

NEBRASKA

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DEPT. OF HEALTH AND HUMAN SERVICES



Pete Ricketts, Governor

**Carbapenem Resistant Enterobacteriaceae
RESPONSE GUIDELINE
2017**

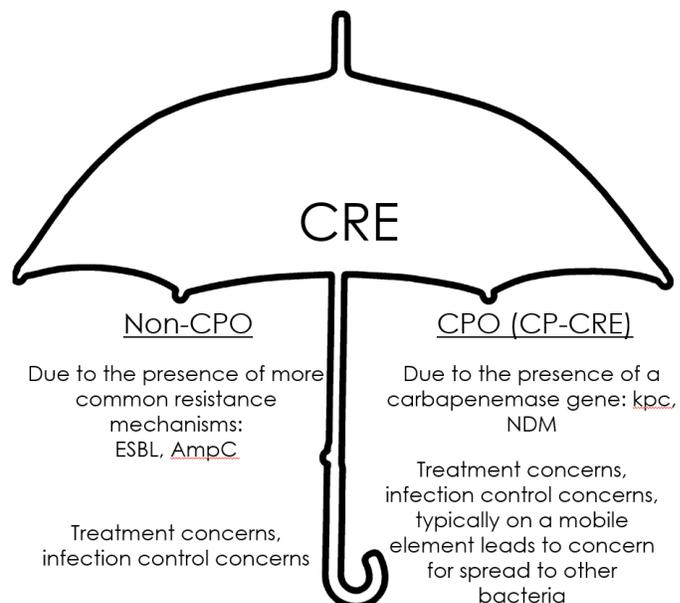
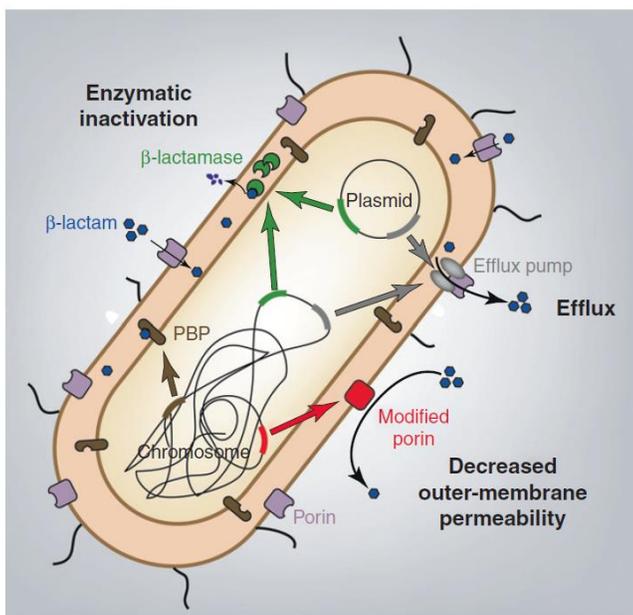
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Helping People Live Better Lives

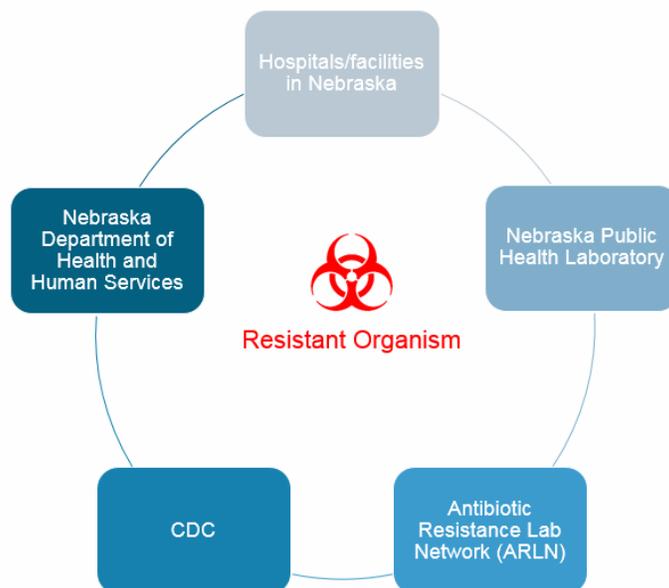
Background

Bacteria that develop resistance to the carbapenem class of antibiotics represent a concerning group of emerging pathogens. The Centers for Disease Control and Prevention (CDC) notes that Carbapenem Resistant Enterobacteriaceae (CRE) are an important cause of invasive infections and are often associated with high mortality rates (up to 50%)¹. CRE have been found in most of the United States and are primarily associated with exposure to the healthcare system, however they have the potential to spread in the community¹.

Carbapenem antibiotics (doripenem, ertapenem, imipenem, meropenem) function by entering a cell wall through an outer membrane protein (porin) and then acylate penicillin binding proteins (PBPs) to inhibit peptide cross-linking. Resistance to this class of antimicrobials can develop in a variety of ways and may be due amino acid substitutions in the penicillin binding proteins (PBP) or the expression of alternative PBPs. However, a more concerning mechanism of resistance involves the presence of a carbapenemase gene. Organisms that produce a carbapenemase are particularly concerning due to their ability to spread this resistance mechanism via a plasmid to other bacteria. This kind of transmission has important implications for public health surveillance and containment activities. Therefore, while all CREs represent treatment and infection control concerns, not all of these organisms will produce a transferrable carbapenemase gene. Currently, public health efforts in Nebraska are directed at performing surveillance for all CREs with a special focus on investigation and containment for carbapenemase-producing organisms in order to minimize spread of this kind of resistance.



The Nebraska Department of Health and Human Services (NDHHS) Healthcare Associated Infections (HAI) program in conjunction with the Nebraska Public Health Laboratory (NPHL) monitor for the presence of CREs in Nebraska. The following protocol outlines the procedure that NDHHS and NPHL have implemented in conjunction with Nebraska hospitals/facilities, local health departments, and federal partners (CDC and the Antibiotic Resistance Lab Network, ARLN) in order to perform surveillance, investigation and containment activities for organisms with concerning resistance patterns.



Contact information

Office of Epidemiology

Name	Designation	Contact number	Email
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Maureen Tierney, MD, MSc.	Healthcare Associated Infections Director	Office: 402-471-6549 Cell: 402-309-3471	maureen.tierney@nebraska.gov

Laboratory

Name	Designation	Contact number	Email
Peter C. Iwen, PhD, D(ABMM)	Director, NE Public Health Laboratory	Office: 402-559-7774	piwen@unmc.edu
Caitlin Murphy, PhD	Assistant Director, Clinical Microbiology Lab at Nebraska Medicine	Office: 402-552-3305	caitlin.murphy@unmc.edu

Surveillance

CRE Definition:

Enterobacteriaceae that are resistant to any carbapenem antimicrobial (i.e., minimum inhibitory concentrations of ≥ 4 mcg/ml for doripenem, imipenem, meropenem or OR ≥ 2 mcg/ml for ertapenem; disc diffusion ≤ 19 mm for doripenem, imipenem, meropenem or OR ≤ 18 mm for ertapenem) OR have been documented to produce carbapenemase.

In addition to routine culture performed as needed for patient care, healthcare facilities can consider performing a screening culture (rectal swab) on patients who are admitted with recent (within 12 weeks) exposure to a healthcare facility in another country.

Reporting of CRE

In accordance with Nebraska Title 173, the following must be reported immediately (within 24 hours by email, fax or phone and by ELR if available): If a lab has the capacity to test for the presence of carbapenemases notification by ELR alone within 24 hours is sufficient)

Carbapenem resistant Enterobacteriaceae (suspected or confirmed)

The NDHHS HAI program conducts daily surveillance for CRE via a database of electronically reported laboratory results that includes patient demographics, specimen source, ordering and reporting organizations, the organism identified and its associated antimicrobial susceptibility pattern. These reports are accessed through the National Electronic Disease Surveillance System (NEDSS) system. They are monitored daily for results that are concerning for a carbapenemase-producing organism.

Submission of Isolates

Results that meet the following criteria are identified as concerning for a carbapenemase-producing organism and are therefore forwarded to the NPHL for follow-up:

Submission of all isolates of Enterobacteriaceae that are non-susceptible (intermediate or resistant) to any of the carbapenems

Exceptions are *Enterobacter cloacae* and *E. aerogenes*: only submit isolates that are non-susceptible to carbapenems other than ertapenem

Submission of all non-mucoid isolates of *Pseudomonas aeruginosa* that are non-susceptible to carbapenems other than ertapenem from non-cystic fibrosis patients; up to 3 per month per facility

Submission of all isolates of in-house or reference laboratory confirmed carbapenemase-producing Enterobacteriaceae

Results

The NPHL performs follow-up testing on qualifying isolates. This includes repeat antimicrobial susceptibility testing (AST) as well as phenotypic and molecular methods as needed for identification of carbapenemase production and associated relevant mutations. The molecular result is shared with the ordering facility and molecular and phenotypic results are shared with the NDHHS HAI program for follow-up.

Investigation

The detection of any single carbapenemase-producing organism in Nebraska will be considered an outbreak that requires investigation. In facilities not able to perform testing for carbapenemases, any CRE detected will be considered a potential carbapenemase producer that may require further investigation and the patient should be put on contact isolation while awaiting results.

As noted above, a potential carbapenemase-producing organism can be identified either through electronic laboratory reporting and subsequent submission to NPHL or by direct submission from the facility to the NPHL. In either case, the NDHHS HAI program and NPHL notify each other via secure messaging (shared Box account) in order to coordinate appropriate isolate submission, document relevant epidemiologic data using the Nebraska Case Investigation Form and provide support to facilities while awaiting confirmatory test results from NPHL.

Epidemiologic information is collected for all submitted CRE isolates as follows:

- Patient demographics (name, date of birth, location)
- Local health department jurisdiction
- Ordering and reporting facility
- Inpatient/facility status

Additional information is collected for carbapenemase-producing organisms as follows:

- Antibiotic treatment course and duration as well as repeat testing
- Procedures with reusable devices
- History of prior contact with healthcare facilities

- Travel history
- Occupation

Containment

Efforts should be made to contain any organism that demonstrate resistance to the carbapenem class of antibiotics, regardless of the mechanism by which they are resistant. Facilities should take precautions to prevent the spread of a particular CRE from one patient to another. Additional steps might be needed for CREs that produce a carbapenemase due to the potential for spread of such a plasmid from one organism to others.

Infection Control Recommendations for facilities/providers:

- Confirm appropriate hand hygiene practices are being followed
- Confirm use of contact precautions (gowns and gloves available and used correctly)
- Private room if at all possible, cohorting if not possible
- Minimize device utilization where possible (indwelling lines, endotracheal tubes, urinary catheters, etc)
- Facility should examine need for special precautions if patient has a procedure with a reusable device
- Ensure appropriate antimicrobials are being used (stewardship)
- Cohort affected patients with minimal shared staff when possible
- Establish clear communication methods if inter-facility transfer is needed (Nebraska Interfacility Transfer Form can be used if there is not a current method in place)
- Ensure appropriate environmental cleaning is performed²
- Perform screening/surveillance cultures if needed
- Identify a primary care provider to coordinate follow-up with test of cure culture 10 to 14 days after completion of antibiotics

Screening for Colonization

Screening cultures will be considered as part of a containment strategy in the event that a carbapenemase-producing organism is identified from a patient that is currently admitted to a hospital, long-term care facility or similar institution. Screening via rectal swabs of relevant asymptomatic epidemiologic contacts of an identified case can provide important information on transmission and also allow for targeted containment efforts. The determination of who to screen will be made by the NDHHS HAI program and NPHL

and based on assessing the most likely persons at risk (individuals who share rooms, bathrooms, provide assistance with toileting, changing undergarments etc).

Point prevalence surveys might be considered in this scenario and could be repeated depending on the number of identified cases and extent of spread. Additionally, active surveillance cultures performed upon admission might also be considered if multiple cases or a particularly high risk setting are identified.

Screening cultures will be performed as follows:

- Discuss with IP at facility the level of state epidemiology support they would like
 - Facility can run internal screening program with notification to state if carrier found
 - Facility can run internal screening program with guidance from state
- Identify appropriate epidemiologic contacts for screening
 - Consider facility layout, timing of contact precautions and antibiotics for risk determination
 - Roommates
 - Patient on the same hallway for 3 or more days of shared admission with index patient
 - Pursue outpatient screening only for highest risk patients (particularly roommates)
 - Can perform screening for at-risk contacts every other week while case is admitted in facility
- Obtain appropriate swabs to be sent directly to facility (from NPHL or ARLN)
 - NPHL screening performed by rectal swab for routine stool culture
 - ARLN screening performed by rectal swab with Cepheid-specific swab
- Swabs will be sent to either NPHL or ARLN for testing (facilitated by NDHHS)
- NPHL or ARLN will notify the facility and NDHHS HAI program with results
- Establish method for communication CRE status upon transfer of patients to other facilities
- NDHHS HAI program and NPHL will work with CDC/ARLN as needed for notification/support
- If transmission is identified, perform follow-up point prevalence surveys until two sequential surveys are negative (no additional cases identified)
- Consider performing active surveillance cultures upon admission to a unit if transmission is identified
- Consider use of daily 2% chlorhexidine bathing for patients in high-risk settings/units

References

1. CDC. Guidance for Control of Carbapenem-Resistant *Enterobacteriaceae*. 2012 CRE Toolkit. <https://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf>
2. Rutala WA and Weber DJ and HICPAC. Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008. https://www.cdc.gov/hai/pdfs/Disinfection_Nov_2008.pdf

APPENDIX: NPHL requisition Form

Found at <http://nphl.org/documents/500005%20NPHL%20Supplemental%20Form020317.pdf>

NEBRASKA PUBLIC HEALTH LABORATORY
 UNIVERSITY OF NEBRASKA MEDICAL CENTER PHONE: 402.559.2440
 981180 NEBRASKA MEDICAL CENTER TOLL FREE: 866.290.1406
 OMAHA, NEBRASKA 68198-1180 FAX: 402.559.9497

**Special Microbiology
 Supplemental Form**

PATIENT LAST NAME		FIRST NAME		MI	COLLECTION DATE ___ / ___ / ___		
DOB	/	/	GENDER <input type="checkbox"/> MALE <input type="checkbox"/> FEMALE	PT. ID# / ADDITIONAL INFO		TIME	AM/PM
Source: ___ Blood		___ Bronchial Aspirate		___ Cervical	___ CSF	___ Nasopharyngeal	___ Sputum
___ Stool		___ Throat		___ Urethral	___ Urine	___ Vaginal	___ Other

**Molecular Detection of Carbapenemase
 (NPHL Test Code: CARBAR)**

Guidelines:

- Submission of all isolates of Enterobacteriaceae that are non-susceptible (intermediate or resistant) to any of the carbapenems
- Exceptions are *Enterobacter cloacae* and *E. aerogenes*: only submit isolates that are non-susceptible to carbapenems other than ertapenem
- Do not submit Enterobacteriaceae with known intrinsic resistance to carbapenems; i.e. Proteus species, Providencia species, and Morganella morganii
- Submission of all non-mucoid isolates of *Pseudomonas aeruginosa* that are non-susceptible to carbapenems other than ertapenem from non-cystic fibrosis patients
- Submission of all isolates of in-house or reference laboratory confirmed carbapenemase-producing Enterobacteriaceae

*For questions regarding the sample submission requirements contact:
 Caitlin Murphy, PhD, Assistant Director of Clinical Microbiology _402-552-3305 _ Caitlin.Murphy@unmc.edu*

Isolate ID: _____

Isolate Identification Method:

___ Vitek ___ MicroScan ___ MALDI-TOF ___ Other: _____

Susceptibility:

Imipenem MIC: _____ Interp: _____
 Meropenem MIC: _____ Interp: _____
 Ertapenem MIC: _____ Interp: _____
 Doripenem MIC: _____ Interp: _____

Susceptibility Method*:

___ Vitek ___ MicroScan ___ Kirby Bauer ___ Other: _____

***Attach MIC Report if Available**



Packaging and Shipping to Nebraska Public Health Laboratory Category A Infectious Substances, Affective Humans UN2814 Category B Biological Substances, UN3373

Specimen Handling:

Practice universal blood and body fluid precautions when handling specimens. Specimens must be collected in or transferred to leak-proof primary containers. The container must have at least two patient identifiers and be placed into a secondary sealed biohazard bag to prevent contamination. The biohazard bag should be equipped with an absorbent material, large enough to absorb the entire contents if spilled. The person determining if a package can be shipped as exempt, biological or infectious substance, must be trained in the classification process. All materials must be accompanied by the appropriately completed requisition. Most clinical specimens can be handled as an exempt or category B biological substance, placed in a biohazard bag and offered to the ground courier service. All organism isolates on culture media or in broth must be triple packaged in either the Biological Substances UN3373 (Category B) or the Infectious Substances UN2814 (Category A) provided by Nebraska Public Health Laboratory (NPHL). Contact Karen Stiles at 402.598.2348 or page 402.888.5588 for shipping additional material or instructions.

Shipping Certification:

To ensure the safety of laboratory personnel and the public, proper handling of specimens and propagated organisms is mandatory. The shipper is legally responsible to comply with the rules and guidelines for transport of Division 6.2 infectious substances, which is regulated as a hazardous material under the U.S. Department of Transportation's (DOT) Hazardous Materials Regulations (HMR; 49 CFR Parts 171-178). Purpose of adherence to these regulations and requirements is to minimize the potential for damage to the contents of the package during transport and to reduce the exposure of the shipper to the risks of criminal and civil liability associated with the improper shipment of dangerous goods. Specimens and organism isolates will be rejected if submitted improperly.

Anyone involved in the classification, packaging, shipping or transportation of dangerous goods (including infectious substances) must be trained and certified in the shipment of dangerous goods (Division 6.2). Training must be function-specific, i.e., directly relevant to role the person plays in the packing and shipping process. Persons who pack and ship Category B infectious substances and exempt specimens must receive clear instructions, understand classification and be familiar with regulations. However, persons who pack and ship Category A infectious substances or ≥ 5 kg Dry Ice must receive the aforementioned training plus specific training for all functions involved in packing and shipping more hazardous Category A substances, and be certified to do so.

Transport Instructions:

After determining the exact nature and category of the substance to be shipped, the shipper must follow the appropriate packing instructions, provided by Nebraska Public Health Laboratory in each shipping box and at training sessions.

Courier Services:

Category A Infectious Substance UN2814 shipped from Omaha area must be transported to NPHL by exclusive couriers, as they are only courier specifically trained and licensed to transport Category A. Do not use routine NPHL courier. Call Client Services to arrange an exclusive courier.

All Lincoln and greater Nebraska laboratories must first notify NPHL and ship all Category A Infectious Substances via FedEx, to include airbill and shippers declaration.

To inquire about scheduled stops, and after hours courier ground service, call client services Toll Free 866.290.1406 or 402.559.2440.

Packages going by FedEx, ship to address:

CATEGORY A

Client Services
Nebraska Public Health Laboratory
4400 Emile Street MSB 3500
Omaha, NE 68105
Phone: 866.290.1406

CATEGORY B

Client Services
Nebraska Public Health Laboratory
981180 Nebraska Medical Center, MSB 3500
Omaha, NE 68198-1180
Phone: 866.290.1406

Packages going by Ground, courier to address:

CATEGORY A*

Client Services
Nebraska Public Health Laboratory
981180 Nebraska Medical Center, MSB 3500
Omaha, NE 68198-1180
Phone: 866.290.1406

CATEGORY B

Client Services
Nebraska Public Health Laboratory
981180 Nebraska Medical Center, MSB 3500
Omaha, NE 68198-1180
Phone: 866.290.1406

*Courier specifically trained and licensed to transport Category A. Do not use routine NPHL courier.