Carbapenem-Resistant Enterobacteriaceae (CRE): The Public Health Response in Wisconsin

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Topics

- CRE basics
- Surveillance
- Case studies
- Response and prevention
Enterobacteriaceae

Gram negative rods found in the gut of humans and animals
Common human pathogens

<table>
<thead>
<tr>
<th>Escherichia coli</th>
<th>Salmonella</th>
<th>Shigella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella</td>
<td>Yersinia</td>
<td>Serratia</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>Proteus</td>
<td>Citrobacter</td>
</tr>
</tbody>
</table>

Account for 21% of all HAIs

Practical Healthcare Epidemiology, 3rd edition

Beta-lactam Antibiotics: Inhibit Cell Wall Synthesis

- Penicillins (penicillin G, penicillin V, ampicillin, amoxicillin)
- Monobactams (aztreonam)
- Cephalosporins (cefadroxil, cefazolin, ceftriaxone, ceftazadime)
- Carbapenems (doripenem, meropenem, imipenem)

Microb. Mol. Biol. Rev. September 2010 vol. 74 no. 3; 417-433
The first KPC producer was identified during 1996 in the eastern U.S.; the organisms spread globally within a few years. KPC-producing isolates are most prevalent in the eastern states, and in Puerto Rico, Columbia, Greece, Israel, China. *Klebsiella pneumoniae* and *E. coli* are the most common CRE in the U.S.
2013 CDC Threat Report

Microorganisms with threat level of “urgent”

- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

CDC Antibiotic Resistance Threats in the U.S., 2013

- 9,300 cases of CRE infections annually among hospitalized patients (85% Klebsiella spp. vs. E. coli)
- 610 deaths
- 11% of infections with *Klebsiella* spp. and 2% of infections with *E. coli* are carbapenem-resistant

CRE

- “Triple threat”
  - Invasive infections are associated with high mortality rates (40–50 percent).
  - Many are resistant to almost all antibiotic agents.
  - The potential for community transmission is significant.

...HICPAC recommends an “aggressive infection control strategy, including managing all CRE patients with contact precautions...”
Not all CRE are created equal.
- Non-carbapenemase producers: resistant to at least one of the carbapenems but are usually susceptible to other antibiotics
- Carbapenemase producing CRE (CP-CRE): resistant to all B-lactam antibiotics

The focus of CRE surveillance in Wisconsin is CP-CRE.
Mechanisms of Carbapenemase Production

- Klebsiella pneumoniae carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Oxacillin-48 (OXA-48)
- Verona integron-encoded metallo-beta-lactamase (VIM)

CRE

Laboratory-based: 2010
Hospital: 2011
Skilled nursing facilities: 2016

Data base: National Healthcare Safety Network

Goals:
- Determine areas of high CRE prevalence
- Identify “high risk” facilities
- Detect incidents of healthcare transmission
The purpose of CRE surveillance is to enable facilities to collect, report and analyze data that will inform infection prevention strategies.

The multidrug-resistant organism (MDRO) module in the National Healthcare Safety Network (NHSN) is used for CRE surveillance.

Laboratory results are used without clinical evaluation of the resident.

Data are collected facility-wide.

CRE Surveillance Definition

CRE: Any *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, or *Enterobacter* spp. determined to produce a carbapenemase (i.e., KPC, NDM, VIM, IMP, OXA-48) using a recognized test (e.g., polymerase chain reaction, metallo-β-lactamase test, modified-Hodge test, Carba-NP).

Source: National Healthcare Safety Network (NHSN)
Figure 2. MDRO Test Result Algorithm for Laboratory-identified (LabID) Events.

1. MDRO isolate from any specimen source
   - NO
     - 1st in calendar month
       - YES
         - Report as Lab ID Event
       - NO
         - Duplicate MDRO isolate
           - Source = BLOOD
             - NO
               - Duplicate - Not a Lab ID Event
             - YES
               - Prior positive with same MDRO from blood in ≤ 2 weeks (including across calendar months)
                 - YES
                   - Duplicate - Not a Lab ID Event
                 - NO
                   - Unique blood source MDRO - Report as Lab ID Event

CP-CRE Surveillance Case Studies
Case 1

6/16: A 70 YO female resident requests a bedside commode and complains of frequent and painful urination. A urine culture is collected via a straight catheter. The resident is afebrile.

6/19: Urine culture is positive for *E. coli* (>100,000 cfu/ml), and antibiotic susceptibility testing (AST) indicates the organism is resistant to imipenem.

6/25: Your reference laboratory flags the final result with the message “KPC gene detected.”

What should be reported if you are conducting CP-CRE surveillance?
A. One CRE LabID event
B. Two CRE LabID events
C. Definition of a UTI is not met; therefore, do not report any LabID event
D. Insufficient information to determine a CRE event

Case 1, con’t

6/26: The resident spikes a fever of 101°F and blood cultures X 2 are collected, which grow out *E. coli*, resistant to imipenem. Results from the state lab indicate carbapenemase production.

What should be reported?
A. No LabID event, a CRE has already been reported for the month for this resident
B. One CRE LabID event
C. No LabID event, because the blood isolate is the same species as the urine isolate
D. Insufficient information to determine
Case 2

A blood culture is collected from an 84 YO male resident on 5/29 and grows out a CP-CRE Klebsiella pneumoniae. A second blood culture is collected 6/2 and also grows out CP-CRE K. pneumoniae.

How many CRE LabID events should be reported? _____

Why?__________________________________________

Identify the CRE LabID Events

<table>
<thead>
<tr>
<th>Resident</th>
<th>Admit Date</th>
<th>Specimen Collection Date</th>
<th>Source</th>
<th>Lab Result</th>
<th>LabID Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>06/01/12</td>
<td>Stool</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>06/02/12</td>
<td>Blood</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>06/12/12</td>
<td>Blood</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>06/20/12</td>
<td>Blood</td>
<td>negative</td>
<td>Y N</td>
</tr>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>07/10/12</td>
<td>Blood</td>
<td>CRE K. oxytoca</td>
<td>Y N</td>
</tr>
<tr>
<td>Jack</td>
<td>6/01/12</td>
<td>07/15/12</td>
<td>Blood</td>
<td>CRE K. oxytoca</td>
<td>Y N</td>
</tr>
</tbody>
</table>
### Identify the CRE LabID Events

<table>
<thead>
<tr>
<th>Resident</th>
<th>Admit Date</th>
<th>Specimen Collection Date</th>
<th>Source</th>
<th>Lab Result</th>
<th>LabID Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill</td>
<td>06/15/12</td>
<td>06/16/13</td>
<td>Blood</td>
<td>CRE Klebsiella spp.</td>
<td>Y N</td>
</tr>
<tr>
<td>Bill</td>
<td>06/15/12</td>
<td>06/20/13</td>
<td>Blood</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Bill</td>
<td>07/02/12</td>
<td>07/01/13</td>
<td>Sputum</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Eve</td>
<td>07/02/12</td>
<td>07/06/13</td>
<td>Stool</td>
<td>CRE E.coli</td>
<td>Y N</td>
</tr>
<tr>
<td>Eve</td>
<td>07/02/12</td>
<td>07/10/13</td>
<td>Stool</td>
<td>CRE Klebsiella spp.</td>
<td>Y N</td>
</tr>
<tr>
<td>Helen</td>
<td>06/01/12</td>
<td>06/06/13</td>
<td>Urine</td>
<td>CRE E. coli</td>
<td>Y N</td>
</tr>
</tbody>
</table>
CRE Denominator Data

- Resident-days
  - Calculated using the daily census of residents in the facility each day of the month and totaled at the end of the month

- Admissions
  - Number of residents admitted each calendar day of the month and totaled at the end of the month

- Must be entered into NHSN every month, even when there are no LabID events

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### Denominators for LTC facilities

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of residents</th>
<th>Number of residents with urinary catheter</th>
<th>Number of admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>1</td>
<td>0</td>
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<tr>
<td>6</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

- Count at same time each day
- Total each column at end of month and enter into NHSN

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[Link to denominator form](http://www.cdc.gov/nhsn/PDFs/LTC/forms/07.142_DenominatorTCF_BLANK.pdf)
CRE Surveillance Data

Number of Wisconsin patients with at least one reported CRE isolate, 2014-2016

*addition of Enterobacter spp. and Emergency Department patients to the CRE case definition
Wisconsin 2016 CRE Surveillance Data Summary

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of carbapenem-non-susceptible Klebsiella, E. coli, and Enterobacter isolates submitted to WSLH</td>
<td>351</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of carbapenemase positive isolates</td>
<td>58 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenemase mechanism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of KPC</td>
<td>56 (97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of OXA-48-like</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of NDM-1</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimen source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of urine</td>
<td>34 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of skin/soft tissue</td>
<td>16 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of sterile sites</td>
<td>6 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of respiratory</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of Klebsiella spp.</td>
<td>33 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of E. coli</td>
<td>13 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of Enterobacter spp.</td>
<td>12 (21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory-identified CRE events per 100,000 admissions, Wisconsin 2014-2016

*LabID event = a clinical specimen positive for CRE (Klebsiella spp. or E. coli) per patient, per month, per facility
CRE Surveillance Summary

- CRE prevalence is highest in the Southeastern Public Health Region.
- One “high risk” facility, located in SE Wisconsin, has been identified. All residents admitted to referring hospital are preemptively placed on contact precautions.
- At least 4 incidents of healthcare transmission have been detected.

Incidents of CRE Transmission in Wisconsin Healthcare Facilities
Transmission of KPC *Klebsiella pneumoniae* from long-term care to acute care, 2012

- Unidentified CRE-positive Patient 1 was transferred from a long-term to an acute care facility.
- CRE was transmitted to Patient 2, located in a hospital room adjacent to Patient 1.
- Rectal cultures of all patients on the affected unit did not reveal additional transmission.
- Patient 2 was not discharged to another facility, thus no follow-up with receiving facilities was required.

Transmission of NDM-1 *E. coli* via a common duodenoscope, 2013

- NDM-1-Positive Index Patient 3
- Patient 4
- Patient 5
- Patient 6
- Patient 7
A patient being treated in the ICU for several months was infected at multiple sites with KPC *K. pneumoniae*. The isolate was resistant to ALL antibiotics tested.

The isolate underwent testing for the mcr-1 gene at CDC, and was negative.

The ICU has been placed on active surveillance, and patients are screened for CRE upon admission, weekly, and at discharge. To date, the same organism was transmitted to 4 additional patients in the unit.
CRE Response: Toolkit for NHs

https://www.dhs.wisconsin.gov/disease/cre.htm

Management of Residents with Carbapenem-resistant *Enterobacteriaceae* (CRE) in Wisconsin Skilled Nursing Facilities, 2016

- Detection of *K. oxytoca*, *K. pneumoniae*, *E. coli*, or *Enterobacter* spp isolates testing non-susceptible to one of the following carbapenem agents: imipenem, doripenem, meropenem or ertapenem.

Ensure microbiology laboratory alerts infection prevention and unit staff immediately.

Place resident on alert list and notify receiving facilities and agencies that the resident has a history of CRE.

If resident has no signs/symptoms of infection, use standard precautions. Instruct resident to perform good hand hygiene and to wear clean clothes when leaving his/her room. Ensure body fluids and wound drainage are contained.

If resident has signs/symptoms of infection, use contact precautions. Place resident in private room if possible. Staff should wear gown and gloves upon entry to room. Disinfect items before removing from room or discard disposable items, and limit movement of resident outside the room.

- Microbiology laboratory submits isolates to WSLHD to test for carbapenemase production.

- No detection of carbapenemase-producing CRE. Not reportable to DPH, entry into NHN is optional.

- DPH will arrange for active surveillance of exposed residents if deemed necessary.

Minimum inhibitory concentrations (MIC) considered resistant:

- Doripenem (MIC ≥ 2 μg/mL)
- Imipenem (MIC ≥ 4 μg/mL)
- Meropenem (MIC ≥ 2 μg/mL)
- ertapenem (MIC ≥ 2 μg/mL)

Minimum inhibitory concentrations (MIC) considered non-susceptible:

- CarbaPEnem MIC ≥ 2 μg/mL
- Imipenem MIC ≥ 4 μg/mL
- meropenem MIC ≥ 2 μg/mL
- ertapenem MIC ≥ 2 μg/mL

Residents screening positive for carbapenemase-producing CRE will be placed in contact precautions during nursing home stay and future hospital admissions.

- Manage resident with standard and contact precautions for duration of stay. Place resident in private room with private bathroom. Staff should wear gown and gloves upon entry to room or when providing care or therapy outside the room. Disinfect all items before removing from room or discard disposable items. Resident may leave room if not actively infected and if all body fluids and wound drainage can be contained. If more than one resident with the same species of CRE is identified, cohort residents and use dedicated staff when possible. Residents may be housed in semi-private rooms in cohorted areas.

Appendix 1: Sample Nursing Home CRE Policy and Procedures

Management of residents with Carbapenem-resistant Enterobacteriaceae (CRE)

Effective date

Department

<table>
<thead>
<tr>
<th>Dates of review/revision</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Background

CRE are a group of bacteria resistant to the last line of drugs that were developed to treat infections with certain drug-resistant organisms. CRE can be divided into two

Appendix 2: Instructions for Collecting and Submitting Rectal Swabs to the Wisconsin State Laboratory of Hygiene (WSLH) to Detect Carbapenemase Production

Supplies

- Culturette,™ ESwab,™ or similar suitable collection system (do not use calcium alginate swabs)
- Disposable gloves
- Alcohol hand sanitizer

NOTE: As an alternative to collecting a rectal swab, a swab of a stool specimen can be obtained and submitted for CRE surveillance testing.
Appendix 3: Sample Scripts to Inform Residents/Responsible Parties of CRE Screening Results

If active surveillance testing indicates the resident is colonized with CRE, the following script may be used to inform the resident/responsible party of the positive test results.

"The results of your CRE screening test indicate you are colonized with, that is you carry, CRE in your intestinal tract. Even though you may not feel any symptoms of illness at this time, we will continue to take precautions to help prevent the CRE from spreading to others. We will place you in a private room, and we will be wearing a gown and gloves whenever we come into your room to care for you. You will also be placed in a private room if you are hospitalized. A more detailed care plan will be provided in the near future. Please read this pamphlet for more information on CRE, and let me know if you or your family members have any questions."
**CRE Educational Resources…**

- CRE patient and family education pamphlet available at [http://www.dhs.wisconsin.gov/publications/P0/P00486.pdf](http://www.dhs.wisconsin.gov/publications/P0/P00486.pdf)
- CRE healthcare staff education pamphlet available at [http://www.dhs.wisconsin.gov/publications/P0/P004868.pdf](http://www.dhs.wisconsin.gov/publications/P0/P004868.pdf)
- CRE fact sheet available at [http://www.dhs.wisconsin.gov/publications/P0/P00470.pdf](http://www.dhs.wisconsin.gov/publications/P0/P00470.pdf)
- Aurora Health Care CRE staff education slides available at [https://www.dhs.wisconsin.gov/disease/cre.htm](https://www.dhs.wisconsin.gov/disease/cre.htm) under the “Healthcare Professionals” tab

**CRE Response Checklist…**

- CRE policies and procedures have been written and are available to nursing home staff.

- The clinical laboratory has a mechanism of immediately alerting infection prevention and unit staff when microbiology results identify a CRE isolate.

- During absence of the infection preventionist, back-up staff has been identified and trained to ensure immediate reporting of CRE cases and prompt implementation of infection control measures.

- Infection prevention staff has the authority to collect specimens from residents as part of active CRE surveillance testing and monitoring for transmission.
CRE Response Checklist…

☐ Staff education regarding CRE prevention has been conducted at least once.

☐ CRE educational pamphlets are available for residents and their families when needed.

FAQs…

1. Does consent need to be obtained before collecting rectal swabs for CRE surveillance testing?
   Because this is a surveillance activity for purposes of preventing disease transmission and is not a research project, no separate consent to test for CRE colonization is required.

2. What should we do if a resident refuses to be screened for CRE colonization?
   If screening tests among other residents on the same unit indicate possible CRE transmission, it may be necessary to assume the declining resident is also CRE-positive, and to manage him/her accordingly. The non-tested resident, however, should not be cohorted with other CRE-positive residents.
FAQs...

3. What types of specimens can be collected to conduct CRE screening?  
The preferred specimen is a rectal swab, but a perirectal swab or a swab of stool material may also be submitted for testing.

4. Who should order the CRE screening tests?  
Infection prevention staff may request an order from the medical director of the facility, or from the individual resident’s personal physician.

5. Who usually collects the specimens?  
Usually the resident’s nurse or other appropriate care provider will explain the purpose of the CRE screening test to the resident/responsible party, collect the specimen and report the results to the resident or his/her family.

FAQs...

6. Should family members of CRE-positive patients be tested?  
It is not usually necessary to test family members, as they are less likely to acquire CRE than hospitalized patients or residents being treated with invasive devices or who are receiving antibiotics. The current CDC recommendations do not include testing of a resident’s family members.

7. Should healthcare workers exposed to cases of CRE be tested?  
There are no recommendations to test healthcare workers for CRE colonization. Transmission of CRE usually occurs from resident-to-resident due to contaminated hands of healthcare workers. Healthcare workers are usually healthy individuals and are therefore at lower risk of acquiring CRE.
In summary...

- CRE are highly drug-resistant organisms that remain an important public health threat.
- Several incidents of healthcare-associated transmission of CRE have been detected among Wisconsin healthcare facilities.
- Statewide surveillance and prevention strategies have been implemented in Wisconsin to prevent further emergence of CRE.
DPH CRE Website
https://www.dhs.wisconsin.gov/disease/cre.htm

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