Carbapenem-resistant Enterobacteriaceae (CRE) in Minnesota

Melissa Hargreaves, PhD
Ruth Lynfield, MD
651-201-5414
www.health.state.mn.us
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Objectives

- Describe the landscape of CRE nationally and in Minnesota
- Describe laboratory testing methods for CRE and CP-CRE
- Explain the 2016 surveillance definition for statewide reporting of CRE
- Define the process for reporting cases and submitting isolates when a possible CRE is identified
- Discuss the importance of collaboration between the laboratory and infection prevention entities

The Enterobacteriaceae

- Facultatively anaerobic, Gram-negative bacilli
- Enteric organisms
- Common human pathogens
  - Urinary tract infections
  - Bacteremia
  - Pneumonia
  - Wound infections
- Klebsiella, Escherichia coli, Enterobacter, Serratia, Citrobacter
Carbapenem antibiotics

- Newest class of FDA-cleared beta-lactamase antibiotics
- Broad spectrum activity
- Usually reserved as “antibiotics of last resort”
- Used to treat hospitalized patients with multi-drug-resistant bacterial infections
- Bacterial resistance to carbapenems is increasing

Carbapenem-Resistant Enterobacteriaceae (CRE)

- Emerging problem worldwide
- Concerning resistance mediated by carbapenemase enzymes
  - genes carried on highly transferrable plasmids
- Spread confounded by ease of travel and medical treatment in endemic areas
- Lack of proper patient screening or communication between facilities also increases spread
- Long-term carrier state

Important Mechanisms of Resistance

- Many mechanisms of carbapenem resistance exist; some isolates encode multiple mechanisms
  - Plasmid-mediated carbapenemase genes
    - KPC, NDM, OXA-48, IMP, VIM, etc.
    - Geographically distributed
    - Carbapenemase enzymes hydrolyze carbapenems
  - AmpC (intrinsic/plasmid-mediated + porin loss mimics)
    - Also, ESBLs
    - MYSPACE organisms

Plasmid-bearing carbapenemase genes

Porin

AmpC gene
Inter-bacterial spread of carbapenemase genes

From one isolate...

Plasmid with carbapenemase gene

E. coli

K. pneumoniae

...to three!

Plasmid with carbapenemase gene

E. coli

K. pneumoniae

Evolving Terminology

**CRE**: Carbapenem-Resistant Enterobacteriaceae
  - Example: MIC values from ATI or manual method

**CP-CRE**: Carbapenemase-Producing, Carbapenem-Resistant Enterobacteriaceae
  - Example: Test for carbapenemase production (e.g., MHT, Carba NP)

**KPC**: *Klebsiella pneumoniae* carbapenemase
  - Example: Test for presence of specific carbapenemase-producing gene (e.g., PCR)
Carbapenem-Resistant Enterobacteriaceae

Carbapenemase Producing CRE
- KPC*
- NDM*
- OXA
- VIM
- IMP

Non Carbapenemase Producing CRE
- ESBL (+ porin loss)
- AmpC (+ porin loss)
- Other mechanisms

*Routinely tested for at MDH PHL

Microorganisms with a threat level of URGENT:
- Clostridium difficile, drug-resistant Neisseria gonorrhoeae, and CRE

Minnesota Epidemiology

CDC Antibiotic Resistance Threat Report, September 16, 2013
Microorganisms with a threat level of URGENT:
- Clostridium difficile, drug-resistant Neisseria gonorrhoeae, and CRE
Importance of CRE (Including CP and non-CP-CRE)

1. Infections are difficult to treat
   • Emergence of pan-resistant strains
   • New antibiotics are slow to develop
2. Invasive infections are associated with high mortality rates
3. Infections have risen sharply among patients in healthcare facilities
4. Resistance can spread to other bacteria (CP-CRE)

National CRE (CP and Non-CP-CRE) Trends

• Proportion of CRE* reported to NNIS/NHSN increased from 1.2% in 2001 to 4.2% in 2011
• Most of the increase was observed in *Klebsiella* spp. (from 1.6% to 10.4%)
• 4.6% of U.S. hospitals had ≥ 1 patient with a CRE infection during the first half of 2012
  • 17.8% long-term acute care hospitals
  • 3.9% short-stay hospitals
• CP-CRE reported in almost every US state

* E. coli, *Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, or Enterobacter spp. that were nonsusceptible to imipenem, meropenem, or doripenem

Types of Infections

• Urinary tract, intestinal or abdominal, respiratory tract, and wound infections
• Most frequently isolated from urine or blood
• Bloodstream infections are associated with higher rates of death than infection at other sites

Patel JB. Presented at 107th ASM General Meeting, 2007
Agmon O. Presented at 8th Congress of IFIC, 2007
Minnesota CRE Surveillance

- 2009: first KPC-producing CRE identified in MN
- Initiated passive statewide CRE surveillance with voluntary isolate submission
- In 2011 MDH initiated active CRE surveillance in Hennepin and Ramsey Counties

Reported CRE Cases with Isolates by Year
Minnesota, 2011-2014

CP-CRE and Non-CP-CRE Case Isolates by Species, Minnesota, 2014
Hospitalized CRE Patients, Minnesota, 2014

- Hospital Onset (>3 days after admission)
- Community Onset (≤ 3 days after admission)
- Unknown

Infection Prevention and Control Recommendations for CRE

- Carbapenemase Producing (CP) CRE
- Non Carbapenemase Producing (CP) CRE

- Contact precautions
- Consider Surveillance cultures
- Patient/staff cohorting

MDH CRE Recommendations

- Recommendations developed in collaboration with the Association for Professionals in Infection Control and Epidemiology-Minnesota (APIC)
  - Based on CDC guidance
  - Additional guidance for environmental cleaning, visitors, and long-term care setting

- Acute and Long-term Acute Care Facilities
- Long-term Care Facilities

CRE Reporting 2016

IP-Lab Collaboration

- Collaboration between laboratory and infection prevention staff especially important for CRE
- Challenge: Not all antibiotics reported from lab to patient chart
- Most successful when staff from both disciplines work together to identify a CRE case

Minneapolis CRE Surveillance Criteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Past Criteria</th>
<th>New Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Enterobacteriaceae</td>
<td>Klebsiella spp., Enterobacter</td>
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<tr>
<td></td>
<td>spp., E. coli and Citrobacter</td>
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<tr>
<td></td>
<td>spp.</td>
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<tr>
<td>Culture sites</td>
<td>All body sites (sterile/non-</td>
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<td></td>
<td>sterile)</td>
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<td></td>
<td>All body sites (sterile/non-</td>
<td></td>
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<td></td>
<td>sterile)</td>
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</tr>
<tr>
<td>Definition</td>
<td>Nonsusceptible to a</td>
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<tr>
<td></td>
<td>carbapenem antibiotic*</td>
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<tr>
<td></td>
<td>Resistant to 3rd generation</td>
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<tr>
<td></td>
<td>cephalosporins</td>
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<td></td>
<td>Resistant to any carbapenem</td>
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<tr>
<td></td>
<td>antibiotic*</td>
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<tr>
<td></td>
<td>imipenem, meropenem, doripenem,</td>
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<tr>
<td></td>
<td>or ertapenem</td>
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<tr>
<td></td>
<td>Demonstrates production of a</td>
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<tr>
<td></td>
<td>carbapenemase (i.e. MHT)</td>
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*According to current CLSI guidelines
Minnesota CRE Surveillance Criteria (cont’d)

- Resistance is based on current Clinical Laboratory Standards Institute (M100) guidelines
  - Challenge: many labs have not adopted the current carbapenem breakpoints
  - May have to visually review results (MICs) to assess resistance
  - Special queries or flags may be useful in LIMS or Automated Systems

“New” CLSI Carbapenem Susceptibility Interpretive Criteria for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Agent</th>
<th>CLSI M100 S19: 2005</th>
<th>CLSI M100 S24: 2014</th>
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<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
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<tr>
<td>Ertapenem</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Doripenem</td>
<td>-</td>
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How and What to Report

http://www.health.state.mn.us/divs/idepc/dtopics/reportable/forms/reptcard.pdf
How and What to Report (cont.)

- Demographics:
  - Patient name, birthdate, gender, race, ethnicity, telephone number and address
- Culture data:
  - Specimen source, collection date, isolate genus and species and carbapenemase test results (if available)
- Facility data:
  - Name of hospital (including date of admission/discharge) or other healthcare facility, medical record number, report date, physician name and telephone number

Surveillance Cultures

- When isolates test positive for a carbapenemase (e.g. KPC+ by PCR), MDH Epidemiology staff contact hospitals and long-term care facilities where patient is (or was) a patient
- Following case assessment supplemental measures to prevent CRE transmission, including surveillance cultures (rectal swabs) to detect CRE colonization may be recommended
- MDH-PHL can process and test surveillance specimens in setting of a patient with CP-CRE
- Contact epidemiologists at 651-201-5414 if testing is desired, based on CP-CRE or ongoing transmission of other CRE strains
- More detail in the CDC “CRE Toolkit”:

Evolving Laboratory Detection
**Current MDH Laboratory Testing Algorithm**

- Suspect CRE Isolate Submitted
- Isolate identification confirmed (MALDI-TOF, biochemical)
- Examination of AST Report (Microscan, etc.) from submitter
- MIC Profile Assessed against current case definition
- KPC/NDM real-time PCR performed
- Isolate ID and KPC/NDM results reported to submitter
- Additional testing performed (as needed)

**PCR Results for CRE, MN, 2009-2014**

- Initiated active surveillance in Hennepin and Ramsey Counties, June 2011
- PCR negative
- KPC PCR positive (2009)
- MDM PCR positive (2013)
- Percent carbapenemase-producing Enterobacteriaceae

**How and What to Submit - Laboratory**

The MDH Public Health Laboratory requests the following for each isolate submission:

1. CRE Isolate: a pure, low passage culture (RT or refrigerated)
2. Clinical Testing and Submission form
3. MDH CRE Isolate Submission Form
4. AST Report Printout
How and What to Submit (cont.)

Clinical Testing and Submission Form

Be sure to include:
- project number (1380)
- patient information
- specimen source
- collection date
- isolate genus/species

http://www.health.state.mn.us/divs/phl/clin/print_mdh.pdf

How and What to Submit (cont.)

MDH CRE Isolate Submission Form

Be sure to include any AVAILABLE CRE test results:
- Modified Hodge Test
- E-test Results
- Disk Diffusion Results
- Select antimicrobial agent results
- Results from other tests performed (i.e. Carba NP, PCR)

Form available on website soon

How and What to Submit (cont.)

AST Report Printout

Be sure to submit MIC profile obtained from your AST Instrument

i.e. Vitek2, Microscan, Phoenix

Note: Make sure to submit the raw data from your testing platform; not a printout from a patient chart
Clinical Laboratory Detection of Carbapenemases

Current methods:
- Modified Hodge Test (CLSI M100)
- Disk diffusion (with carbapenemase inhibitors)
- Etest strips (with carbapenemase inhibitors)

Clinical Laboratory Detection of Carbapenemases

Current methods, continued:
- CHROM Agars (not FDA cleared)
- Carba NP test (CLSI M100-S25)

Clinical labs directly detecting resistance targets in blood cultures using:
- Nanosphere Verigene® - KPC, NDM, IMP, VIM, OXA-48, CTX-M ESBL
- Biofire® - KPC

Reference or Public Health Laboratory Detection of Carbapenemases

Additional detection methods:
- Carba NP test, (CLSI M100-S25)
- KPC/NDM multiplex PCR (CDC)*
- PCR for additional mechanisms
  - Check Points system (Not FDA cleared)
- Multiplex Real-Time PCR
The Modified Hodge Test

- Standard test in some clinical laboratories
- Limitations with MBL detection
- Can observe false positives with AmpC producers (Enterobacter spp.)

The Modified Hodge Test: Examples

- Weak, true positive – OXA-48

The Modified Hodge Test: Examples

- False positive
- True positive
The Carba NP test

Rapid colorimetric biochemical screening test to detect carbapenemase production

- 37°C, 2 hrs

1 Set of Reaction Tubes
Pre-inoculation

With Imipenem
Without Imipenem
With Imipenem
Without Imipenem
With Imipenem
Without Imipenem

Carbapenemase
Positive Isolate

Carbapenemase
Negative Isolate

CRE Multiplex Real-Time PCR Assays

- Specifically characterize mechanisms of carbapenem resistance; can detect the following genes:
  - Carbapenemases: KPC, NDM (validated at MDH)
  - Carbapenemases*: VIM, IMP, OXA-48
  - ESBLs*: CTX-M, SHV, TEM

  *Available at MDH, not validated

CRE Outbreak and Surveillance Testing

- Capacity to provide outbreak investigation testing for CRE to MN healthcare facilities
- Can also provide guidance to outbreak detection protocols in your facility
- Follow established CDC protocol:
  http://www.cdc.gov/hai/pdfs/labSettings/Klebsiella_or_Ecoli.pdf
- Contact MDH for information or to request testing
**Summary: What should clinical laboratories be doing?**

- At minimum, compare isolate MICs with 2016 CRE definition
- Use updated CLSI guidelines for interpretations
- Consult expert comments from your system (if available)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
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<tbody>
<tr>
<td>Cephalosporin</td>
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<tr>
<td>Imipenem</td>
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<tr>
<td>Meropenem</td>
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<tr>
<td>Piperacillin</td>
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- Perform in-house phenotypic testing (i.e., MHT, if available)
- Molecular testing (if available)
- Submit suspicious isolates to MDH-PHL
- Call MDH for consultation 651-201-5073
- Rectal swab cultures for patients receiving healthcare abroad

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**Summary**

- CRE infections are increasingly common in the U.S. and occur in Minnesota
  - Goal of this surveillance program is to measure the burden of CRE and identify opportunities to prevent transmission, particularly of CP-CRE
  - Statewide surveillance starting in 2016 will be based on a new simplified definition of CRE
    - Resistant to any carbapenem antibiotic according to CLSI (M100) guidelines
    - *Enterobacter* spp., *E. coli*, *Klebsiella* spp. and *Citrobacter* spp.
    - All body sites

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**Call or Contact us with Questions**

- MDH Public Health Laboratory
  - Paula Snippes Vagnone, 651-201-5581
  - paula.snippes@state.mn.us
  - Melissa Hargreaves, 651-201-5572
  - melissa.hargreaves@state.mn.us

- Healthcare Associated Infection and Antibiotic Resistance Unit
  - Medora Witwer, 651-201-4569 or 651-201-5414
  - medora.witwer@state.mn.us

- [http://www.health.state.mn.us/divs/idepc/dtopics/cre/](http://www.health.state.mn.us/divs/idepc/dtopics/cre/)

Thank you for attending!