CARBAPENEMASE PRODUCING CARBAPENEM-RESISTANT *Enterobacteriaceae* (CP-CRE)

REPORTING INFORMATION

- **Class B:** Report by the end of the next business day after the case or suspected case presents and/or a positive laboratory result to the local public health department where the patient resides. If patient residence is unknown, report to the local public health department in which the reporting healthcare provider or laboratory is located.
- Reporting Form(s) and/or Mechanism:
    - The Ohio Disease Reporting System (ODRS) should be used to report lab findings to the Ohio Department of Health (ODH). For healthcare providers without access to ODRS, you may use the Ohio Confidential Reportable Disease form (HEA 3334).
- Key fields for ODRS reporting include: purpose of culture (clinical or screening/surveillance), whether there has been a previous positive for the same organism and when that culture was collected, sensitive occupation (e.g. direct patient care, child care provider, food handler), sensitive setting (e.g. day care or preschool attendee, long term care facility resident), import status (whether the infection was travel-associated or Ohio-acquired), date of illness onset, the interview fields, the fields in the Travel and Other Exposures module.

AGENT

Enterobacteriaceae are a family of rod-shaped gram-negative bacteria that are often found in a person's gastrointestinal tract. *Enterobacteriaceae* can cause infections in both community and healthcare settings. Carbapenem-resistant *Enterobacteriaceae* (CRE) have developed a high level of resistance to the carbapenem class of antibiotics. Carbapenemase-producing (CP) CRE produce an enzyme, carbapenemase, that breaks down carbapenem antibiotics, rendering them ineffective. CP-CRE subtypes:

CP-CRE *Enterobacter spp.*
CP-CRE *Escherichia coli*
CP-CRE *Klebsiella spp.*
CP-CRE Other

Infectious dose: Varies according to organism and site.

CASE DEFINITION

Laboratory Criteria for Diagnosis

Laboratory evidence of carbapenemase production in an isolate by a phenotypic method or positive for a known carbapenemase resistance mechanism by specific testing methods, such as:

- Phenotypic methods for carbapenemase production:
    - Carba NP positive
    - Metallo-β-lactamase testing (e.g., E-test) positive
    - Modified Carbapenem Inactivation Method (mCIM) positive or indeterminate
    - Carbapenem Inactivation Method (CIM) positive
    - Modified Hodge Test (MHT) positive
    - Positive for phenotypic carbapenemase production (e.g., mCIM, CIM, CarbaNP) but negative by polymerase chain reaction (PCR) (e.g., Xpert Carba-R) for all known resistance mechanisms (e.g. *Klebsiella pneumoniae* Carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], oxacillinase-48 [OXA-48], Verona integron-encoded metallo-β-lactamase [VIM], imipenemase [IMP])

- Molecular methods for resistance mechanism:
  - PCR positive (for KPC, NDM, OXA-48, IMP, or VIM)
  - Xpert Carba-R positive (for KPC, NDM, OXA-48, VIM, IMP)
  - PCR or Xpert Carba-R positive for novel carbapenemase

Criteria to Distinguish a New Case from an Existing Case

- Different organisms/species/carbapenemases are counted as separate events from other organisms/species/carbapenemases
- There is at least a 12-month interval from previous notification event for clinical cases
- A person with a clinical case should not be counted as a screening/surveillance case thereafter (e.g., patient with known infection who later has colonization of GI tract is not counted as more than one case)
- A person with a screening case can be later categorized as a clinical case (e.g., patient with positive peri-rectal screening swab who later develops blood stream infection would be counted in both categories)

Case Classification

Confirmed: *E. coli*, *Klebsiella* spp., *Enterobacter* spp. or CP-CRE "Other" from any isolate that is:

- Positive for known carbapenemase resistance mechanism (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., PCR, Xpert Carba-R); **OR**
- Positive on a phenotypic test for carbapenemase production (e.g., metallo-β-lactamase test, modified Hodge test, Carba NP, Carbapenem Inactivation Method [CIM], or modified CIM).

Case Classification Comments

1. Cases involving isolates that are phenotypically positive for carbapenemase production (e.g., mCIM), but negative for KPC, NDM, OXA-48, VIM, and IMP should be counted as confirmed CP-CRE. Isolates should be submitted to the regional laboratories of the ARLN for further characterization (potential novel carbapenemase).
2. A positive Modified Hodge Test (MHT) can be used to confirm CP-CRE for *Klebsiella* spp and *E. coli* but not *Enterobacter* spp. An isolate that tests positive on MHT but negative PCR for KPC, NDM, OXA-48, VIM and IMP should have additional characterization performed with another phenotypic test for carbapenemase such as mCIM.
3. If isolate is indeterminate on mCIM and negative by PCR for KPC, NDM, OXA-48, VIM and IMP, isolate should be tested using CarbaNP (at state public health laboratory or regional ARLN lab).
4. CP-CRE should be stratified by the 4 subtypes (genera): *Klebsiella* spp, *Enterobacter* spp, E. *coli,* and Other. Each subtype/genus should be stratified by whether the cultures were clinical (i.e., collected for the purpose of diagnosing or treating disease in the course of normal care) versus for screening/surveillance (i.e., collected for the detection of colonization and not for the purpose of diagnosing or treating disease). Because it can be difficult to differentiate screening cultures from clinical cultures based on microbiology records, screening tests should generally be limited to rectal swabs. Cultures from such sites can be assumed to be for screening unless specifically noted otherwise. Laboratory may also note screening culture for other sites (e.g., wounds, tracheostomy or central line sites). Laboratories do not need to change their practice; public health wants to identify all CP-CRE whether they come from screening or clinical cultures.

SIGNS AND SYMPTOMS

CP-CRE infections may be invasive or non-invasive. Signs and symptoms vary according to organism and location. CP-CRE usually cause healthcare-associated infections, primarily affecting those with chronic medical conditions (e.g., diabetes, obesity, hemodialysis, non-healing wounds) and compromised immune function. CP-CRE can cause pneumonia, bloodstream infections, urinary tract infections, intra-abdominal infections, and surgical site infections, among others. Patients that are colonized with CP-CRE, (positive clinical culture without symptoms of infection), can serve as vectors to other patients or sources for healthcare facility outbreaks.

DIAGNOSIS

Laboratory test.

EPIDEMIOLOGY

Source

Enterobacteriaceae are a large family of gram-negative bacilli that are normal inhabitants of the gastrointestinal tract of humans and other animals.

Occurrence

CP-CRE are an emerging and epidemiologically important threat. Since the first detection of CP-CRE in the United States (1), CP-CRE have spread rapidly, with cases reported in all 50 states (2). Infections with CP-CRE are difficult to treat and associated with high mortality rates (3). Carbapenem antibiotics are often used as the last line of treatment for infections caused by highly resistant bacteria, including those in the *Enterobacteriaceae* family. Increased antimicrobial resistance limits treatment options (4). CP-CRE contain mobile resistance elements that facilitate transmission of resistance to other Gram-negative bacilli (5). Early detection and aggressive implementation of infection prevention and control strategies are necessary to prevent further spread of CP-CRE, especially novel CP-CRE. These strategies require an understanding of the prevalence or incidence of CP-CRE.

Reservoir

Enterobacteriaceae can be carried in the intestines of many mammals and birds. The reservoir for CP-CRE infections in the United States is colonized and infected individuals, especially patients with frequent contact with the healthcare system. *Enterobacteriaceae* can survive on inanimate objects.

Mode of Transmission

CP-CRE is transmitted person-to-person through direct contact with infected bodily tissues or fluids. CP-CRE can cause infections when they enter the body, often through medical devices like ventilators, intravenous catheters, urinary catheters, or wounds caused by injury or surgery. In healthcare settings, CP-CRE are spread mainly through the hands of healthcare workers and direct contact with contaminated environmental services, such as bed rails and computer keyboards.

Period of Communicability

CP-CRE can potentially be transmitted as long as the organisms are present in a person's bodily tissues or fluids. It is unknown how long CP-CRE can live on inanimate surfaces.

Incubation Period
The incubation period is not well defined, particularly due to the ability of CRE to colonize an individual for an extended interval of time.

PUBLIC HEALTH MANAGEMENT

Case Investigation

Detection of CP-CRE in the laboratory should trigger timely notification by the healthcare facility. All CRE isolates should be sent to ODHL. Notification should include:

- Local Health Department (LHD) by the end of the next business day after identification of organism
- Patients primary caregiver and healthcare staff, per facility policy, to ensure timely infection control measures
- Prior healthcare facility, or receiving facility, if applicable
  LHD case investigation should also include patient exposures in the last 12 months along with patient demographics
- Overseas travel? if yes – country(ies), dates of travel, and any healthcare exposures
- Complex medical devices (e.g., duodenoscopes)? if yes-facility name, date(s) and type(s) of procedures performed (e.g., ERCP), type(s) of invasive device(s) used
- Exposure to healthcare in areas in U.S. with high rates of CRE or CP-CRE during the past year?
- Other healthcare exposures in past year, including admissions, surgeries, dialysis, long terms care facilities (LTCF), long term acute care hospitals (LTACH)?
  - if yes – name of facility and dates
- Medical devices (catheters, Foley, trach, etc.) in place within 2 calendar days prior to culture?
- Antibiotic exposures last 30 days?
- Other information of interest
  - Was there was evidence of infection, was CRE isolate identified as part of a screening protocol, active surveillance testing, or contact investigation?
  - Previous CRE isolated?

Given the public health importance, positive CP-CRE cultures should trigger an investigation that includes a contact investigation to determine the extent of transmission.

- Identify and categorize contacts: Contacts should be categorized based on their level of interaction (i.e., extensive, moderate, or minimal) with the colonized or infected patient.
- Priority should be given to contacts with extensive interaction with the CP-CRE patient, such as roommates.
- Line listing should include at least the prior three months of healthcare exposures
- If transmission is noted in initial contact screenings, facilities should consider expanding screenings to the unit/ward etc. to determine extent of transmission
- Review the patient's healthcare exposures prior to and after the positive culture including overnight stays in healthcare settings, and home health visits.
- Facilities should consider performing surveillance cultures to rule out CP-CRE in patients admitted following an overnight stay within the last 6 to 12 months in a healthcare facility outside the United States, or in an area within the Unites States known to have a higher prevalence of CP-CRE.
- Acute care facilities should review clinical culture results for the proceeding 6-12 months to determine whether previously unrecognized CP-CRE have been present

in the facility.

Specimen
Data analysis will be stratified by whether the cultures were clinical (i.e., collected for diagnosing or treating disease in the course of normal care) versus screening cultures (i.e., collected for the detection of colonization and not for the purpose of diagnosing or treating disease). Prior to the collection of specimens for screening, ODH must be contacted to provide the current collection procedures. Because it can be difficult to differentiate screening cultures from clinical cultures based on microbiology records, screening tests should be limited to rectal swabs.

Treatment
Currently, the best treatment for CP-CRE is prevention. CP-CRE infections can be difficult to treat due to resistance to most antibiotics, and in some cases, all. Antibiotic sensitivities should be performed, and treatment should be determined on a case-by-case basis. Colonized patients do not need to be treated with antibiotics if they are not symptomatic, but additional steps should be taken to prevent further transmission.

Isolation and Follow-up Specimens
In general, any patient colonized or infected with an organism that is non-susceptible to a carbapenem warrants the use of Standard Precautions, Contact Precautions, and other transmission-based precautions as indicated by the patient's status in acute care settings, to decrease the risk for transmission of these organisms. However, for isolates known or suspected to be carbapenemase producers (i.e., likely CP-CRE or unknown CP-CRE) consideration should be given to implementation of more aggressive interventions including screening cultures of known contacts, cohorting of patients and staff, interfacility communication (i.e., communicating patient's CP-CRE status to receiving facility upon patient transfer or when results become available and report CP-CRE to previous care setting following recent transfer).

Contacts
Contacts of newly diagnosed CP-CRE patients, or newly identified carriers, should be screened based on epidemiological importance to determine the extent of transmission. Screenings may start with close contacts, such as roommates, patients sharing the same healthcare personnel (HCP), or family members sharing the same bed. Screening should be expanded if transmission is identified in initial contacts to include unit/ward then floor, etc.to determine the extent of transmission. Additional ongoing surveys should be considered to determine that transmission has ceased.

Prevention and Control
Healthcare facilities should develop a written plan for the management of CP-CRE positive and colonized individuals. The plan should include a treatment protocol, follow-up monitoring guidance, inter-agency communication, and information about work issues. Below is a checklist of important infection control recommendations. However, these may need to be customized for special healthcare-settings (e.g., dialysis, home healthcare).

- Acute Care Settings(ACS) and Long-Term Care Settings (LTCS)
  - Educate and inform the appropriate healthcare personnel about the presence of a patient with CRE and the need for Contact Precautions.
  - Implement the appropriate infection control precautions during patient care.
    - Use contact precautions (gown and gloves for room entry) in ACS

        - Additional transmission based precautions (e.g. droplet) added per patient status
        - Per standard precautions, wear facemask and eye protection or face shield if performing procedures likely to generate splash or splatter (e.g., wound manipulation, suctioning) of CP-CRE-contaminated material (e.g., blood, body fluids, secretions, and excretions)
        - Perform hand-hygiene using appropriate agent (e.g., alcohol-based hand sanitizer or hand washing with plain or antimicrobial soap and water)
        - Dedicate non-disposable items that cannot be cleaned and disinfected between patients (e.g., adhesive tape, cloth-covered blood pressure cuffs) for use only on the patient with CP-CRE
        - Monitor and strictly enforce compliance with Contact Precautions
    - Minimize the number of persons caring for the patient (e.g., assign dedicated staff to care for CP-CRE patient).
    - Minimize use of invasive devices when possible
    - Promote Antimicrobial Stewardship
    - Ensure that the patient's CP-CRE status and required infection control precautions are communicated upon transfer
    - Flag the patient's chart to indicate infection/colonization with CP-CRE to insure prompt infection control if readmitted
    - Consider more aggressive interventions (e.g. screening, cohorting of staff/patients) based on clinical circumstance, patient history of travel, and local CP-CRE epidemiology

<u>Outpatient Settings and Home Healthcare</u>

- Providers should generally follow the same CP-CRE precautions as hospital based healthcare providers
    - Wear gown and gloves where patient care will be provided
    - Per standard precautions, wear mask and eye protection or face shield if preforming procedures likely to generate splash or splatter of CP-CRE material (e.g., blood, body fluids, secretions, and excretions)
    - Perform hand hygiene using appropriate agent (e.g., alcohol based hand sanitizer or hand washing with plain or antibacterial soap and water)
- Minimize the number of persons with access to the CP-CRE colonized/infected patient (e.g., dedicate a single staff person to care for this patient)
- Dedicate non-disposable items that cannot be cleaned and disinfected between patients (e.g., cloth-covered blood pressure cuffs) for use only on a single patient
- If household members are providing care to the CP-CRE patient (e.g., wound care), these persons should follow the same precautions as healthcare personnel

Disease Fact Sheet **CARBAPENEMASE PRODUCING CARBAPENEM-RESISTANT *Enterobacteriaceae* (CP-CRE)**

What are CP-CRE?

CRE, which stands for Carbapenem-resistant *Enterobacteriaceae*, are a family of bacteria that are difficult to treat because they have high levels of resistance to antibiotics. CP-CRE, which stands for Carbapenemase Producing Carbapenem-resistant *Enterobacteriaceae*, are CRE that are capable of breaking down Carbapenems. CP-CRE are an important emerging threat to public health.

Common *Enterobacteriaceae* include *Klebsiella* species and *Escherichia coli (E. coli).* These germs are found in normal human intestines (gut). Sometimes these bacteria can spread outside the gut and cause serious infections, such as urinary tract infections, bloodstream infections, wound infections, and pneumonia. *Enterobacteriaceae* can cause infections in people in both healthcare and community settings.

Carbapenems are a group of antibiotics that are usually reserved to treat serious infections, particularly when these infections are caused by germs that are highly resistant to antibiotics. Sometimes carbapenems are considered antibiotics of last resort for some infections. Some *Enterobacteriaceae* can no longer be treated with carbapenems because they have developed resistance to these antibiotics (i.e., CRE); resistance makes the antibiotics ineffective in killing the resistant germ. Resistance to carbapenems can be due to a few different mechanisms. One of the more common ways that *Enterobacteriaceae* become resistant to carbapenems is due to production of *Klebsiella pneumoniae* carbapenemase (KPC). KPC is an enzyme that is produced by some CRE that was first identified in the United States around 2001. KPC breaks down carbapenems making them ineffective. Other enzymes, in addition to KPC, can breakdown carbapenems and lead to the development of CRE, but they are uncommon in the United States.

How are CP-CRE spread?

To get a CP-CRE infection, a person must be exposed to CP-CRE bacteria. CP-CRE bacteria are usually spread person-to-person through contact with infected or colonized people, particularly contact with wounds or stool. CP-CRE can cause infections when they enter the body, often through medical devices like ventilators, intravenous catheters, urinary catheters, or wounds caused by injury or surgery.

Who is most likely to get an infection with CP-CRE?

Healthy people usually don't usually get CP-CRE infections. CP-CRE primarily affects patients in acute and long-term healthcare settings, who are being treated for another condition. CP-CRE are more likely to affect those patients who have compromised immune systems or have invasive devices like tubes going into their body. Use of certain types of antibiotics might also make it more likely for patients to get CP-CRE.

Can CP-CRE be treated?

Many people with CP-CRE will have the bacteria in or on their body without it producing an infection. These people are said to be colonized with CP-CRE, and they do not need antibiotics. If the CP-CRE are causing an infection, the antibiotics that will work against it are limited but some options are available. In addition, some infections might be able to be treated with other therapies, like draining the infection. Strains that have been resistant to all antibiotics are very rare but have been reported.

What are some things hospitals are doing to prevent CP-CRE infections?
To prevent the spread of CP-CRE, healthcare personnel and facilities can follow infection-control precautions provided by CDC. These include:

- Washing hands with soap and water or an alcohol-based hand sanitizer before and after caring for a patient
- Carefully cleaning and disinfecting rooms and medical equipment
- Wearing gloves and a gown before entering the room of a CP-CRE patient
- Keeping patients with CP-CRE infections in a single room or sharing a room with someone else who has a CRE infection
- Whenever possible, dedicating equipment and staff to CP-CRE patients
- Removing gloves and gown and washing hands before leaving the room of a CP-CRE patient
- Prescribing antibiotics only when necessary
- Removing temporary medical devices as soon as possible
- Testing patients for bacteria to identify them early to help prevent them from being passed on to other patients

What can patients do to prevent CP-CRE infections?
Patients should:

- Tell your doctor if you have been hospitalized in another facility or country
- Take antibiotics only as prescribed
- Expect all doctors, nurses, and other healthcare providers wash their hands with soap and water or an alcohol-based hand rub before and after touching your body or tubes going into your body. If they do not, ask them to do so.
- Clean your own hands often, especially:
    - Before preparing or eating food
    - Before and after changing wound dressings or bandages
    - After using the bathroom
    - After blowing your nose, coughing, or sneezing
- Ask questions. Understand what is being done to you, the risks and benefits.

What if I have CP-CRE?
Follow your healthcare provider's instructions. If your provider prescribes you antibiotics, take them exactly as instructed and finish the full course, even if you feel better. Wash your hands, especially after you have contact with the infected area and after using the bathroom. Follow any other hygiene advice your provider gives you.

I am caring for someone with CP-CRE at home; do I need to take special precautions?
CRE have primarily been a problem among people with underlying medical problems, especially those with medical devices like urinary catheters or those with chronic wounds. Otherwise healthy people are at lower risk for problems with CRE. People providing care at home for patients with CP-CRE should be careful about washing their hands, especially after contact with wounds or helping the CP-CRE patient to use the bathroom or after cleaning up stool. Caregivers should also make sure to wash their hands before and after handling the patient's medical device (e.g., urinary catheters). This is particularly important if the caregiver is caring for more than one ill person at home. In addition, gloves should be used when anticipating contact with body fluids or blood.

Is CP-CRE infection related to medical care abroad?
A variety of enzymes produced by *Enterobacteriaceae* make them resistant to carbapenems. Several of these enzymes appear to be more common in other countries than they are in the United States. As with medical care in the United States, medical care

abroad can be associated with healthcare–associated infections and/or resistant bacteria. Learn about those risks and how to minimize them.