Carbapenem-Resistant *Acinetobacter* (CRA)

Investigative Guidelines

October 2023

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To prevent transmission of carbapenem-resistant *Acinetobacter* spp. (CRA) between patients, within or among health care facilities, or between health care facilities and the community.
2. To prevent CRA from becoming endemic in Oregon, requiring empiric use of even broader-spectrum antibiotics.
3. To identify outbreaks and potential sources or sites of ongoing transmission.
4. To better describe 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 to the Oregon State Public Health Laboratory (OSPHL) isolates from any sterile or non-sterile site (e.g., urine, blood, sputum, endotracheal aspirate, bronchoalveolar lavage, wound) that meet the confirmed CRA case definition below, along with the automated antimicrobial susceptibility testing (AST) system printouts (e.g., Vitek 2 or Microscan report).

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 as necessary with the Acute and Communicable Disease Prevention Section (ACDP) on-call epidemiologist. Minimum inhibitory concentration (MIC) values are needed to verify that 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 CRA case report.
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

Acinetobacter species are Gram-negative bacilli commonly found in soil and water. Certain species are part of the normal bacterial flora of the skin. Most species of *Acinetobacter* do not typically cause infections. The exception is *Acinetobacter baumannii,* an opportunistic pathogen, infection by which is mostly associated with healthcare. *A. baumannii* survive for prolonged periods of time on surfaces and medical equipment. Most *Acinetobacter* infections (90–95%) are *A. baumannii*.

A. baumannii that cause clinical infections show high rates of resistance to commonly used antibiotics. Carbapenem antibiotics (e.g., doripenem, ertapenem, imipenem and meropenem), sometimes described as "antibiotics of last resort," are used to treat healthcare-associated infections caused by multi-drug resistant *Acinetobacter* species and other Gram-negative bacilli (e.g., *Enterobacterales* order bacteria, *Pseudomonas aeruginosa*). Unfortunately, when carbapenem antibiotic resistance develops, few safe and effective treatment options remain, and the risk of patient morbidity and mortality increases. Carbapenem-resistant *Acinetobacter baumannii* are commonly referred to as CRAB in the scientific literature.

Non-*baumannii Acinetobacter* species are less likely to cause infections and less likely to display carbapenem resistance. However, when these organisms do acquire carbapenem resistance, they also represent a transmission risk and a risk to patient health. For this reason, Oregon requires reporting of all carbapenem-resistant *Acinetobacter* (CRA) species and submission of isolates to OSPHL.[1]

Carbapenemase-producing CRA

Resistance to carbapenems and other antibiotics in *Acinetobacter* spp. can be caused by many cellular mechanisms including production of extended-spectrum β-lactamases (ESBLs), efflux pumps, decreased cell permeability, and production of carbapenemases.[2,3] Carbapenemases are enzymes that degrade carbapenem antibiotics. Resistance genes that code for carbapenemases can be exchanged among different Gram-negative bacteria via genetic packets called transposons or plasmids. Carbapenemases can be found in many Gram-negative bacteria and include:

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Imipenem-hydrolyzing-lactamase (IMP)
- Verona integron-encoded metallo-beta-lactamase (VIM)
- Oxacillinase-48 (OXA-48)

Acinetobacter species carry other oxacillinase variants that are unique to this genus. Examples include OXA-23, OXA-24/40, OXA-58, and OXA-235.

Acinetobacter that have carbapenemase genes are sometimes referred to as carbapenemase-producing CRA (CP-CRA) or simply carbapenemase-producing organisms (CPOs). From a public health perspective, CP-CRA are the most concerning CRA because their resistance can be easily spread, and they are associated with higher morbidity and mortality. Unfortunately, most CRA are CP-CRA; CDC found that carbapenemase genes were detected in 83% of CRA isolates.

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

2.2 Description of Illness

CRA typically causes healthcare-associated infections, especially in intensive-care units (ICUs). Patients at highest risk of infection are those requiring prolonged or intensive care, especially patients on mechanical ventilation, with open wounds from surgery, or with indwelling medical devices such as catheters. The two most common kinds of infection caused by CRA are pneumonia and bloodstream infections. Pneumonia occurs most often in the presence of mechanical ventilation. Bloodstream infections are typically catheter-related infections or complications of respiratory tract infections. CRA can also cause wound or surgical-site infections, urinary-tract infections (typically associated with urinary catheters), endocarditis and meningitis.[4,5]

2.3 Reservoirs

Acinetobacter species are commonly found in the environment in soil and water. Many species, including *A. lwoffii, A. johnsonii, A. radioresistens, A. pittii,* and *A. junii*, can harmlessly colonize the skin of healthy individuals as part of normal human flora. The most clinically important species, *A. baumannii*, is most frequently found in patients and the hospital environment. It has been less commonly detected in various non-hospital environments including soil, water, and high-touch surfaces like tables.[6] *A. baumannii* can survive for long periods in healthcare environments on surfaces, medical equipment, and water sources such as sinks. Patients infected or colonized with *A. baumannii* in healthcare settings can act as reservoirs, shedding bacteria into their environment. Various body sites including skin, respiratory, and gastrointestinal tracts may be colonized by CRA.[7, 8]

2.4 Sources and Routes Transmission

CRA are transmitted from person to person, often via:

- contaminated hands of healthcare workers,
- contact with contaminated surfaces, and
- shared medical equipment that has not been properly cleaned.

2.5 Incubation Period

Because CRA and other carbapenem-resistant organisms (CROs) can colonize people without causing infection, the incubation period is unknown.

2.6 Period of Communicability

Persons can potentially transmit CRA to others if the organism is present in bodily fluids or on the body. Patients may be intermittently positive on serial surveillance cultures and colonized for long periods of time.

2.7 Treatment

Differentiating between colonization and infection can be difficult. Treatment with antibiotics is not typically recommended for persons merely colonized. Antibiotic options may be limited and may cause adverse reactions. Infectious disease consultation is recommended for treatment decisions.[5]

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

Use minimum inhibitory concentration (MIC) values to interpret resistance (the automated antimicrobial susceptibility testing result from the laboratory is preferred; see Table 1). In some cases, Kirby-Bauer disc-diffusion results may be provided; see Table 2. A confirmed case of CRA is a patient whose clinical or surveillance specimen:

1. yields an isolate of *Acinetobacter* species on culture that is resistant to any carbapenem other than ertapenem (doripenem, imipenem, or meropenem) using the current CLSI breakpoints:

Table 1. Carbapenem MIC Breakpoints for *Acinetobacter* spp.

	Current MIC Breakpoints (µg/mL)[1]		
	MIC Interpretation[2]		
Carbapenems	**Susceptible**	**Intermediate**	**Resistant**
Doripenem	≤2	4	≥8
Ertapenem*	-	-	-
Imipenem	≤2	4	≥8
Meropenem	≤2	4	≥8

[1]MIC = minimum inhibitory concentration
[2]CLSI. Table 2B-2. Zone Diameter and MIC Breakpoints for *Acinetobacter* spp. In: CLSI M100-ED33:2023 Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition. Mar 2023. Available from: http://em100.edaptivedocs.net/dashboard.aspx
*Ertapenem has weak activity against *Acinetobacter* spp. and should not be used to determine carbapenem resistance.

Table 2. Kirby-Bauer Disc-Diffusion Interpretations for *Acinetobacter* spp.

	Current Disk Diffusion Zone Diameters (mm)[1]		
	Zone Size Interpretation[2]		
Carbapenems	**Susceptible**	**Intermediate**	**Resistant**
Doripenem	≥18	15–17	≤14
Ertapenem*	-	-	-
Imipenem	≥22	19–21	≤18
Meropenem	≥18	15–17	≤14

[1]mm = millimeters
[2]CLSI. Table 2B-2. Zone Diameter and MIC Breakpoints for *Acinetobacter* spp. In: CLSI M100-ED33:2023 Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition. Mar 2023. Available from: http://em100.edaptivedocs.net/dashboard.aspx
*Ertapenem has weak activity against *Acinetobacter* spp. and should not be used to determine carbapenem resistance

OR

2. tests positive by a molecular test, such as PCR or next-generation sequencing (NGS), for a carbapenemase (e.g., KPC, NDM, IMP, VIM, OXA-48, OXA-23, OXA-24/40, OXA-58, or OXA-235).

Some labs will suppress carbapenem results on reports. If you receive a report that calls the *Acinetobacter* species isolated a CRA or CRAB, but the available carbapenem results are "susceptible," call the lab to ask for any suppressed carbapenem results. These results will be on the automated antimicrobial susceptibility testing report.

Note: *Acinetobacter radioresistens* isolates are excluded from this definition if they are carbapenem-susceptible and the only carbapenemase gene detected is OXA-23. This is because this species carries a chromosomal OXA-23 gene that may not be expressed.

3.2 Resistance Mechanism

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

Table 3. Type of CRA

Description	Organisms Included	Recommended Measures
Carbapenemase-producing CRA (**CP-CRA**)	*Acinetobacter* positive by PCR or NGS for KPC, NDM, IMP, VIM, OXA-48, OXA-23, OXA-24/40, OXA-58, OXA-235, or other carbapenemase	Most aggressive control measures: see Oregon CRE Toolkit http://bit.ly/CRE-Toolkit

CRA with acquired resistance NOT due to carbapenemase production	*Acinetobacter* that meet definition, but are PCR or NGS negative for carbapenemases	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)

Laboratories are required to submit all CRA identified from Oregon residents to OSPHL. These isolates will be tested for carbapenemase production at OSPHL. All species will be tested by whole-genome sequencing (WGS). In 2023, OSPHL plans to validate PCR testing for *Acinetobacter baumannii* for the following carbapenemases: KPC, NDM, IMP, VIM, OXA-48, OXA-23, OXA-24/40, OXA-58, and OXA-235. Following validation, PCR testing will be performed for *A. baumannii*; all other CRA isolates will continue to be tested by WGS.

4. CASE INVESTIGATION

4.1 Confirm case definition

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

4.2 Case Follow-up

For all CRA, refer to the Oregon CRE Toolkit (pdf): http://bit.ly/CRE-Toolkit

1. If case meets criteria, open an Orpheus CRA case record and begin investigation within one working day.
2. LPHA will work with the healthcare 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-CRA, the ACDP HAI Epidemiologists will work with the LPHA and the facility or physician. See http://bit.ly/CRE-Toolkit
    a. If multiple healthcare facilities are involved, LPHA will work with all facilities to institute appropriate control measures. If a case is to be transferred to a new facility, the transferring facility is required to notify the receiving facility (OAR 333-019-0052), and the LPHA will work with the receiving facility to ensure they are prepared to implement appropriate infection-control measures.
3. In the CRA case record, provide:
    - Name, address, date of birth, sex
    - Race, ethnicity, language, and disability (REALD)
    - Hospitalization status at the time of culture, admission and discharge dates, and name of hospital
    - Any admissions to acute or long-term care facilities in the 30 days before specimen collection through the time of investigation (365 days for CPO)

- Any healthcare transfers and confirmation of interfacility transfer notice
- Date of initial culture collection
- Organism genus and species (as “subtype” in Orpheus)
- Patient location on 4th calendar date prior to initial culture date; (under “MDRO” tab in Orpheus)
- If case was hospitalized or in a skilled nursing facility, whether they were on contact or enhanced barrier precautions (EBPs)?
- Was patient education provided emphasizing hand hygiene?
- Any medical care outside of Oregon during the last 12 months
- Any medical care outside of the United States during the last 12 months
- Any travel history in the 12 months 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 healthcare facilities should use contact precautions for patients with CRA infection or colonization to reduce transmission among high-risk populations.
    - Long-term care facilities should use contact precautions for patients with CRA infections, patients with CP-CRA infections or colonization, and CRA-colonized patients at higher risk of transmission (e.g., with draining wounds, or incontinent of urine or stool). See the CRE Toolkit for additional details. CDC recommends EBPs 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 EBPs is available through CDC: https://www.cdc.gov/hai/pdfs/containment/PPE-Nursing-Homes-H.pdf.
    - In all settings, appropriate transmission-based precautions should be maintained for one year for CRA cases and indefinitely for CP-CRA cases
- Enhanced environmental cleaning, including high touch surfaces;
- Interfacility communication of patient’s CRA status at transfer or time of discharge.
    - Interfacility transfer notification is required by OAR 333-019-0052

- CP-CRAs also require communication to the LPHA when there is a new transfer or admission of a case.

Keep in mind the “NICE” mnemonic: Notify, Intervene, Communicate, and Educate when CRA are encountered.

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

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

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

Educate patients, staff and visitors about CRA.

Table 4. Recommendations for hospital setting

HOSPITALS	Response and Control Measures by Local Public Health Authorities
CP-CRA	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-CRA 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 according to OAR 333-019-0052. • 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, pages 10–15.
Non-CP-CRA	• 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-CRA 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 according to OAR 333-019-0052 • Educate about importance of aggressive control measures (transmission-based precautions). See CRE Toolkit, pages 10–15.

Table 5. Recommendations for skilled nursing facilities

SKILLED NURSING FACILITIES	**Response and Control Measures by Local Public Health Authorities**
CP-CRA	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-CRA 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 according to OAR 333-019-0052 • 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, pages 16–23.
Non-CP-CRA	• Confirm case meets case definition • Obtain case information for Orpheus case report • Advise staff responsible for infection control • Discuss relevant non-CP-CRA 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 colonized residents at higher risk in contact precautions; for low-risk colonized residents, standard precautions can be used. See CRE Toolkit, pages 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-CRA	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-CRA infection control measures and possible surveillance • If patient is admitted, clinic notifies receiving facility of CRA 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, pages 24–27.
Non-CP-CRA	• 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-CRA infection measures for future visits. See CRE Toolkit, pages 24–27.

Table 7. Recommendations for cases living at home

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

4.3 Repeat Culture Results

Any repeat-positive culture results for the same carbapenem-resistant organisms collected within 30 days of the initial positive collection date should be entered as new labs in the existing Orpheus case record. After 30 days, review the various susceptibility results. 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 whether the case should be entered in Orpheus as a new case. A positive culture for a different CRO (different species) should be entered as a new incident case, regardless of the collection date.

REFERENCES

1. CDC. Antibiotic Resistance Threats in the United States. 2019. Available from: https://www.cdc.gov/drugresistance/Biggest-Threats.html
2. Bonomo RA, Szabo D. Mechanisms of multidrug Resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. Clin Infect Dis. 2006; 43(Suppl 2):S49–S56. Available from: https://academic.oup.com/cid/article/43/Supplement_2/S49/332756
3. Bello-Lopez E, Rocha-Gracia RC, Castro-Jaimes S, Cevallos MA, Vargas-Cruz M, Verdugo-Yocupicio R, et. al. Antibiotic resistance mechanisms in *Acinetobacter* spp. strains isolated from

patients in a paediatric hospital in Mexico. J Glob Antimicrob Resist 2020; 23:120–9. Available from: https://www.sciencedirect.com/science/article/pii/S2213716520302204

4. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and Pathophysiological overview of *Acinetobacter* infections: a century of challenges. Clin Microbiol Rev 2016; 30(1):409–47. Available from: https://journals.asm.org/doi/10.1128/CMR.00058-16
5. Bartal C, Rolston KV, Nesher L. Carbapenem-resistant *Acinetobacter baumannii*: colonization, infection and current treatment options. Infect Dis Ther 2022; 11(2):683–94. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8960525/
6. Eveillard M, Kempf M, Belmonte O, Pailhories H, Joly-Guillou ML. Reservoirs of *Acinetobacter baumannii* outside the hospital and potential involvement in emerging human community-acquired infections. Int J Infect Dis 2013; 17(10):E802–5. Available from: https://www.ijidonline.com/article/S1201-9712(13)00156-2/fulltext
7. Atrouni AA, Joly-Guillou ML, Hamze M, Kempf M. Reservoirs of non-*baumannii Acinetobacter* species. Front Microbiol 2016; 7:49. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2016.00049/full
8. Shamsizadeh Z, Nikaeen M, Esfahani BN, Mirhoseini SH, Hatamzadeh M, Hassanzadeh A. Detection of antibiotic resistant *Acinetobacter baumannii* in various hospital environments: potential sources for transmission of *Acinetobacter* infections. Environ Health Prev Med 2017; 22:44. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664838/

UPDATE LOG

October 2023: Newly created guidelines in line with new reporting requirements. CRE Investigative Guidelines used as a template. (Heather Hertzel, Evelyn Donahoe)