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**ANTIBIOTIC RESISTANCE THREATS
CARBAPENEM RESISTANT ENTEROBACTERIACEAE (CRE)**

Introduction

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. To fight back against antibiotic resistance, there are four core actions. They are:

- 1) Preventing infections and preventing the spread of resistance;
- 2) Tracking antibiotic resistant infections;
- 3) Improving antibiotic prescribing/stewardship;
- 4) Developing new drugs and diagnostic tests;

In 2013, CDC published a report outlining the top 18 drug-resistant threats to the United States. The CDC's web page list all 18 threats:

https://www.cdc.gov/drugresistance/biggest_threats.html

These threats were categorized based on level of concern: urgent, serious, and concerning¹. Urgent threats are high-consequence antibiotic-resistant (AR) threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission. The top three threats are:

- *Clostridium difficile* (C. diff)
- Carbapenem-Resistant Enterobacteriaceae (CRE)
- *Neisseria gonorrhoeae*

This is the first in a series of Epi-News article that will address some of these threats using national and local data. In this issue of Epi-News, CRE is the subject.

About Resistance Mechanisms²

Bacteria will inevitably find ways to avoid the effects of antibiotic drugs. Some of these resistance mechanisms are listed below.

1. Restrict access of the antibiotic:
2. Get rid of the antibiotic
3. Destroy the antibiotic
Some resistant bacteria use enzymes to break down the antibiotic drug and make it ineffective.
4. Change the antibiotic
5. Bypass the effects of the antibiotic
6. Change the targets for the antibiotic

¹ https://www.cdc.gov/drugresistance/biggest_threats.html

² <https://www.cdc.gov/drugresistance/emerging.html>

Carbapenem-Resistant Enterobacteriaceae (CRE)

Enterobacteriaceae are a family of bacteria that cause infections both in community and healthcare settings. They may present as urinary tract infection, wound infection, blood stream infection, ventilator-associated pneumonia, and etc. The most common examples of bacteria in this family are *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Serratia*, *Salmonella*, and *Shigella*. CRE are bacteria of the Enterobacteriaceae family that are non-susceptible to the carbapenem class of antimicrobials. Carbapenems are broad spectrum antibiotics that can be used to treat infections caused by bacteria resistant to other antibiotics. There are four primary antibiotics in this class including Ertapenem, Doripenem, Imipenem, and Meropenem. CRE can present as an infection or colonization. Both infected and colonized patients can transmit CRE to others.

Unlike other multi-drug resistant organisms (MDRO), CRE can become non-susceptible to carbapenem due to a number of mechanisms. For example, mechanisms #1 or #3 described above are not uncommon. In 2001, a *K. pneumoniae* isolate that possessed a novel carbapenemase called KPC was recognized in the United States. The genes that code for KPC are on a highly mobile genetic element that can be transmitted from one bacterium to another thereby spreading resistance. KPC-producing bacteria have spread widely across the United States. In addition to KPC, a number of other carbapenemases exist that can lead to carbapenem resistance; examples of these include New Delhi Metallo-beta-lactamase (NDM), Verona Integron-Encoded Metallo-beta-lactamase (VIM), Imipenemase Metallo-beta-lactamase (IMP), and Oxacillinase (OXA)-48-Type carbapenemase. CRE are important for a number of reasons.

- 1) These organisms are often resistant to multiple classes of antimicrobials substantially limiting treatment options.
- 2) Infections caused by these organisms are associated with high mortality rates, up to 50% in some studies.
- 3) Many CRE possess carbapenemase (KPC, NDM, VIM, IMP, OXA-48-type) which can be transmitted from one Enterobacteriaceae to another potentially facilitating transmission of resistance.
- 4) Enterobacteriaceae are a common cause of infections in both community and healthcare settings. Carbapenem resistance among these organisms could therefore have far-reaching impact.

CRE - National Perspective

An estimated 140,000 healthcare-associated Enterobacteriaceae infections occur in the United States each year; about 9,300 (~7%) of those are caused by CRE. Up to half of all bloodstream infections caused by CRE result in death. Each year, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem-resistant *Klebsiella spp.* and carbapenem-resistant *E. coli*.³ Carbapenemase producing CRE (CP-CRE) have been reported in all states except Idaho as of January 6, 2017.⁴ KPC-CRE have spread widely across the United States. But a number of other carbapenemases such as NDM, VIM, IMP are more common outside the United States but have been identified rarely in this country, most commonly in patients with exposure to healthcare in endemic countries.

CRE – Local Perspective

On January 13, 2017, an article reporting a pan-resistant New Delhi Metallo-beta-lactamase (NDM)-producing *Klebsiella pneumoniae* in a Washoe County resident was published by CDC in the Morbidity and Mortality Weekly Report (MMWR).⁵ This publication got the world's attention. This patient had a wound infection and the isolate was resistant to all 26 antibiotics currently available in the United States to treat this type of infection. The patient had a fatal outcome. There was no further transmission within the healthcare facility as determined by active screening.

Washoe County⁶ has been tracking aggregated the laboratory-based CRE rate in the community on an annual basis. CRE rate is calculated using the following formula:

CRE Rate (%) = (# of Enterobacteriaceae isolates non-susceptible to any carbapenem / total # of Enterobacteriaceae isolates tested for carbapenem) * 100.

The most recent data show that the CRE rate increased from 0.2% in 2012 to 0.34% in 2015. Although the overall rate remained low, the magnitude of increase was significant.

Since 2010, Washoe County Health District (WCHD) has been collaboratively working with local hospitals to actively monitor multi-drug resistant bacilli-carbapenem resistant (MDRB-CR). During the seven year period from 2010 through 2016, 291 MDRB-CR cases were reported with a median of 33 cases per year (range: 18-78 cases per year). A total of 52 Multi-drug resistant CRE cases were reported with a median of 7 cases per year (range: 4-13 cases per year). Of 52 CRE cases, three cases had KPC CRE and one case had NDM CRE. All these four cases were caused by *Klebsiella pneumoniae*.

Beginning in 2017, working with the local hospitals, the Nevada Division of Public and Behavioral Health (NDPBH), and the Nevada State Public Health Laboratory (NSPHL), WCHD expanded MDRB-CR surveillance to a broader

scope of surveillance for Gram negative bacilli including CRE (not just multi-drug resistant CRE), Carbapenem resistant *pseudomonas aeruginosa* (CRPA), and Carbapenem resistant *Acinetobacter*. Because non-Enterobacteriaceae organisms may also produce carbapenemase and can transmit the antibiotic resistance to other bacterial infections. The existing surveillance system is named CPO which stands for Carbapenemase Producing Organisms. In order to have an early detection of CPO and implement interventions in a timely fashion, carbapenem resistant organisms are mandatorily reportable by hospital laboratories in Washoe County effective in 2017. More surveillance findings will be published through Epi-News.

Recommendations for HCPs

WCHD strongly recommends that healthcare providers (HCPs) in Washoe County take the following actions in terms of combating CRE:⁷

1. Stay aware of facility specific CRE rates and community-wide CRE rates by reading WCHD's annual antibiogram at www.tinyurl.com/WashoeAntibiogram.
2. Ask if a patient has received medical care somewhere else, including in another country.
3. Place patients currently or previously colonized or infected with CRE on Contact Precautions. Whenever possible, dedicate rooms, equipment, and staff to CRE patients.
4. Wear a gown and gloves when caring for patients with CRE.
5. Perform hand hygiene – use alcohol-based hand rub or wash hands with soap and water before and after contact with the patient or their environment.
6. Alert the receiving facility when you transfer a CRE patient, and find out when a patient with CRE transfers into your facility.
7. Make sure labs immediately alert clinical and infection prevention staff when CRE are identified.
8. Prescribe and use antibiotics wisely.
9. Discontinue devices like urinary catheters as soon as no longer necessary.

Recommendations for Health Care Facilities⁷

1. Require and strictly enforce CDC guidance⁸ for CRE detection, prevention, tracking, and reporting.
2. Make sure the lab can accurately identify CRE
3. Promote antimicrobial stewardship
4. Recognize these organisms as important to patient safety
5. Understand their prevalence in the facility and in the region
6. Identify colonized and infected patients in the facility and ensure precautions are implemented
7. When transferring a patient, require staff to notify the other facility about infections, including CRE.
8. Participate in regional and facility-based prevention efforts designed to stop the transmission of these organisms
9. **Notify WCHD of outbreaks or extraordinary cases by calling 775-328-2447.**

³ <https://www.cdc.gov/drugresistance/threat-report-2013/index.html>

⁴ <https://www.cdc.gov/hai/organisms/cre/trackingcre.html>

⁵ <https://www.cdc.gov/mmwr/volumes/66/wr/mm6601a7.htm>

⁶ www.tinyurl.com/WashoeAntibiogram

⁷ <https://www.cdc.gov/hai/organisms/cre/cre-clinicians.html>

⁸ <https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html>