



Carbapenem-resistant Enterobacteriaceae (CRE)

Enterobacteriaceae are a large family of Gram-negative, rod-shaped bacteria often found in the gastrointestinal tract^{1,2}. Common genera include *Escherichia*, *Klebsiella* and *Enterobacter*¹. Some species have developed resistance to multiple classes of antibiotics, including carbapenems². In addition to being multidrug resistant, CRE are associated with high mortality rates (up to 50%) and can transmit resistance between species, making them a concern for transmission in healthcare settings².

A. Agent

Any species in the Enterobacteriaceae family. The most commonly encountered carbapenem-resistant Enterobacteriaceae are in the following genera:

- Citrobacter* spp.
- Enterobacter* spp.
- Escherichia coli*
- Klebsiella* spp.
- Proteus* spp.
- Providencia* spp.
- Morganella* spp.
- Raoultella* spp.
- Serratia* spp.

B. Clinical Description²

Most CRE infections are urinary tract infections, often caused by catheter use or urinary retention. CRE can cause many other kinds of infections including bloodstream infections, ventilator-associated pneumonia, and intra-abdominal abscesses.

C. Reservoirs

Humans are a reservoir of Carbapenem-resistant Enterobacteriaceae.

D. Mode of Transmission²

In healthcare settings, CRE are usually transmitted from person to person often via the hands of healthcare personnel or via contaminated medical equipment. As Enterobacteriaceae can commonly be found in stool or wounds, contact with these might be particularly concerning.

E. Incubation period

The incubation period is variable and indefinite.

F. Period of Communicability²

When found in clinical culture, CRE can represent an infection or colonization. Colonization means that the organism can be found on the body but it is not causing any symptoms or

disease. CRE can potentially be transmitted as long as the organisms are present in or on a person's body.

G. Susceptibility and Resistance²

In general, CRE test resistant to at least one of the carbapenem antibiotics (ertapenem, doripenem, imipenem, and meropenem) and/or produce an enzyme (carbapenemase) that can make them resistant to these antibiotics. These bacteria often have other resistance mechanisms that render them non-susceptible to many other classes of commonly used antibiotics and some *Enterobacteriaceae* have become resistant to all or almost all antibiotics.

H. Treatment

Though typically resistant to many commonly prescribed antibiotics, CRE may remain susceptible to some antibiotics. Decisions regarding treatment of CRE infections are made on a case-by-case basis by a health care provider. Some people may be colonized rather than infected with CRE and may not require any treatment.

Disease Management

I. Clinical Case Definition

Classification of CRE is based entirely on laboratory criteria; no clinical criteria are provided.

J. Lab Criteria for Diagnosis³

Species in the Enterobacteriaceae family isolated from any clinical specimen and:

- A. Resistant to any carbapenem (minimum inhibitory concentrations (MIC) of ≥ 4 mcg/ml for meropenem, imipenem*, and doripenem or ≥ 2 mcg/ml for ertapenem),

* Note: Do not use imipenem for *Proteus* spp., *Providencia* spp. Or *Morganella* spp., as these bacteria may be intrinsically non-susceptible to imipenem.

OR

- B. Demonstrating laboratory evidence of carbapenemase production (for laboratories performing any of this testing):
 - a. Positive for known carbapenemase resistance mechanism (e.g., *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo- β -lactamase (NDM), Verona integron-encoded metallo- β -lactamase (VIM), imipenemase (IMP), oxacillinase-48-like carbapenemase (OXA48)) demonstrated by a recognized test (e.g., polymerase chain reaction (PCR), Xpert CarbaR), OR
 - b. 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 (mCIM)).

Case Classification³

Confirmed	<p>A case that meets:</p> <ul style="list-style-type: none"> ● Laboratory criterion A, as confirmed by a public health laboratory; OR ● Laboratory criterion B (public health laboratory confirmation is not required).
Probable	<p>A case that:</p> <ul style="list-style-type: none"> ● Meets laboratory criterion A, but not confirmed by a public health laboratory*, AND ● Does not meet Laboratory criterion B.

**The probable definition will generally apply only when testing at a public health laboratory cannot be performed. If a public health laboratory identifies that the specimen/isolate is not an Enterobacteriaceae or is not carbapenem-resistant, the case should be classified as "Not a case", even if the original testing met criterion A.*

K. Classification of Import Status

Not applicable

L. Laboratory Testing

- Antibiotic Susceptibility Testing (AST)
 - Minimum Inhibitory Concentration (MIC)
- Carbapenemase Production Testing:
 - (modified) Carbapenem Inactivation Method (CIM/mCIM)
 - metallo-β-lactamase test
 - modified Hodge test
 - Carba NP
 - PCR determines which carbapenemase production mechanisms the organism has (e.g. KPC, IMP, NDM, VIM, OXA-48)

TEST	SPECIMEN TYPE	AVAILABILITY
Culture	Specimen from any site	Commercial lab
Antibiotic Susceptibility Testing (AST)	Isolate	Commercial lab
Modified Carbapenem Inactivation Method (mCIM)	Isolate	ASPHL
PCR	Isolate	ASPHL

M. Assessing Lab Results

Algorithm to classify CRE cases

<https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associated-infection/cre/cre-classification.pdf>

Algorithm for Reporting and Submitting Isolates of Carbapenem-Resistant Enterobacteriaceae (CRE) to ADHS

<https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/providers/cre-algorithm.pdf>

N. Outbreak Definition

An increase in cases of CRE in time or place that is greater than expected.

Investigation Guidelines

O. Time Frame⁴

- Laboratories must submit a report of Carbapenem-resistant *Enterobacteriaceae*, within five working days.
- Laboratories must submit an isolate of the organism for each positive culture to the Arizona State Laboratory within one working day.

P. Forms

Epidemiological investigation report should be submitted in MEDSIS by filling out the full DSO (including the travel table) and the healthcare facility tracking table.

Q. Investigation Steps

- **Confirm Diagnosis**
 - Positive CRE results from a commercial lab indicate a probable case and positive CRE results from ASPHL indicate a confirmed case.

For all probable or confirmed CRE cases (as soon as a positive CRE result is reported, either from a commercial lab or ASPHL):

- **Conduct Case Investigation**
 - Obtain information from the infection preventionist, provider or medical chart.
 - Obtain medical records, including admission notes, progress notes, and discharge summary.
 - The following information should be recorded in the DSO:
 - Is the organism Carbapenemase Producing (determined by ASPHL confirmatory testing)
 - Organism genus and species
 - Reason for testing
 - Was the isolate collected due to infection or screening? Most cases will be collected due to infection.
 - Colonization screening/point prevalence screening (PPS) is a method to detect asymptomatic carriers and is only performed through the regional Antibiotic Resistance Laboratory Network and coordinated by ADHS.

Colonization screening/PPS is typically performed when an MDRO case or cluster is detected in a healthcare facility but can also be performed preventatively in order to identify colonized individuals upon admission (aka admissions screening).

- Patient diagnosed with any multidrug resistant organisms (MDRO) in the past?
- All healthcare admissions since the collection date and in the 12 months prior to collection date should be recorded in the Healthcare Facility Tracking Table in MEDSIS.
- **Initiate Control and Prevention Measures^{5,6,7}**
 - Provide recommendations and education to infection preventionist or provider if case is inpatient:
 - Inform of patients positive CRE results
 - Patients with CRE in acute care settings should be placed on contact precautions.
 - Residents with CRE in long-term care settings should be placed on contact precautions when ongoing CRE transmission is suspected in the facility or when there is presence of acute diarrhea, draining wounds or other sites of secretions or excretions that are unable to be covered or contained. Enhanced barrier precautions can be considered for other residents with CRE when ongoing CRE transmission is not suspected in the facility. See CDC's [Implementation of Personal Protective Equipment in Nursing Homes to Prevent Spread of Novel or Targeted Multidrug-resistant Organisms](#).
 - Provide infection control recommendations to facilities involved including transmission based precautions, HCP education, hand hygiene and environmental cleaning.
 - Whenever possible, dedicate rooms, equipment, and staff to CRE patients.
 - See CDC's Facility Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE) for additional infection control recommendations <https://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf>
 - Ensure that the patient's CRE status and required infection control precautions are communicated during inter-facility transfer (Per A.A.C. R9-6-315). <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/providers/multidrug-resistant-organisms-list.pdf>
 - **Before completing the investigation, wait for confirmatory testing from ASPHL**
 - CRE specimens are forwarded to ASPHL for additional testing, including antimicrobial resistance mechanism testing. If a resistance mechanism of concern is identified, additional investigation may be needed.

- Check myLIMS to ensure an isolate was submitted to ASPHL. If it wasn't, classify the case according to the commercial lab results (probable or NAC) and complete the investigation.

Additionally, for Carbapenemase-Producing CRE:

- **Collect Travel History**
Please add any travel in the 12 months prior to sample collection date to the Travel Table located at the bottom of the case management section.
- **Conduct Contact Investigation⁶**
Colonization screening and an infection control assessment may be indicated depending on the circumstances of the healthcare admission and the resistance mechanism of the organism. See CDC's Interim Guidance for a Public Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs) <https://www.cdc.gov/hai/pdfs/containment/Health-Response-Contain-MDRO-H.pdf> and contact HAI@azdhs.gov for assistance conducting colonization screening of contacts or infection control assessments.
- **Recommend prospective and retrospective surveillance to identify additional cases**
 - Remind facilities involved to submit CRE isolates to ASPHL
 - Retrospective Surveillance: Review clinical lab data for 6 months before identification of index case to find any additional cases
 - Prospective Surveillance: Prospective surveillance should occur for at least three months after identification of the index patient or, if transmission is identified through surveillance or screening, three months after the last case is identified. All isolates identified during prospective surveillance should be promptly tested to investigate whether they have the same mechanism of resistance as the index case.
- **Isolation, Work and Child Care Restrictions**
In most cases, restrictions are not necessary for CRE infections outside of the healthcare setting. See CDCs CRE Patient FAQ page for additional information on managing CRE at home. <https://www.cdc.gov/hai/organisms/cre/cre-patientfaq.html>
- **Outbreak Guidelines**
 - Contact hai@azdhs.gov for assistance with the following outbreak response activities:
 - In the case of a CP CRE outbreak/transmission event, colonization screening should be repeated until 2 consecutive rounds of screening are negative.
 - WGS analysis is available to assess relatedness of cases in a potential outbreak.

- Refer to the general outbreak guidelines section for details on investigating an outbreak or healthcare acquired infection and utilize the ADHS outbreak definition.
- If case(s) meets outbreak definition, report suspected outbreak to ADHS via outbreak module protocol (see general outbreak guidelines section for details).

References

1. American Academy of Pediatrics. 2021 Red Book: Report of the Committee on Infectious Disease, 32nd Edition. Illinois, Academy of Pediatrics, 2021.
2. Carbapenem-resistant Enterobacteriaceae (CRE) [Internet]. Centers for Disease Control and Prevention; 2015 [cited 2019July31]. Available from: <https://www.cdc.gov/hai/organisms/cre/cre-clinicianfaq.html>
3. Arizona Department of Health Services. In: Case Definitions for Reportable Communicable Morbidities: 2022. 2022 [cited 2022Feb24]; Available from: <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/casedefinitions/case-definitions.pdf>
4. Arizona Administrative Code [Internet]. 2013Sep30 [cited 2019Aug1]; Available from: http://apps.azsos.gov/public_services/Title_09/9-06.pdf
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6. Interim Guidance for a Public Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs) [Internet]. Centers for Disease Control and Prevention; 2019 [cited 2019Aug1]. Available from: <https://www.cdc.gov/hai/pdfs/containment/Health-Response-Contain-MDRO-H.pdf>
7. Implementation of Personal Protective Equipment (PPE) in Nursing Homes to Prevent Spread of Novel or Targeted Multidrug-resistant Organisms (MDROs) [Internet]. Centers for Disease Control and Prevention; 2019 [cited 2019Sep4]. Available from: <https://www.cdc.gov/hai/containment/PPE-Nursing-Homes.html>

Additional information and resources

Centers for Disease Control and Prevention

- Carbapenem-resistant Enterobacteriaceae in Healthcare Settings <https://www.cdc.gov/hai/organisms/cre/index.html>
- Facility Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE) <https://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf>

- Interim Guidance for a Public Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs) <https://www.cdc.gov/hai/pdfs/containment/Health-Response-Contain-MDRO-H.pdf>
- Implementation of Personal Protective Equipment (PPE) in Nursing Homes to Prevent Spread of Novel or Targeted Multidrug-resistant Organisms (MDROs) <https://www.cdc.gov/hai/containment/PPE-Nursing-Homes.html>

Arizona Department of Health Services

- ADHS CRE webpage <https://www.azdhs.gov/preparedness/epidemiology-disease-control/healthcare-associated-infection/index.php#hai-cre>
- Reporting Algorithm <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/providers/cre-algorithm.pdf>
- Case Classification Algorithm <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associated-infection/cre/cre-classification.pdf>
- Required Notification of Interfacility Transfers <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/communicable-disease-reporting/providers/multidrug-resistant-organisms-list.pdf>
- CDC's Inter-Facility Infection Control Transfer Form <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associated-infection/advisory-committee/long-term-care/inter-facility-infection-control-transfer-form.pdf>
- ADHS Interfacility Infection Prevention Transfer Tool <https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associated-infection/advisory-committee/long-term-care/isolation-precaution-form.pdf>