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Epidemiology of Carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* in New Mexico, 2015-2017

Lourdes Irizarry, MD, William Hudspeth, PhD, MPH, Marla Sievers, MPH, Holly Simpson, MSPH
Epidemiology and Response Division
New Mexico Department of Health

The emergence and dissemination of carbapenem resistant *Enterobacteriaceae* (CRE) and *Pseudomonas aeruginosa* (CRPA) in the United States represents a serious threat to public health. These organisms cause antibiotic resistant infections that are associated with high mortality rates, up to 50% among patients with CRE bloodstream infections[1], and have the potential to spread widely. Recognizing the importance of CRE and CRPA surveillance, these conditions became notifiable in New Mexico on June 15, 2016. Decreasing the impact of these organisms will require a coordinated effort among stakeholders including healthcare facilities and providers, public health, and industry. The current recommended approach to control transmission of these organisms in healthcare facilities includes the following:

- Recognizing these organisms as epidemiologically important
- Quantifying the magnitude of CRE and CRPA within the facility and regionally
- Identifying colonized and infected patients when present in healthcare facilities
- Implementing interventions designed to stop the transmission of these organisms

Current CRE prevention strategies are based on the identification of patients colonized or infected with CRE followed by implementation of contact precautions. Active case detection and immediate implementation of interventions, often including cohorting staff and CRE patients (i.e., segregating CRE-colonized or CRE-infected patients and the health-care personnel who care for them from those without CRE and the health-care personnel who care for them), has been used successfully to control CRE in acute-care and long-term–care settings. Efforts to ensure appropriate antibiotic use in hospitals and nursing homes also are critical to slowing CRE emergence.[1]

Much of the increase in CRE since 2000 has been due to the spread of CRE that produce *Klebsiella pneumoniae* Carbapenemase (KPC). Carbapenemases are ß-lactamase enzymes that have the ability to hydrolyze penicillins, cephalopsorins, monobactams, and carbapenems rendering these antibiotics ineffective. Enzymes can be chromosomally or plasmid encoded and can be transferred among different species. In addition to KPC, several other types of carbapenemases have been identified in the United States since 2009. These include the New Delhi Metallo-β-lactamase (NDM), Verona Integron-encoded Metallo-βlactamase (VIM), Oxacillinase-48-type carbapenemases (OXA-48), and the Imipenemase (IMP) Metallo-β-lactamase. Organisms producing these non-KPC enzymes are more common in some areas of the world; in the United States, they have generally been found among patients who received medical care in countries where organisms with these carbapenemases are known to be present. Beginning in 2012, however, NDM has been increasingly reported among U.S. patients without a recent history of exposure to healthcare outside of the United States. More recently, reports of *Enterobacteriaceae* producing OXA-48-type enzymes have also increased in the United States.

Methods

Data used in this analysis were derived from two sources: the New Mexico Emerging Infections Program (NM-EIP) Multi-site Gram-Negative Surveillance Initiative (MuGSI) database and the CRE/CRPA database, maintained by the New Mexico Department of Health (NMDOH) Healthcare-associated Infections (HAI) Program. The MuGSI project in partnership with the Centers for Disease Control and Prevention (CDC) supports active population and laboratory-based

surveillance of seven carbapenem resistant organisms (*Escherichia coli, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Acinetobacter baumannii* and *Pseudomonas aeruginosa*) within Bernalillo County only. NMDOH surveillance captures notifiable CRE and CRPA cases throughout New Mexico.

Because the MuGSI case definition for CRE was modified effective January 1st, 2016, this study combines cases defined by both earlier and later definitions, and includes samples collected between June 2015 and May 2017. The previous MuGSI CRE case definition included organisms that were non-susceptible to imipenem, meropenem, ertapenem, or doripenem, and resistant to all third generation cephalosporins. This definition, however, was modified by the CDC in January 2016 to include only those organisms resistant to imipenem, meropenem, or doripenem, or documentation that the isolate produces a carbapenemase. MuGSI CRE cases are restricted to sterile sites or urine, whereas CRPA also includes non-sterile sites such as the lower respiratory tract and wounds.

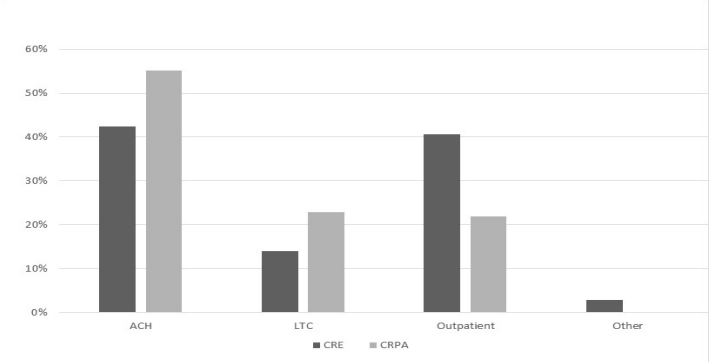
The combined sample of CRE and CRPA used in this analysis consists of 283 records, 234 of which were contributed from the EIP/MuGSI database. Because the analysis dataset is dominated by records from this database, the vast majority of cases originate from Bernalillo County, with poor representation of other regions in the state. Variables selected for the analysis dataset included gender, age, provider type, zip code, specimen source, organism, and susceptibility profiles for 31 different types of antibiotics belonging to one of 8 antibiotic classes. Because susceptibility and demographic data were derived from different database sources or testing laboratories, case records contained missing values for selected attributes. Descriptive statistics for the each of the variables of interest (e.g. gender, age, provider type, organism, etc.) only included those records for which relevant data were available.

Results

NMDOH identified 183 case reports of CRE between June 2015 and May 2017. Of these, 88 (48%) were *Enterobacter* species of which 82 (44.8%) were *E. cloacae* and 6 (3%) were *E. aerogenes.* In contrast with reports in the literature, *E.coli* was the second most frequently reported CRE; 61 (33%) of the total reported CRE were *E.coli.* The third most frequently identified CRE was *Klebsiella* species with 30 (16%) reported cases. Of these, 25(14%) were *K. pneumoniae* and 5 (2.7%) *K. oxytoca.* Other reported species included 1 *Citrobacter* (0.5%), 1 *Morgnella morganii (*0.5%) and 2 *Serratia* species (1%) (Figure1).

The median age of individuals with CRE was 68 (range 1 month to 99 years). Data pertaining to the facility type where the culture was initially collected were available for 172 isolates. More CRE were reported from acute care hospitals (73 or 42%), and from outpatient clinics (70 or 41%), than from long-term care facilities (24 or 14%). Five isolates (3%) were reported from hospice or home health settings, with the remaining CRE cases lacking facility type information (Figure 2). Seventy percent of the isolates were from women and 30% from men. Culture specimen site data were available for 180 isolates. The majority of isolates came from urine cultures (86%), followed by blood cultures (6%), and respiratory cultures (6%). Three percent of the isolates came from an unreported source (Figure 3).

Figure 2. CRE and CRPA by Facility Type



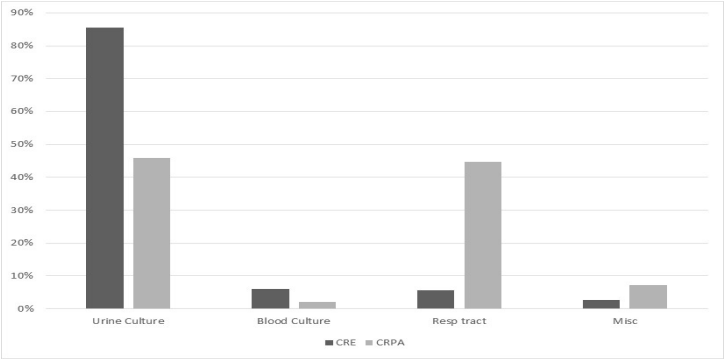
Consistent with published literature, both CRE and CRPA were commonly found to also have resistance to other antibiotics. Among CRE and CRPA for which susceptibilities were done for the monobactam aztreonam, 63.9% and 80.5%, respectively, were found to be resistant to this agent. Seventy-one percent of the CREs were also resistant to ceftazidime, and 40.6% of the CRPA also exhibited resistance to this antibiotic. Fifty-one percent of the CRE were resistant to cefepime as were 49.2% of the CRPA. A large percentage of CRE also exhibited resistance to piperacillin/tazobactam with 80.9% of the isolates tested exhibiting resistance. Among CRE and CRPA tested against fluoroquinolones, 29.1% and 57.1% respectively exhibited resistance to levofloxacin; 44.5% and 57.1% were resistant to ciprofloxacin. Aminoglycoside resistance

was found less frequently, with amikacin demonstrating the overall best profile. Only 0.6% of CRE tested against amikacin were found to be resistant while 4.3% of CRPA exhibited resistance. Resistance to tobramycin and gentamicin were as follows: 23.4% and 20.7% for CRE and 12.1% and 12.5% for CRPA, respectively.

Discussion

The exact prevalence of disease associated CRE and CRPA in the USA is not fully known. At the present time, we do not have enough data to determine the burden of disease and true prevalence of these organisms in New Mexico. *Enterobacteriaceae* and *P. aeruginosa* are frequently cultured from clinical specimens. *P. aeruginosa* is found less frequently than *Enterobacteriaceae* as a colonizer. *Enterobacteriaceae* on the other hand, are common organisms of the human microbiome. It is currently unknown what percent of the US population may be colonized with CRE.

Figure 3. CRE and CRPA by Culture Source



We believe that the numbers presented in this report are biased toward Bernalillo County and do not fully represent the actual numbers of CRE and CRPA in the state, as these conditions became notifiable relatively recently.

The data point out that both CRE and CRPA are found in all healthcare settings, and in the community. As published in the literature, the sites from which CRE and CRPA are most frequently reported are the urinary and respiratory tracts.[2,3] The relatively high percentage of carbapenem-resistant *E. coli* identified in this study is an unexpected finding. Carbapenem-resistant *E. coli* is reported infrequently, while outbreaks of carbapenem- resistant *Enterobacter* species and *Klebsiella* species have been reported at increasing rates.[4] It is known that CRE geographical differences exist.[5] Whether differences are based on lack of reporting or regional variations is unknown.

The degree to which many of the CRE and CRPA exhibit resistance to other antibiotics is not surprising, highlighting the need to continue surveillance so that prompt containment interventions to prevent the spread of these organisms occur. Treatment options for multidrug resistant CRE and CRPA are limited. Options include tigecycline, fosfomycin, polymyxins and aminoglycosides; all of which are associated with high rates of side effects and toxicity. The combination of ceftazidime/avibactam ceftolozane/tazobactam may offer additional options.[4] Currently no standard definitions for susceptibility and resistance breakpoints have been defined and published for this agent, and commercial laboratories do not test with these antibiotics. Imipenem/relebactam, another combination agent currently under research, may offer additional options in the future.

Preventing the transmission of CRE and CRPA is central to limiting their spread. Patients in long-term acute care facilities are particularly prone to infections and colonization with these organisms due to prolonged lengths of stay, common device and antimicrobial use. Employing appropriate infection prevention precautions to avoid person to person transmission and transmission through the environment of care or equipment are effective decreasing acquisition rates. Notification to receiving facilities upon transfer of patients known to have CRE and CRPA is indispensable to contain regional spread.

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Michael G. Landen, M.D., M.P.H.
State Epidemiologist & Editor

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www.health.state.nm.us

Figure 1. Carbapenem Resistant *Enterobacteriaceae* by Species, New Mexico, 2015-2017