

# **Recommendations for the Management of Carbapenem- Resistant Enterobacteriaceae (CRE) in Acute and Long-term Acute Care Hospitals**

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## Purpose

These recommendations are intended to provide: (1) infection prevention and control guidance for health care personnel in acute and long-term acute care hospitals in the management of patients infected or colonized with carbapenem-resistant Enterobacteriaceae (CRE) and (2) resources and guidance for surveillance and laboratory testing, including Minnesota Department of Health (MDH) CRE surveillance definitions and requirements. The infection prevention and control recommendations were created to enhance rather than duplicate existing published recommendations and guidelines for CRE control in acute care and long-term acute care settings. Literature reviews, the Centers for Disease Control and Prevention's (CDC) *Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing Enterobacteriaceae in Acute Care Facilities*, expertise from the Association for Professionals in Infection Control and Epidemiology (APIC) Emerging Pathogens Task Force, and discussions with national content experts served as the basis for the recommendations.<sup>1</sup> MDH will review the recommendations regularly and modify them as needed to reflect new scientific developments concerning effective CRE prevention and control.

## Classification and Epidemiology

The term CRE refers to carbapenem-resistant and/or carbapenemase-producing Enterobacteriaceae. Over the past decade, Enterobacteriaceae bacteria that are resistant to carbapenems have emerged and spread throughout the United States. Carbapenem antibiotics (ertapenem, imipenem, meropenem, and doripenem) are often used as the last line of treatment for infections caused by resistant Gram-negative bacilli (GNB) including bacteria in the Enterobacteriaceae family. Multidrug-resistant GNB, such as CRE, are an emerging threat in healthcare facilities across the continuum of care (e.g., acute care, long-term acute care, and long-term care facilities).

Currently, the most common carbapenemase in the United States is the *Klebsiella pneumoniae* carbapenemase (KPC). This plasmid-mediated carbapenemase is most commonly found in *Klebsiella* spp. and *Escherichia coli* but is also found in other species of Enterobacteriaceae. In 2009, upon detection of the first KPC-producing Enterobacteriaceae in Minnesota, MDH began statewide passive surveillance for CRE. In 2010, two carbapenemases known as metallo- $\beta$ -lactamases (MBL) were first detected in the U.S.: New Delhi MBL (NDM) and Verona integron-encoded MBL (VIM).<sup>2,3</sup> CDC reports a history of healthcare exposure in India or Pakistan has been reported in patients in whom NDM positive isolates have been detected. In late 2011, two isolates carrying the NDM resistance mechanism

were detected in a single MN resident with a history of travel to and receipt of medical care in India. Plasmids and other mobile genetic elements are instrumental in the horizontal transmission of resistance genes such as KPC and NDM. During 2011, MDH established active, population-based laboratory surveillance for CRE in Hennepin and Ramsey Counties to assess the population-based incidence of CRE and to better describe known resistance mechanisms.

## Detection

Identification of CRE in clinical laboratories is based on the antimicrobial susceptibility values for carbapenems and third-generation cephalosporins. Enterobacteriaceae that test non-susceptible (i.e. intermediate or resistant) to carbapenems and resistant to third generation cephalosporins are classified as CRE. Other tests, such as the Modified Hodge Test (MHT), can be utilized to identify carbapenemase production.<sup>4,5</sup> Also available, but rarely performed in clinical laboratories, is polymerase chain reaction (PCR) testing for specific carbapenemases.<sup>6</sup> The PCR test identifies genes encoding for carbapenemases (e.g., *bla*<sub>KPC</sub>, *bla*<sub>NDM</sub>). Regardless of the mechanism(s) responsible for CRE, infection prevention and control measures outlined in this document should be implemented upon detection of a CRE.

## Prevention

MDH supports aggressive implementation of infection prevention and control strategies when a CRE is detected. Infections caused by CRE are difficult to treat and associated with high morbidity and mortality.<sup>7,8</sup> Early detection and prompt implementation of infection prevention and control measures have been effective in reducing the likelihood of transmission in health care settings.<sup>9,10</sup> CDC and the Healthcare Infection Control Practices Advisory Committee also recommend an aggressive infection control strategy, including Contact Precautions for all patients colonized or infected with CRE.<sup>1</sup>

Prompt implementation of infection prevention and control measures requires close collaboration between clinical laboratory staff, infection prevention staff, clinicians, and nursing staff. As part of this collaboration, it may be prudent for the clinical laboratory to share with infection prevention staff the complete antimicrobial susceptibility report for any CRE identified, including susceptibilities for carbapenems and third-generation cephalosporins, even if this information is routinely suppressed in the patient report.

# MDH CRE Infection Prevention and Control Measures for Hospitals

Infection prevention and control measures for CRE positive patients should be implemented regardless of the mechanism(s) causing carbapenem resistance.

For the management of patients colonized or infected with a CRE, we recommend the following infection prevention and control strategies be implemented in addition to those included in your hospital's infection control policy/protocols for multidrug resistant organisms (MDROs). Ensure that compliance with the MDRO policy is high among all staff interacting with the CRE positive patient and/or patient environment. This includes, but is not limited to: Isolation precautions, donning/doffing of appropriate personal protective equipment (PPE), hand hygiene, and environmental cleaning and disinfection.<sup>11</sup>

## 1. Laboratory testing

Ensure the hospital laboratory is utilizing appropriate laboratory methods for detection of CRE (see *MDH CRE Surveillance Activities*).

Adopt a standardized definition for CRE (see *MDH CRE Surveillance Activities*) and ensure the definition is being utilized by all departments including laboratory, infection prevention, and pharmacy, in addition to hospitalists and infectious disease physicians.

Communicate positive CRE results immediately to infection prevention and staff providing patient care.

## 2. Patient placement

Preferentially place patients with a CRE in a single room with Contact Precautions, or if no single room is available, cohort in the same room with another patient colonized or infected with CRE, regardless of species.

## 3. Laboratory retrospective review

Infection prevention, in collaboration with the clinical laboratory, should conduct a one-time retrospective review (6 – 12 months) of laboratory records to identify previously unrecognized patients with CRE.<sup>1</sup> This one-time retrospective review will serve as a baseline for your hospital and ensure proper processes are in place for prospective CRE surveillance.

- If previously unrecognized CRE positive patients are identified, conduct a single round of active surveillance testing (AST) of patients on units where these cases have been identified. For information regarding laboratory protocols for CRE active surveillance testing (AST), please see the CDC Protocol for AST at: [http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella\\_or\\_Ecoli.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf).
- If no previously unrecognized cases are identified, continue to monitor for CRE in clinical cultures.

#### **4. Active surveillance testing (AST)/Screening**

The goal of AST is to identify undetected carriers of CRE who are a potential source of transmission. There is insufficient evidence to recommend routine screening of patients (including screening of patients with epidemiologic risk factors) for colonization with CRE. Consider rectal screening cultures and preemptive isolation (Contact Precautions while awaiting the results of screening cultures) of patients admitted to healthcare facilities after recently being hospitalized (within the last 6 months) in countries outside the United States.<sup>12</sup>

If a patient with previously unrecognized CRE or hospital-onset CRE infections are identified through clinical cultures or point prevalence surveys:<sup>13</sup>

- Consider conducting AST of patients with epidemiologic links to the CRE-positive patient.
- Place newly identified patients with CRE in a single room with Contact Precautions.

Recommended sites for AST are rectal or peri-rectal swabs.<sup>1,9,14,15</sup>

There is no indication for AST of health care workers, family members or visitors.

#### **5. Discontinuation of Contact Precautions**

No recommendations exist for discontinuing Contact Precautions during the current or future admissions to any health care facility.<sup>1</sup>

When considering discontinuation of Contact Precautions, recognize that prolonged carriage of CRE has been documented.<sup>16</sup>

- At a minimum, maintain Contact Precautions for the duration of the current hospitalization.

Determine a method of identifying patients with a history of CRE upon readmission (e.g., flag medical records of CRE positive patients).<sup>17,18</sup>

#### **6. Intra-facility communication**

Implement measures to ensure timely communication between the clinical laboratory and infection prevention when a CRE is detected in a clinical or AST culture.

#### **7. Inter-facility communication**

Communicate patient's CRE status to the receiving health care facility upon patient transfer.<sup>18</sup>

If a patient is identified with CRE following transfer to another health care facility, the receiving facility should be notified of the results.

Admission to the receiving health care facility should not be denied solely on the basis of CRE status.

#### **8. Education**

Implement measures to educate staff and ensure compliance with hospital MDRO and CRE-specific prevention and control strategies.<sup>18</sup>

## 9. Visitors to CRE patients

The use of gowns, gloves, or masks by visitors in health care settings to prevent transmission of MDROs has not been addressed specifically in the scientific literature.<sup>19-21</sup>

Visitors to patients with CRE should follow hospital policy for visitors to patients with other MDROs, including:

- Wear PPE to perform direct patient care.
- Perform hand hygiene upon entering and exiting the patient room.
- Avoid roaming on the unit or entering other patient rooms.

## 10. Stewardship<sup>13</sup>

Antimicrobial stewardship: Promote judicious use of antimicrobials.

- Monitor antimicrobial use.
- Ensure empirically prescribed antimicrobials are adjusted as necessary in a timely manner based on laboratory results.

Device utilization: Minimize use of invasive devices (e.g., urinary catheters).

- Promote adherence to appropriate indications for urinary catheter use.
- Ensure urinary catheters and other invasive devices are in place only as long as needed.



## MDH Enhanced CRE Infection Prevention and Control Measures for Hospitals

If there is evidence of possible CRE transmission (e.g., two or more epidemiologically-linked CRE positive patients, regardless of Enterobacteriaceae species), infection prevention or the clinical laboratory should contact MDH, reinforce infection prevention measures, and implement enhanced control measures including one or more of the following:

1. Perform AST on all patients who may have had contact with the CRE positive patient (e.g., patients with epidemiologic links to this patient such as patients in the same patient room or on the same unit).<sup>1</sup>

- If new cases are detected, continue weekly AST on patients with epidemiologic links to the CRE positive patient(s) until no new cases are identified.

Periodically conduct point prevalence surveys to detect patients colonized with CRE on units where CRE transmission has been detected.

Recommended sites for AST are rectal or peri-rectal swabs.<sup>1,9,14,15</sup>

There is no indication for AST on health care workers, family members or visitors.

2. Consider admission CRE screening for high-risk patients (e.g., facility or patients with a history of CRE).
  - Place patients in pre-emptive Contact Precautions until screening results are available.
    - If negative, discontinue Contact Precautions, unless otherwise indicated, and cohort with CRE negative patients.
    - If positive, continue Contact Precautions and cohort in the same area on a given unit with other CRE positive patients.
  - This process should be repeated upon every readmission.
3. Monitor cleaning and disinfection practices to ensure consistent implementation of hospital environmental service protocols.
4. Focus on cleaning and disinfection of surfaces in close proximity to the patient and high touch surfaces (e.g., bedrails, bedside commodes) in the patient room.
5. If enhanced strategies are ineffective and transmission continues, consider cohorting CRE positive patients in the same area on a given unit, temporarily closing unit to new admissions, and/or providing dedicated nursing staff.<sup>9,10,13,18,22</sup>
6. If a novel resistance mechanism is identified for the first time in a facility, perform AST on all patients who may have had contact with the CRE positive patient (see 1 under *MDH Enhanced CRE Infection Prevention and Control Measures for Hospitals*).

## **CDC Guidance (2013)<sup>12</sup>**

When a CRE is identified in a patient (infection or colonization) with a history of an overnight stay in a healthcare facility (within the last 6 months) outside the United States, send the isolate to a reference laboratory for confirmatory susceptibility testing and perform testing to determine the carbapenem resistance mechanism; at a minimum, this should include evaluation for KPC and NDM carbapenemases.

For patients admitted to healthcare facilities in the United States after recently being hospitalized (within the last 6 months) in countries outside the United States, consider each of the following:

- Perform rectal screening cultures to detect CRE colonization.
- Place patients on Contact Precautions while awaiting the results of these screening cultures.

## MDH CRE Surveillance Activities

Health care professionals across the continuum of care play an integral role in preventing CRE. MDH conducts surveillance to identify the burden of CRE in Minnesota and guide recommended infection prevention interventions related to CRE. The MDH PHL performs additional characterization (polymerase chain reaction for KPC and NDM carbapenemases, and if applicable, VIM) on a select group of CRE isolates.

### What to report to MDH

- **Hennepin and Ramsey Counties:** All laboratories in Hennepin and Ramsey Counties are **required** to report cases of CRE (patients who are infected or colonized with CRE) to the MDH (651-201-5414 or 1-877-676-5414) and submit the isolate to the MDH Public Health Laboratory (MDH PHL).
- **All other Minnesota counties:** All laboratories outside Hennepin and Ramsey Counties are strongly encouraged to **voluntarily** report CRE to the MDH and submit CRE isolates to the MDH PHL.

#### Surveillance definition for notifying MDH Epidemiology and submitting isolates to MDH PHL\*:

Submit all Enterobacteriaceae\*\* isolates that are:

- Intermediate or Resistant to imipenem, meropenem, or doripenem; **AND**
- Resistant to all tested 3<sup>rd</sup> generation cephalosporins (Tables 1 & 2).

Some isolates of *Proteus* spp., *Providencia* spp., and *Morganella morganii* may have different resistance mechanisms that result in elevated imipenem MICs. Therefore, submit these isolates **ONLY** if they are:

- Intermediate or Resistant to **at least two** carbapenem antibiotics (ertapenem, imipenem, meropenem, or doripenem); **AND**
- Resistant to all tested 3<sup>rd</sup> generation cephalosporins (Tables 1 & 2).

\*The guidelines for notification and submission are based on the best knowledge currently available. Facilities not utilizing the most current CLSI breakpoints should continue to report and submit all modified Hodge test positive isolates to MDH.

\*\**Klebsiella pneumoniae*, *K. oxytoca*, *Escherichia coli*, and *Enterobacter cloacae* organisms that meet the CRE definition are a priority for detection and containment in MN.

### Applying the CRE surveillance definition in clinical laboratories/hospitals

All laboratories should aim to implement the current CLSI interpretive criteria (Table 1) for carbapenems and cephalosporins.<sup>5,23</sup> MDH strongly encourages hospitals to use the above definition for hospital surveillance; however, we recognize there are limitations to its use such as:

- Laboratories may not test all carbapenems/cephalosporins stated in the definition (e.g., card/panel only has one carbapenem), and/or
- Laboratories may not have breakpoints that go low enough to detect CRE based on the current CLSI breakpoints.

Given these limitations, some laboratories may need to modify the surveillance definition to align with their current laboratory practices. Laboratories that implement modifications to the above surveillance definition should communicate this to appropriate hospital personnel.

**Table 1. Clinical and Laboratory Standards Institute M100-S23 (January 2013) MIC Interpretive Criteria for Enterobacteriaceae**

<b>Cephalosporin Agent</b>	<b>Susceptible</b>	<b>Intermediate</b>	<b>Resistant</b>
Cefotaxime	≤1	2	≥4
Ceftriaxone	≤1	2	≥4
Ceftazidime	≤4	8	≥16
<b>Carbapenem Agent</b>	<b>Susceptible</b>	<b>Intermediate</b>	<b>Resistant</b>
Doripenem	≤1	2	≥4
Imipenem	≤1	2	≥4
Meropenem	≤1	2	≥4
Ertapenem	≤0.5	1	≥2

Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Twenty-third informational supplement; M100-S23. Wayne, PA 2013.

**Table 2. Clinical and Laboratory Standards Institute M100-S23 (January 2013) Zone Diameter Interpretive Criteria for Enterobacteriaceae**

<b>Cephalosporin Agent</b>	<b>Susceptible</b>	<b>Intermediate</b>	<b>Resistant</b>
Cefotaxime	≥26	23-25	≤22
Ceftriaxone	≥23	20-22	≤19
Ceftazidime	≥21	18-20	≤17
<b>Carbapenem Agent</b>	<b>Susceptible</b>	<b>Intermediate</b>	<b>Resistant</b>
Doripenem	≥23	20-22	≤19
Imipenem	≥23	20-22	≤19
Meropenem	≥23	20-22	≤19
Ertapenem	≥22	19-21	≤18

Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Twenty-third informational supplement; M100-S23. Wayne, PA 2013.

## Additional Resources

### MDH Infection Prevention and Control Consultation

Infection preventionists are encouraged to contact MDH during regular business hours to report CRE cases and for consultation regarding patient management, including surveillance and infection prevention and control measures (651-201-5414 or 877-676-5414).

### MDH Laboratory Consultation

MDH PHL Special Microbiology Laboratory is available during regular business hours for consultation for CRE testing and result interpretation (651-201-5581).

For information regarding laboratory protocols for CRE active surveillance testing please see the CDC Protocol: [http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella\\_or\\_Ecoli.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf).

Laboratory protocol for the Modified Hodge Test:

[http://www.cdc.gov/HAI/pdfs/labSettings/HodgeTest\\_Carbapenemase\\_Enterobacteriaceae.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/HodgeTest_Carbapenemase_Enterobacteriaceae.pdf).

Laboratory protocol for the Multiplex Real-Time PCR Detection of *Klebsiella pneumoniae* Carbapenemase (KPC) and New Delhi metallo- $\beta$ -lactamase (NDM-1) genes:

<http://www.cdc.gov/HAI/pdfs/labSettings/KPC-NDM-protocol-2011.pdf>.

### CDC Guidance

Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE): 2012 CRE Toolkit<sup>24</sup>

Further information about the prevention of CRE transmission:

<http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html>.

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