Carbapenem-Resistant Enterobacterales

Investigative Guidelines

September 2022

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To prevent transmission of infections with carbapenem-resistant Enterobacterales (CRE) between patients, within or among health care facilities, or between health care facilities and the community.
2. To prevent CRE from becoming endemic in Oregon, necessitating empiric use of even broader-spectrum antibiotics.
3. To identify outbreaks and potential sources or sites of ongoing transmission.
4. To better characterize the epidemiology of these infections.

1.2 Laboratory and Physician Reporting Requirements

1. Providers and laboratories must report cases to local public health authorities (LPHAs) within one working day.
2. Clinical and reference laboratories must forward isolates from any sterile or non-sterile site (e.g., urine, blood, sputum, endotracheal aspirate, bronchoalveolar lavage, wound) that meet the confirmed CRE case definition below along with the automated test system susceptibility printouts (Vitek or Microscan report) to the Oregon State Public Health Laboratory (OSPHL).
3. Isolates of *Proteus, Providencia*, or *Morganella* which show only imipenem non-susceptibility, in the absence of resistance to another carbapenem, do not need to be submitted.

1.3 Local Public Health Authority Reporting and Follow-Up Responsibilities

1. LPHAs will confirm that a case meets the case definition by reviewing the isolate's susceptibility information (antibiogram), consulting with the ACDP on-call epidemiologist as necessary. Both minimum inhibitory concentration (MIC) values and interpretations are needed to verify a case meets the definition. (See Confirmed Case §3.1.)
2. If a case meets the case definition, the LPHA will investigate.
3. Report cases to ACDP within one working day. Use the Orpheus CRE case report. A paper CRE case investigative form is also available online.
4. Intervene to prevent the spread of the organism and take action based upon the resistance mechanism of the isolate (See §3.2 and Case Investigation §4.1 below).

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

The Enterobacterales are a large order of gram-negative bacilli, many members are residents of the human gastrointestinal tract. A full list of genera can be found in Appendix 1.

However, with the increasing complexity of patients and invasiveness of medical treatments, some of these Enterobacterales and other gram-negative bacilli can cause health care-associated infections (HAI). The broad spectrum of carbapenem antibiotics (e.g., doripenem, ertapenem, imipenem and meropenem) are used to treat severe healthcare-associated infections caused by Enterobacterales and other Gram-negative bacilli (e.g., *Acinetobacter baumannii, Pseudomonas aeruginosa*). Unfortunately, when carbapenem antibiotic resistance develops, few safe and effective treatment options remain, and the risk of patient morbidity and mortality increase.

Carbapenem resistance in Enterobacterales can occur by several mechanisms, including the production of carbapenemases (enzymes) such as *Klebsiella pneumoniae* carbapenemase, (KPC), or New Delhi metallo-beta-lactamase (NDM) that inactivate carbapenem antibiotics. Other examples of carbapenem-destroying enzymes include imipenem-hydrolyzing-lactamase (IMP). Verona integron-encoded metallo-beta-lactamase (VIM), and oxacillinase-48 (OXA-48). Resistance genes code for carbapenemases that can be exchanged between different gram-negative bacteria via genetic packets called transposons or plasmids ("jumping genes"). Enterobacterales that possess these carbapenemase genes are sometimes referred to as carbapenemase-producing CRE (CP-CRE). From a public health perspective, CP-CRE are the most concerning CRE because their resistance is easily spread. Additional information about CRE and CP-CRE is available through CDC.

CRE has been reported in all 50 states. Once CRE have become entrenched in a region or health care facility, the carbapenem antibiotics may lose their effectiveness and patients may die for lack of appropriate treatment. If CRE become prevalent, empiric therapy will necessitate 2nd and 3rd line antibiotics, which may be less effective, cost more, and cause more side effects. Incidence of CRE has remained stable in Oregon for the last five years, and CP-CRE cases remain rare. If health care providers and public health officials can rapidly identify and isolate patients with CRE in Oregon, we may be able to prevent or delay their becoming endemic.

2.2 Nomenclature

In 2016, a taxonomy change was proposed that split the family *Enterobacteriaceae* into 7 new families under the renamed order Enterobacterales. These seven families are *Enterobacteriaceae*, *Erwiniaceae*, *Pectobacteriaceae*, *Yersiniaceae*, *Hafniaceae*, *Morganellaceae*, and *Budviciaceae*. Prior to this, the acronym “CRE” referred to carbapenem-resistant

Enterobacteriaceae. Enterobacteriaceae was the only family in the order Enterobacterales, and it encompassed all the genera in Appendix 1.

In 2020, CDC adopted the proposed taxonomy change. “Carbapenem-resistant Enterobacterales” has replaced “carbapenem-resistant *Enterobacteriaceae*.” Fortunately, this has not required a change to the acronym: CRE.

2.3 Description of Illness

Up to this point in the United States, CRE have mainly caused healthcare-associated infections, primarily affecting those with chronic medical conditions (e.g., diabetes, hemodialysis, non-healing wounds), medical conditions that require invasive lines or tubes, and compromised immune function. CRE can cause pneumonia, bloodstream infections, urinary tract infections, intra-abdominal infections, and surgical site infections. Patients who are colonized with CRE (positive clinical culture without symptoms of infection) can serve as reservoir of infection for other patients or sources for health care facility outbreaks and may themselves be more likely to develop a CRE infection.

2.4 Sources and Routes Transmission

CRE colonizes the gut, and CRE can be isolated from the stool of colonized or infected patients. CRE from the stool may be transmitted to wounds, medical devices, tracheostomy tubes, urinary catheters, and central line venous catheters, typically via the hands of health care workers and less commonly via contaminated environmental surfaces, medical devices, or equipment. Healthy people may be colonized in the health care setting or community.

Studies have shown that the patients most at risk for CRE infection are those with chronic medical conditions, frequent or prolonged stays in health care settings, invasive medical devices (e.g., ventilators or intravenous catheters), or a history of taking certain antibiotics for long periods of time.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

Use the MIC values to interpret resistance (the automated test system result directly from the laboratory is preferred, see Table 1). In some cases, Kirby Bauer disc diffusion results may be provided, see Table 2.

1. A confirmed case of CRE is a patient whose clinical or surveillance specimen culture yields an isolate of the Enterobacterales order (see Appendix 1) that is resistant to any carbapenem, including doripenem, ertapenem, imipenem, or meropenem using the current M100-S32 CLSI breakpoints.

Table 1. Carbapenem MIC Breakpoints

	Current MIC Breakpoints (µg/mL)[1]		
	MIC Interpretation[2]		
Carbapenems	**Susceptible**	**Intermediate**	**Resistant**
Doripenem	≤1	2	≥4
Ertapenem*	≤0.5	1	≥2
Imipenem	≤1	2	≥4
Meropenem	≤1	2	≥4

[1]MIC = minimum inhibitory concentration
[2]CLSI. Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales. In: CLSI M100-ED32:2022 Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition. Feb 2022. Available from: http://em100.edaptivedocs.net/dashboard.aspx
* A value of >1 indicates resistance by outdated break points. There is no further dilution. If the lab is not doing any other method for confirmation the >1 value is considered resistant and meets our definition.

Table 2 Kirby Bauer Disc Diffusion Interpretations

	Current Disk Diffusion Zone Diameters (mm)[1]		
	Zone Size Interpretation[2]		
Carbapenems	**Susceptible**	**Intermediate**	**Resistant**
Doripenem	≥23	20-22	≤19
Ertapenem	≥22	19-21	≤18
Imipenem	≥23	20-22	≤19
Meropenem	≥23	20-22	≤19

[1]mm = millimeters
[2]CLSI. Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales. In: CLSI M100-ED32:2022 Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition. Feb 2022. Available from: http://em100.edaptivedocs.net/dashboard.aspx

OR

2. Positive for a carbapenemase by a nucleic acid amplification test; (e.g., PCR-positive for KPC, NDM, IMP, VIM, or OXA-48)

   OR

3. Are positive for carbapenemase production by a phenotypic test (e.g., Carba NP on any Enterobacterales or Modified Hodge if *Escherichia coli* or *Klebsiella* spp.).

Laboratories still using MIC breakpoints prior to the June 2010 CLSI update should use the updated MIC cut-offs to determine reporting to public health, independent of the susceptibility interpretation. For example, an isolate with an MIC of 8 µg/mL to meropenem, which would be "intermediate" by pre-2010 CLSI

interpretation but "resistant" by CLSI guidelines starting in 2011, should be reported to public health and submitted to OSPHL for further evaluation.

There are still a few Oregon labs that are using outdated breakpoints for ertapenem. If an MIC for ertapenem is >1 and the lab is not doing further confirmatory testing, >1 is considered resistant and the organism meets our definition for CRE.

To complicate things further, some labs will suppress carbapenems, particularly ertapenem, results on reports. If you receive a report that calls the Enterobacterales species isolated a CRE but the available carbapenem results are susceptible, you need to ask the lab for any suppressed carbapenem results. These results will be on the automated test system susceptibility report.

Note: *Proteus* spp., *Providencia* spp. and *Morganella* spp. are excluded from this definition if only imipenem resistance is detected because these species have intrinsic resistance to imipenem. For example, isolates that test ertapenem susceptible but imipenem resistant would not meet the definition.

3.2 Resistance Mechanism

We are more concerned about some CRE than others, with CP-CRE (see Table 3) being of most concern.

Table 3. Type of CRE

Description	Organisms Included	Recommended Measures
Carbapenemase-producing CRE (**CP-CRE**)	Enterobacterales positive by PCR for KPC, NDM, IMP, VIM, OXA-48; or by Carba NP	Most aggressive control measures: see Oregon CRE Toolkit http://bit.ly/CRE-Toolkit
CRE with acquired resistance NOT due to carbapenemase production	Enterobacterales that meet definition, but are PCR and Carba NP negative	Intensified control measures including contact precautions: see Oregon CRE Toolkit http://bit.ly/CRE-Toolkit

3.3 Services Available at the Oregon State Public Health Laboratories (OSPHL)

All potential CRE isolates received by OSPHL will be further tested for carbapenemase production by the Carba NP Test and OXA-48 PCR; for Carba NP positive isolates we will perform PCR confirmation for KPC, NDM, IMP, VIM and OXA-48 carbapenemases.

4. CASE INVESTIGATION

4.1 Identify Source of Infection

Confirm that a case meets the case definition by reviewing the isolate's susceptibility information or in consultation with the ACDP on-call epidemiologist (See Confirmed Case §3.1)

4.2 Case Follow-up

For CP-CRE and non-CP-CRE, refer to the Oregon CRE Toolkit (pdf): http://bit.ly/CRE-Toolkit

1. If case meets criteria, begin Orpheus case record and investigation within one working day.
2. LPHA will work with the health care facility or physician (if case is an outpatient) to investigate and institute control measures, as indicated in Oregon's CRE Toolkit. If case has a CP-CRE the ACDP HAI epidemiologists will work with the LPHA and the facility or physician. See http://bit.ly/CRE-Toolkit
    a. If multiple health care facilities are involved, LPHA will work with all facilities to institute appropriate control measures. If a case will be transferred to a new facility, the LPHA will work with the receiving facility to ensure they are prepared to implement appropriate infection control measures.
3. Create a case record in Orpheus for confirmed cases and provide:
    - Name, address, date of birth (age) sex, race and ethnicity;
    - Hospitalization status at the time of culture, admit and discharge dates, and name of hospital;
    - Outcome, and name of health care facility discharged to if case survived;
    - Date of initial culture collection;
    - Name of organism (as “subtype” in Orpheus);
    - Patient location on 4th calendar date prior to initial culture date; (under “MDRO” tab in Orpheus)
    - If case was in contact precautions if hospitalized or in a skilled nursing facility
    - Was an interfacility transfer notice for the next transfer completed/updated and placed in the chart if case was hospitalized or in a skilled nursing facility
    - Was education provided if case was an outpatient
    - Was hand hygiene reinforced if case was an outpatient
    - Any medical care outside the state or U.S. during the last 12 months;
    - Any travel history in the year before collection.

In general, infection control measures include: (See Tables 4, 5, 6, 7)

- Emphasis on hand hygiene;
- Standard precautions at all times;
- Transmission-based precautions (e.g., contact precautions); when contact with bodily fluids is a possibility, or there is an active infection;

  - Acute health care facilities should use contact precautions, even for colonized patients to reduce transmission among high-risk populations;
  - Long-term care facilities should use contact precautions for patients with CRE infections and colonized patients at higher risk of transmission (e.g., draining wounds, patients incontinent of urine or stool). See the CRE Toolkit for additional details. CDC also recommends Enhanced Barrier Precautions (EBP) for patients colonized with MDROs when contact precautions do not apply and for MDRO-naïve patients at higher risk of acquiring MDROs (e.g., patients with indwelling medical devices or wounds). More information about EBP is available through CDC: https://www.cdc.gov/hai/pdfs/containment/PPE-Nursing-Homes-H.pdf
  - CP-CRE cases are rare and contact precautions are always recommended
- Enhanced environmental cleaning, including high touch surfaces;
- Interfacility communication of patient's CRE status at transfer or time of discharge;
  - Interfacility transfer notification is required by OAR 333-019-0052
  - CP-CREs also require communication to the LPHA when there is a new transfer or admission of a case.
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Keep in mind the "NICE" mnemonic: Notify, Intervene, Communicate, Educate when CRE are encountered

Notify the LPHA, pertinent clinician groups, and the antibiotic stewardship program to the presence of CRE in the facility,. Additionally, for carbapenemase-producing CRE (CP-CRE) notify the hospital administration.

Intervene in all cases with core infection prevention and control strategies, hand hygiene, contact precautions, private rooms and optimized environmental cleaning. Reduce unnecessary antibiotics and use of invasive devices. Additionally, for CP-CRE screen patient contacts and cohort staff and patients.

Communicate CRE infection or colonization status to the receiving facility upon patient transfer.

Educate patients, staff and visitors about CRE.

Table 4. Recommendations for hospital setting

HOSPITALS	Response and Control Measures by Local Public Health Authorities
CP-CRE	Most aggressive • Confirm case meets case definition • Obtain case information for Orpheus case report • Advise facility Infection Preventionist (IP) Staff • Work with ACDP to discuss CP-CRE infection-control measures, surveillance, and prevalence as outlined in Oregon's CRE toolkit • If patient is transferred verify that referring facility notifies the receiving facility • If patient is re-hospitalized, dies, or is transferred again, the LPHA must be notified by referring facility • Educate about importance of aggressive control measures (transmission-based precautions). See CRE toolkit page 10-15.
Non-CP-CRE	• Confirm case meets case definition • Obtain case information for Orpheus case report • Advise facility Infection Preventionist (IP) Staff • Work with ACDP to discuss non-CP-CRE infection-control measures, surveillance, and prevalence as outlined in Oregon's CRE toolkit • If patient is transferred verify that referring facility notifies the receiving facility • Educate about importance of aggressive control measures (transmission-based precautions). See CRE toolkit page 10-15.

Table 5. Recommendations for skilled nursing facilities

SKILLED NURSING FACILITIES	Response and Control Measures by Local Public Health Authorities
CP-CRE	Most aggressive • Confirm case meets case definition • Obtain case information for Orpheus case report • Advise staff responsible for infection control • Work with ACDP to discuss CP-CRE infection-control measures, surveillance, and prevalence as outlined in Oregon's CRE toolkit • If patient is transferred verify that referring facility notifies the receiving facility • If patient is re-hospitalized, dies, or is transferred again, the LPHA must be notified by referring facility • Educate about importance of aggressive control measures (transmission-based precautions). See CRE toolkit page 16-23.
Non-CP-CRE	• Confirm case meets case definition • Obtain case information for Orpheus case report • Advise staff responsible for infection control • Discuss relevant non-CP-CRE infection control measures • If patient is transferred referring facility must notify receiving facility • Place those infected in transmission-based precautions (usually contact precautions). Educate about assessing risk level of resident; place those colonized residents at higher risk in contact precautions; for low risk colonized residents, standard precautions can be used. See CRE toolkit page 16–23.

Table 6. Recommendations for outpatient clinics and community-based care

OUTPATIENT Clinics and Community Based Care	**Response and Control Measures by Local Public Health Authorities**
CP-CRE	Most aggressive • Confirm case meets case definition • Obtain case information for Orpheus case report • Advise case and staff about infection control, especially hand washing • Work with ACDP to discuss CP-CRE infection-control measures and possible surveillance • If patient is admitted, clinic notifies receiving facility of CRE status • If patient is re-hospitalized, dies, or is transferred again, the LPHA must be notified by referring facility • Educate about importance of aggressive control measures for future clinic visits. See CRE toolkit page 24–27.
Non-CP-CRE	• Confirm case meets case definition • Obtain case information for Orpheus case report • Advise clinic staff responsible for infection control • Verify the patient has been informed, and good hand hygiene reinforced • Discuss relevant non-CP-CRE infection measures for future visits. See CRE toolkit page 24–27.

Table 7. Recommendations for cases living at home

Individuals living at home	Response and Control Measures by Local Public Health Authorities
CP-CRE	Most aggressive • Confirm case meets case definition • Obtain case information for Orpheus case report • Recommend good hand hygiene • Provide CRE education • Work with ACDP to discuss CP-CRE possible surveillance screening cultures • If patient is admitted, clinic notifies receiving facility of CP-CRE status • If patient is re-hospitalized, dies, or is transferred again, the LPHA must be notified by referring facility • See CRE toolkit page 29–30.
Non-CP-CRE	• Confirm case meets case definition • Obtain case information for Orpheus case report • Recommend good hand hygiene • Provide CRE education • Discuss relevant non-CP-CRE infection measures for future visits to clinic, hospital or skilled nursing. See CRE toolkit page 29–30.

4.3 Repeat Culture Results

Repeat positive culture results for the same carbapenem-resistant organisms collected within 30 days of the initial positive collection date should be entered as a new lab in the existing Orpheus case record. After 30 days, review the susceptibility results for both labs. If the new susceptibility results look very similar to the existing case's susceptibility results, the new lab can be added to the existing case. If the susceptibility results look very different, consult with the ADCP on-call epidemiologist to determine if the case should be entered in Orpheus as a new case. A positive culture for a different CRE organism (different genus and species) should be entered as a new incident case, regardless of the collection date.

APPENDIX

Appendix 1 – List of genera in the Enterobacterales order[1]

Acerihabitans	*Enterobacillus*	*Kosakonia*	*Phytobacter*	*Scandinavium*
Arsenophonus	*Enterobacter*	*Leclercia*	*Plesiomonas*	*Serratia*
Biostraticola	*Erwinia*	*Lelliottia*	*Pluralibacter*	*Shigella*
Brenneria	*Escherichia*	*Leminorella*	*Pragia*	*Shimwellia*
Buchnera	*Ewingella*	*Limnobaculum*	***Proteus****	*Siccibacter*
Budvicia	*Franconibacter*	*Lonsdalea*	***Providencia****	*Sodalis*
Buttiauxella	*Gibbsiella*	*Mangrovibacter*	*Pseudescherichia*	*Tatumella*
Cedecea	*Hafnia*	*Mixta*	*Pseudocitrobacter*	*Trabulsiella*
Chania	*Insectihabitans*	*Moellerella*	*Rahnella*	*Wigglesworthia*
Chimaeribacter	*Intestinirhabdus*	***Morganella****	*Raoultella*	*Xenorhabdus*
Citrobacter	*Izhakiella*	*Obesumbacterium*	*Rosenbergiella*	*Yersinia*
Cosenzaea	*Jinshanibacter*	*Pantoea*	*Rouxiella*	*Yokenella*
Cronobacter	*Kalamiella*	*Pectobacterium*	*Saccharobacter*	
Dickeya	*Klebsiella*	*Phaseolibacter*	*Salmonella*	
Edwardsiella	*Kluyvera*	*Photorhabdus*	*Samsonia*	

* Elevated MICs to imipenem in ***Morganella* spp.**, ***Proteus* spp.**, and ***Providencia* spp.** are frequently due to mechanisms other than carbapenemases. Please do NOT send isolates of these genera to OSPHL unless there is also resistance to other carbapenems.

[1]The most common CRE genera are highlighted

UPDATE LOG

September 2022: Changed "*Enterobacteriaceae*" to "Enterobacterales", see added section 2.2; corrected Kirby Bauer breakpoints; clarified 4.2 case follow-up requirements; updated genera list. (Heather Hertzel, Maureen Cassidy)

December 2019: Clarified ertapenem information in case definition (Maureen Cassidy)

June 2016: Updated data collection in "Case Follow Up" and updated recommendations tables (Maureen Cassidy)

November 2015: Placed into new template and corrected spelling and link errors. (Leslie Byster)

June 2015: Case definition change (Maureen Cassidy)

June 2014: Updated CRE Tier Assignment §3.2 and minor updates to case follow-up (Maureen Cassidy) April 2014: Updated §4.2 Case follow-up. (Maureen Cassidy, G. Buser)

February 2014: Updated case definition. (Maureen Cassidy)

July 2013: Updated case definition; added link for Oregon CRE Tool kit (M Maureen Cassidy) January 2013. Updated new MIC breakpoint for ertapenem. (Tasha Poissant)

November 2012. Fixed broken hyperlinks; added doripenem resistance to case definition. (Tasha Poissant)

April 2012: Clarified reporting procedure for repeat culture results and added list of genera (Margaret Cunningham)

January 2012: Newly created guidelines to be in line with new reporting requirements. (Margaret Cunningham)