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

Minnesota Department of Health

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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); (2) resources and guidance for surveillance and laboratory testing; and (3) an overview of Minnesota Department of Health (MDH) CRE surveillance activities. 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.[1] 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 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.

Currently, the most prevalent carbapenemase in the United States is the *Klebsiella pneumoniae* carbapenemase (KPC). This plasmid-mediated carbapenemase is most commonly found *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 (known as NDM-1) and Verona-Integron encoded MBL (known as VIM).[2,3] As these and other novel resistance mechanisms in GNB evolve, plasmids and other mobile genetic elements are instrumental in the horizontal transmission of resistance genes. 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 (e.g., KPC, NDM-1, VIM).

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.[4,5] Also available, but rarely performed in clinical laboratories, is polymerase chain reaction (PCR) testing.[6] The PCR test is specific for carbapenemase-producing organisms and identifies the genes encoding for carbapenemases (e.g., bla_{KPC}). Regardless of the mechanism(s) responsible for CRE, infection prevention and control measures outlined in this document should be implemented upon identification 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.[7,8] Early detection and prompt implementation of infection prevention and control measures have been effective in reducing the likelihood of transmission in health care settings.[9,10] 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.[1]

Clinical laboratory and infection prevention departments are integral to early detection and management of all multidrug-resistant organisms (MDROs). Hospitals should establish a multi-disciplinary team (e.g., infection preventionist, laboratorian, clinical pharmacist, and a physician with expertise in infectious diseases) responsible for developing policies to detect and manage patients infected or colonized with CRE. Prompt implementation of infection prevention and control measures requires close collaboration between clinical laboratory and infection prevention 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 on 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 (see *CRE surveillance definition*).

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.[11]

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.[1] 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 .
   - 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.

If a patient with previously unrecognized CRE or hospital-onset CRE infections are identified through clinical cultures or point prevalence surveys:[12]

- 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.[1,9,13,14]

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.[1]

When considering discontinuation of Contact Precautions, recognize that prolonged carriage of CRE has been documented.[15]

- 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).[16,17]

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.[17]

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.[17]

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.[18-20]

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. Antimicrobial Stewardship

The hospital should have in place an antimicrobial stewardship program to promote judicious use of antibiotics.

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).[1]

- 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.[1,9,13,14]

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.[9,10,12,17,21]

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*).

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, perform additional characterization on a select group of CRE isolates for epidemiologic purposes, and guide infection prevention interventions related to CRE.

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.

CRE 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 3rd generation cephalosporins (Tables 1 & 2).

Some isolates of *Morganella*, *Serratia*, *Providencia*, *Hafnia*, *Proteus*, or *Yersinia* 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 (imipenem, meropenem, or doripenem; **AND**
- Resistant to all tested 3rd generation cephalosporins (Tables 1 & 2).

* The guidelines for notification and submission are based on the best knowledge currently available.

Applying the CRE surveillance definition in clinical laboratories/hospitals

All laboratories should aim to implement the 2011 CLSI breakpoints (Table 1) for carbapenems and cephalosporins.[4,22] 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 January 2011 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-S21 (January 2011) MIC Breakpoints for *Enterobacteriaceae*[4]

Cephalosporin Agent	Susceptible	Intermediate	Resistant
Cefotaxime	≤1	2	≥4
Ceftriaxone	≤1	2	≥4
Ceftazidime	≤4	4	≥16
Carbapenem Agent	**Susceptible**	**Intermediate**	**Resistant**
Doripenem	≤1	2	≥4
Imipenem	≤1	2	≥4
Meropenem	≤1	2	≥4

Table 2. Clinical and Laboratory Standards Institute M100-S21 (January 2011) Zone Diameter Breakpoints for *Enterobacteriaceae*[4]

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

MDH CRE Resources

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).

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 (AST) please see the CDC Protocol for AST at: http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf.

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Laboratory protocol for the Modified Hodge Test: 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-β-lactamase (NDM-1) genes: http://www.cdc.gov/HAI/pdfs/labSettings/KPC-NDM-protocol-2011.pdf.

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