Carbapenem-Resistant Enterobacteriaceae (CRE)

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance
   - To identify cases and associated outbreaks
   - To prevent further transmission through containment and prompt infection control
   - To better characterize the risk factors and epidemiology of this organism

B. Laboratory and Physician Reporting Requirements
   - Nebraska Administrative Title 173 – Control of Communicable Disease stipulates that laboratories and healthcare providers report immediately (within 24 hours) of identifying a suspected or confirmed CRE

C. Local Health department (LHD) Reporting and Follow-up Responsibilities
   - Report all suspected or confirmed CRE to the Nebraska Department of Health and Human Services (NE DHHS) within 24 hours of initial physician/lab report by: i) faxing lab report, ii) faxing the standard case report form, or iii) reporting through National Electronic Disease Surveillance System (NEDSS) Electronic Laboratory Reporting (ELR)
   - Ensure that labs forward qualifying isolates (See Appendix for requisition form) to the NPHL for additional testing

D. State Health department Responsibilities
   - NE DHHS will notify LHDs of carbapenemase-producing organisms and collaborate on any necessary follow-up including containment recommendations and surveillance testing as needed
2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic agent

- CRE are Enterobacteriaceae that are resistant to any carbapenem antimicrobial (i.e., minimum inhibitory concentrations of $\geq 4 \text{ mcg/ml}$ for doripenem, imipenem, meropenem or $\geq 2 \text{ mcg/ml}$ for ertapenem) OR have been documented to produce carbapenemase.
- 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 community\(^1\).
- Enterobacteriaceae are a family of gram-negative bacteria that include but are not limited to:\(^1,2,3\)

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrobacter</td>
<td>freundii, koseri, amalonaticus</td>
<td>Plesiomonas</td>
<td>shigelloides</td>
</tr>
<tr>
<td>Edwardsiella</td>
<td>tarda</td>
<td>Proteus</td>
<td>mirabilis, vulgaris</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>cloacae, aerogenes, sakasakii</td>
<td>Providencia</td>
<td>stuartii, rettgeri</td>
</tr>
<tr>
<td>Escherichia</td>
<td>coli, albertii</td>
<td>Salmonella</td>
<td>enterica</td>
</tr>
<tr>
<td>Hafnia</td>
<td>alvei</td>
<td>Serratia</td>
<td>marcescens</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>pneumoniae, oxytoca, granulomatis</td>
<td>Shigella (belongs within the E colii species)</td>
<td>dysenterii, flexneri, sonnei, boydii</td>
</tr>
<tr>
<td>Morganella</td>
<td>morganii</td>
<td>Yersinia</td>
<td>pestis, enterocolitica, pseudotuberculosis</td>
</tr>
<tr>
<td>Pantoea (formerly Enterobacter)</td>
<td>agglomerans</td>
<td></td>
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</tbody>
</table>
B. Description of illness
   - Clinical presentation may vary according to what system of the body is affected
   - May include bloodstream infections, pneumonia, wound infections, intra-abdominal abscesses, and urinary tract infections
   - Patients can be infected or colonized (bacteria is present but not causing symptoms/disease)
   - Colonized patients can subsequently develop infections
   - Infected and colonized patients can both spread the organism to others

C. Treatment
   - Treatment options for CRE are extremely limited and may lead to adverse reactions
   - Infectious disease consultation is recommended for treatment decisions

D. Reservoirs
   - Enterobacteriaceae can be carried in the intestines of many mammals and birds
   - The reservoir for 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 and surfaces

E. Modes of Transmission
   - CRE are transmitted person-to-person through direct contact with infected bodily tissues or fluids
   - In healthcare settings, CRE are spread mainly through the hands of healthcare workers and direct contact with contaminated environmental services, such as bed rails and computer keyboards

F. 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

G. Period of communicability
   - 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 CRE can live on inanimate surfaces
CLINICAL AND CASE DEFINITION

A. CRE are defined as *Enterobacteriaceae* that are:

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

OR

Produce a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) as demonstrated by a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified Hodge test, Carba NP)

B. A CP-CRE or CPO is a particularly concerning type of CRE that is resistant to the carbapenem class of antibiotics due to the production of a carbapenemase enzyme. This enzyme is made from a piece of genetic material called a plasmid that can be transferred to other types of bacteria and therefore represents a unique public health threat.

C. 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 an outbreak that requires an investigation.
3. LABORATORY SERVICES

A. Isolates that meet the following criteria should be forwarded to NPHL using the requisition form (see Appendix) for additional testing:

- 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
- Personnel making submissions to NPHL must have proper training in packaging and shipping hazardous materials 6.2 from NPHL
  - Make arrangements for training through the State Training Coordinator, currently:
    Karen Stiles, MT (ASCP) SM
    kstiles@unmc.edu
    Tel: 402-559-3590

4. CASE INVESTIGATION

A. Surveillance

- 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 CREs, especially potential carbapenemase-producing organisms
- The NPHL performs follow-up testing on isolates that are concerning for a carbapenemase-producing organism (criteria for testing on form in Appendix)
- These results are shared with the ordering facility and the NDHHS HAI program for follow-up as needed

B. Epidemiologic information is collected for all submitted CRE reports as follows

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

C. Additional information is collected for carbapenemase-producing organisms as follows

- Treatment course and duration as well as repeat testing
- History of prior contact with healthcare facilities
- Travel history
- Occupation

5. PREVENTING AND CONTROLLING FURTHER SPREAD

Efforts should be made to contain organisms 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.

A. Infection Control Recommendations for facilities

- 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

B. Personal protective equipment
- Contact precautions (gown and glove) in conjunction with appropriate hand-washing are sufficient to protect employees and other patients

C. Environmental Measures

6. MANAGING SPECIAL SITUATIONS

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 and/or use of 2% chlorhexidine bathing for patients in high-risk settings might also be considered depending on the extent of the outbreak.

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
  - Facility can allow state to perform screening in conjunction with NPHL or ARLN
- Identify appropriate epidemiologic contacts for screening
  - Roommates
  - Patient on the same hallway for 3 or more days of shared admission with index patient
  - Consider facility layout, timing of contact precautions and antibiotics for risk determination
  - 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 with stool culture swabs
  - ARLN screening with Cepheid swabs
- 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
- Consider performing follow-up point prevalence surveys or 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

APPENDIX: NPHL requisition Form

Found at [http://nphl.org/documents/500005%20NPHL%20Supplemental%20Form020317.pdf](http://nphl.org/documents/500005%20NPHL%20Supplemental%20Form020317.pdf)

![NPHL requisition Form](http://nphl.org/documents/500005%20NPHL%20Supplemental%20Form020317.pdf)

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

For questions regarding the sample submission requirements contact:
Caitlin Murphy, PhD, Assistant Director of Clinical Microbiology _402-552-3309_ Caitlin.Murphy@unmc.edu

**Isolate ID:**
**Isolate Identification Method:**

- **Vitek**
- **MicroScan**
- **MALDI-TOF**
- **Other**

**Susceptibility:**
- Imipenem MIC:
- Meropenem MIC:
- Ertapenem MIC:
- Doripenem MIC:

**Susceptibility Method**:

- **Vitek**
- **MicroScan**
- **Kirby Bauer**
- **Other**

*Attach MIC Report if Available*

* Document developed by C. Pedati for NDHHS Last Updated 10/24/2017

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