	12.7
Long-term acute care hospital	23	1.9
Unknown	19	1.5

Infection types[a]	No. of Cases	%
Urinary tract infection	849	69.2
Bacteremia[b]	136	11.1
Septic shock	43	3.5
Other	119	9.7
None[c]	160	13.0
Unknown	60	4.9

[a] Patients could have more than one type of infection reported

[b] Bacteremia includes cases with a positive blood specimen (incident or non-incident) or a documented diagnosis of sepsis, septicemia, bacteremia, or blood stream infection

[c] No infection types reported

Table 5. Selected Clinical Characteristics of CRE Cases, 2018[a] (N=1227)

Characteristics	No. of Cases	%
Charlson comorbidity index		
0	206	16.8
1	249	20.3
≥2	732	59.7
Unknown	40	3.3
Median (IQR)	2	1–4

Underlying conditions	No. of Cases	%
Cardiovascular disease[b]	465	37.9
Diabetes mellitus	447	36.4
Neurologic condition, any	445	36.3
Urinary tract problems/abnormalities	372	30.3
Chronic pulmonary disease[c]	321	26.2
Malignancy (hematologic or solid organ)	258	21.0
Skin condition	221	18.0
Chronic renal disease	164	13.4
Gastrointestinal disease[d]	89	7.3
Transplant (solid organ)	46	3.7
Unknown	40	3.3

[a] Patients could have more than one underlying condition reported

[b] Defined as myocardial infarction, congestive heart failure, congenital heart disease, stroke, transient ischemic attack, or peripheral vascular disease

[c] Defined as cystic fibrosis or any chronic respiratory condition resulting in symptomatic dyspnea

[d] Defined as peptic ulcer disease or liver disease

Table 6. Selected Healthcare Exposures or Risk Factors of CRE Cases, 2018[a] (N=1227)

Healthcare facility stay in the year before the date of incident specimen collection	No. of Cases	%
Acute care hospitalization	760	61.9
Long-term care facility residence	408	33.3
Long-term acute care hospitalization	47	3.8

Exposure	No. of Cases	%
Surgery in the year before the date of incident specimen collection	332	27.1
Specimen collected ≥3 days after hospital admission	174	14.2
Chronic dialysis	55	4.5

Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection	No. of Cases	%
Urinary catheter	361	29.4
Central venous catheter	214	17.4
Other[b]	259	21.1
None of the above healthcare exposures[c]	241	19.6
Healthcare exposures are unknown	40	3.3
International travel in the 2 months prior to date of incident specimen	12	1.0

[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

Table 7. Outcomes of Incident CRE Cases, 2018 (N=1227)

Outcomes	**No. of Cases**	**%**
Hospitalized on the day of or in the 29 days after the date of incident specimen collection	616	50.2
ICU admission in the 6 days after the date of incident specimen collection	99	8.1

Discharge location among hospitalized	**No. of Cases**	**%**
Private residence or other discharge location	293/616	47.6
Long-term care facility	250/616	40.6
Died during hospitalization	59/616	9.6
Long-term acute care hospital	11/616	1.8
Unknown	3/616	0.5
Died within 30 days of incident specimen collection date	54	4.4
Cases with an incident sterile site specimen	23/159	14.5
Cases with an incident urine specimen[a]	31/1068	2.9

[a] One incident CRE case had a subsequent non-incident blood specimen collected on the date of incident specimen collection or in the 29 days after

Laboratory Characterization:

Table 8a. Antimicrobial Susceptibility and Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC, 2018(N=733)

Organism	Isolates Submitted to CDC	Carbapenemase-producing [a,b,c], No.	%
Enterobacter cloacae complex	344	30	8.7
Escherichia coli	122	33	27.0
Klebsiella pneumoniae	204	116	56.9
Klebsiella aerogenes	52	1	1.9
Klebsiella oxytoca	11	3	27.3
Total	**733**	**183**	**25.0**

Table 8b. Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC, 2018 (N=733) by Carbapenemase Gene

Organism	*bla*$_{KPC}$, No.	*bla*$_{KPC}$ - %	*bla*$_{NDM}$, No.	*bla*$_{NDM}$ - %	*bla*$_{OXA-48-like}$, No.	*bla*$_{OXA-48-like}$ - %
Enterobacter cloacae complex	28	8.1	1	0.3	0	0.0
Escherichia coli	18	14.8	6	4.9	9	7.4
Klebsiella pneumoniae	109	53.4	4	2.0	3	1.5
Klebsiella aerogenes	0	0.0	1	1.9	0	0.0
Klebsiella oxytoca	3	27.3	0	0.0	0	0.0
Total	**158**	**21.6**	**12**	**1.6**	**12**	**1.6**

Table 8c. Confirmatory Antimicrobial Susceptibility Results of CRE Isolates Submitted to CDC

Organism	Carbapenem-resistant, No.	Carbapenem-resistant - %	Difficult to treat[e], No.	Difficult to treat[e] - %
Enterobacter cloacae complex	173	50.3	21	6.1
Escherichia coli	57	46.7	10	8.2
Klebsiella pneumoniae	148	72.5	91	44.6
Klebsiella aerogenes	28	53.8	0	0.0
Klebsiella oxytoca	6	54.5	2	18.2
Total	**412**	**56.2**	**124**	**16.9**

[a] Testing was performed by PCR

[b] Carbapenemase-producing isolates were collected from urine (n=142/183, 77.6%), blood (n=32/183, 17.5%), and other normally sterile site (n=9/183, 4.9%)

[c] All isolates that were mCIM positive were also PCR positive, except for 17 isolates that were mCIM positive and PCR negative

[d] One isolate had *bla*$_{KPC}$ and *bla*$_{VIM}$

[e] Difficult to treat (2) is defined as non-susceptibility to all first-line agents tested (i.e., carbapenems, extended-spectrum cephalosporins, fluoroquinolones, piperacillin-tazobactam, and aztreonam)

Summary:

Surveillance data from 2018 represent the seventh full year of population-based surveillance for CRE through the Emerging Infections Program. The overall crude incidence rate of CRE in 2018 was 5.35 cases per 100,000 persons. The incidence rate increased with age and was higher in women than in men and higher in persons of Black or African American race than in persons of other races. More CRE were isolated from a urine source than from normally sterile body sites. Underlying conditions were commonly reported, with more than half of CRE cases having a Charlson comorbidity index of ≥2. 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. Approximately half of the CRE cases required hospitalization, and overall crude 30-day mortality was 4.4%, with a higher 30-day mortality observed in cases with a sterile-site specimen source compared to those with a urine specimen source.

Among the 733 CRE isolates submitted to CDC, 25.0% were carbapenemase-producing. KPC was detected in 21.6% of the isolates, NDM in 1.6% isolates, and OXA-48-like in 1.6% isolates.

References:

1. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. CLSI supplement M100 (ISBN 1-56238-838-X). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2018.

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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For more information, visit our web sites:

- Multi-site Gram-negative Surveillance Initiative (MuGSI) (https://www.cdc.gov/hai/eip/mugsi.html)
- Healthcare-Associated Infections - Community Interface Data Visualization (https://www.cdc.gov/hai/eip/haicviz.html)