Carbapenem-resistant Enterobacteriacae (CRE) in Minnesota

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December 15 and 17, 2015

MDH Minnesota Department of Health
Healthcare-Associated Infections and Antimicrobial Resistance Unit

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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

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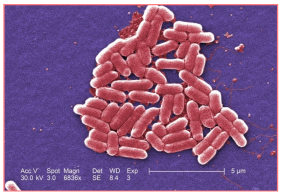
The Enterobacteriaceae

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



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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

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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

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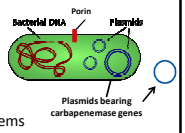
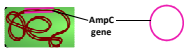
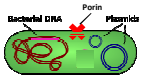
Important Mechanisms of Resistance

- **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





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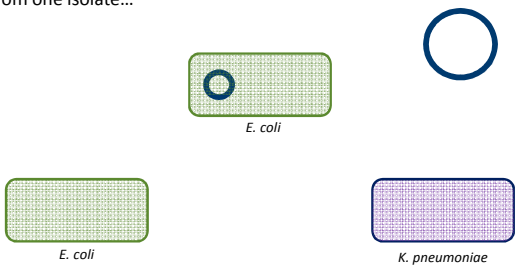
Inter-bacterial spread of carbapenemase genes

From one isolate…

Plasmid with carbapenemase gene



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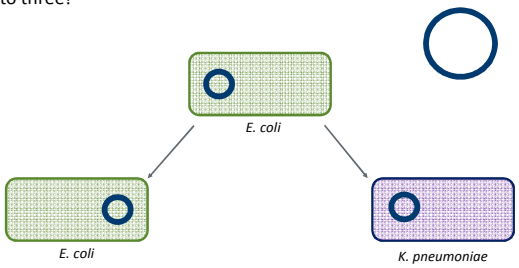
Inter-bacterial spread of carbapenemase genes

…to three!

Plasmid with carbapenemase gene



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Evolving Terminology

Least Specific

Most Specific

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)

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Carbapenem-Resistant Enterobacteriaceae

Carbapenemase Producing CRE	Non Carbapenemase Producing CRE
KPC* NDM* OXA VIM IMP	ESBL (+ porin loss) AmpC (+ porin loss) Other mechanisms

*Routinely tested for at MDH PHL

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Minnesota Epidemiology

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CDC Antibiotic Resistance Threat Report, September 16, 2013

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

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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)

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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*, *Klebsiella oxytoca*, *Enterobacter cloacae*, or *Enterobacter* aerogenes that were nonsusceptible to imipenem, meropenem, or doripenem
NOTE: National Nosocomial Infection Surveillance System/National Healthcare Safety Network
MMWR. Mar 2013;62(09);165-70

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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

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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

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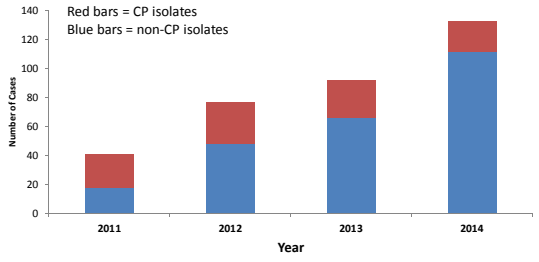
Reported CRE Cases with Isolates by Year Minnesota, 2011-2014



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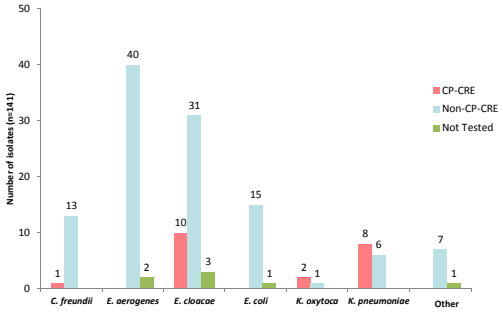
CP-CRE and Non-CP-CRE Case Isolates by Species, Minnesota, 2014



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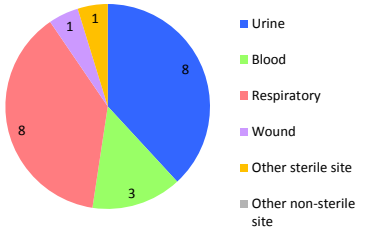
CP-CRE Case Isolates by Specimen Type Minnesota 2014



n = 21

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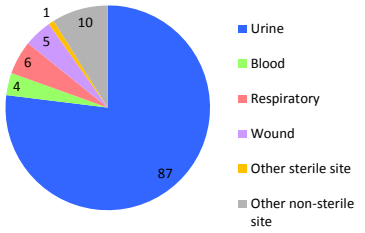
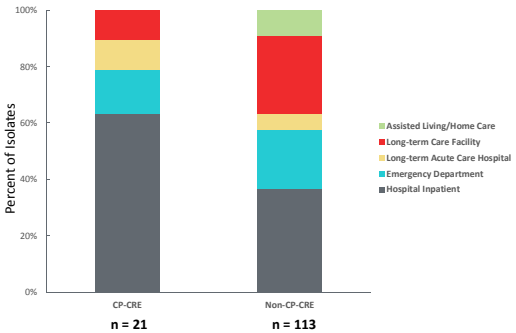
Non-CP-CRE Case Isolates by Specimen Type, Minnesota 2014



n = 113

20

CP-CRE and Non CP-CRE Isolates by Patient Location, Minnesota, 2014



n = 21 **n = 113**

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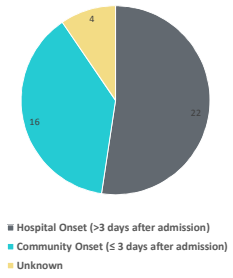
Hospitalized CRE Patients, Minnesota, 2014



n = 42

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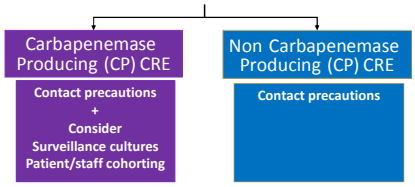
Infection Prevention and Control Recommendations for CRE



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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
  http://www.health.state.mn.us/divs/idepc/dtopics/cre/cre.pdf
- Long-term Care Facilities
  http://www.health.state.mn.us/divs/idepc/dtopics/cre/rec.pdf

Smith P, et al. *Infect Control Hosp Epidemiol* 2008;29(9):785-814

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CRE Reporting 2016

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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

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Minnesota CRE Surveillance Criteria

	Past Criteria	New Criteria
Species	All Enterobacteriaceae	*Klebsiella* spp., *Enterobacter* spp., *E. coli* and *Citrobacter* spp.
Culture sites	All body sites (sterile/non-sterile)	All body sites (sterile/non-sterile)
Definition	• Nonsusceptible to a carbapenem antibiotic* • Resistant to 3rd generation cephalosporins	• Resistant to any carbapenem antibiotic*: imipenem, meropenem, doripenem, or ertapenem • Demonstrates production of a carbapenemase (i.e. MHT)

*According to current CLSI guidelines

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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

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"New" CLSI Carbapenem Susceptibility Interpretive Criteria for Enterobacteriacae

Agent	CLSI M100 S19: 2009			CLSI M100 S24: 2014		
	S	I	R	S	I	R
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4
Doripenem	-	-	-	≤1	2	≥4

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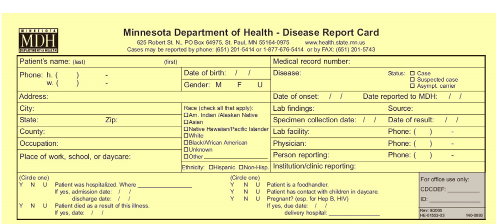
How and What to Report


Minnesota Department of Health - Disease Report Card
625 Robert St. N., PO Box 64975, St. Paul, MN 55164-0975 www.health.state.mn.us
Cases may be reported by phone: (651) 201-5414 or 1-877-676-5414 or by FAX: (651) 201-5743

Patient's name: (last) (first) | Medical record number:
Phone: h. ( ) - w. ( ) - | Date of birth: / / | Gender: M F U | Disease: | Status: ☐ Case ☐ Suspected case ☐ Asympt. carrier
Address: | Date of onset: / / | Date reported to MDH: / /
City: | Race (check all that apply): ☐Am. Indian /Alaskan Native ☐Asian ☐Native Hawaiian/Pacific Islander ☐White ☐Black/African American ☐Unknown ☐Other | Lab findings: | Source:
State: Zip: | Specimen collection date: / / | Date of result: / /
County: | Lab facility: | Phone: ( ) -
Occupation: | Physician: | Phone: ( ) -
Place of work, school, or daycare: | Person reporting: | Phone: ( ) -
Ethnicity: ☐Hispanic ☐Non-Hisp. | Institution/clinic reporting:

(Circle one)
Y N U Patient was hospitalized. Where ______ If yes, admission date: / / discharge date: / /
Y N U Patient died as a result of this illness. If yes, date: / /

(Circle one)
Y N U Patient is a foodhandler.
Y N U Patient has contact with children in daycare.
Y N U Pregnant? (esp. for Hep B, HIV) If yes, due date: / / delivery hospital: ______

For office use only: CDCDEF: ______ ID: ______
Rev: 9/2005 HE-01553-03 140-0093

http://www.health.state.mn.us/divs/idepc/dtopics/reportable/forms/reptcard.pdf

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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

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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" : http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html%20

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Evolving Laboratory Detection

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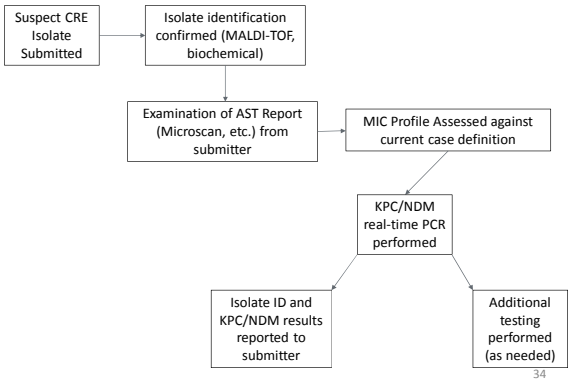
Current MDH Laboratory Testing Algorithm



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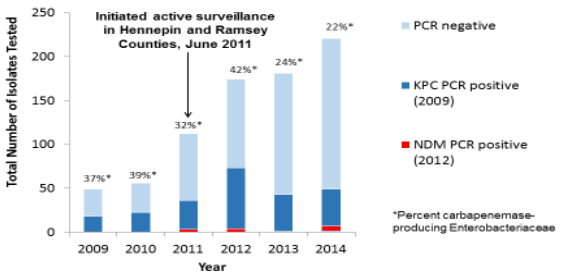
PCR Results for CRE, MN, 2009-2014



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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

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How and What to Submit (cont.)

Clinical Testing and Submission Form

Be sure to include:

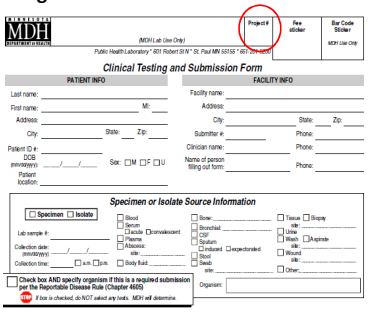
-project number (1380)

-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 results

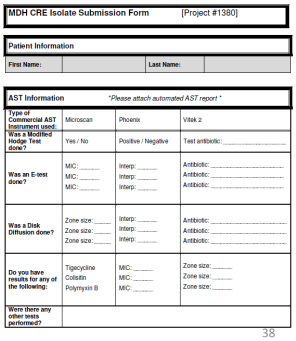
-E-test Results

-Disk Diffusion Results

-Select antimicrobial agent results

-Results from other tests performed (i.e. Carba NP, PCR)

Form available on website soon



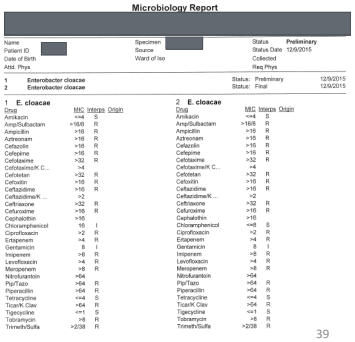
How and What to Submit (cont.)

AST Report Printout

Be sure to submit MIC profile obtained from your AST Instrument

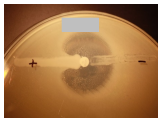
i.e. Vitek2, Microscan, Phoenix

Note: Make sure to submit the raw data from your testing platform; not a printout from a patient chart

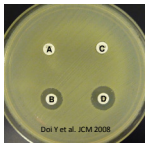


Clinical Laboratory Detection of Carbapenemases

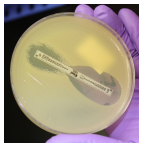
- **Current methods:**
  - Modified Hodge Test (CLSI M100)
  - Disk diffusion (with carbapenemase inhibitors)
  - Etest strips (with carbapenemase inhibitors)



Modified Hodge Test



Disk Diffusion


MBL Etest

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Clinical Laboratory Detection of Carbapenemases

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

CHROMagar KPC

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

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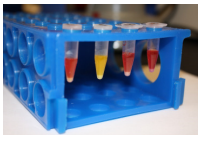
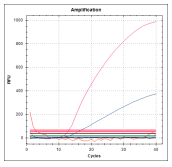
Reference or Public Health Laboratory Detection of Carbapenemases

- **Additional detection methods:**
  - Carba NP test (CLSI M100-S25)
  - KPC/NDM multiplex PCR (CDC)*
  - PCR for additional mechanisms
    - Check Points system (Not FDA cleared)


Carba NP test


Multiplex Real-Time PCR

Check Points Check-MDR Microarray kit

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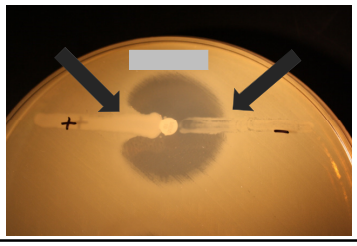
The Modified Hodge Test

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



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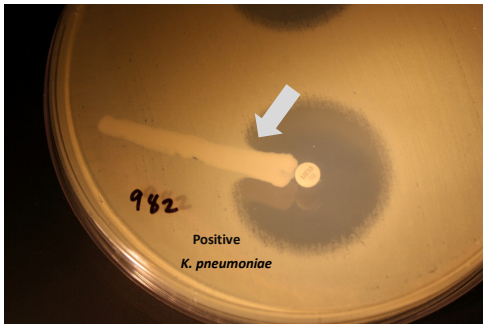
The Modified Hodge Test: Examples



Weak, true positive – OXA-48

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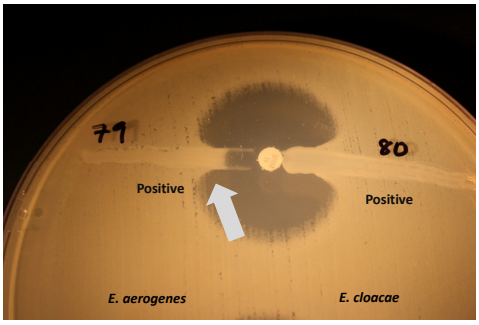
The Modified Hodge Test: Examples



False positive True positive

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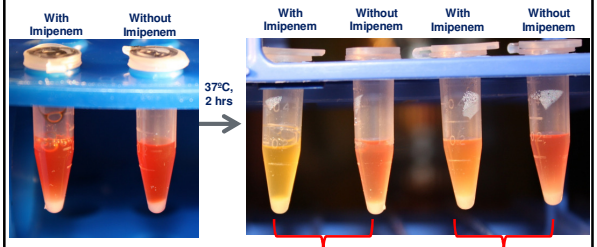
The Carba NP test

Rapid colorimetric biochemical screening test to detect carbapenemase production



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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

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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

CDC

Laboratory Protocol for Detection of Carbapenem-Resistant or Carbapenemase-Producing, *Klebsiella* spp. and *E. coli* from Rectal Swabs

- Contact MDH for information or to request testing

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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)

	CLSI M100-S24 (2014)		
Agent	S	I	R
Ertapenem	≤0.5	1	≥2
Imipenem	≤1	2	≥4
Meropenem	≤1	2	≥4
Doripenem	≤1	2	≥4

- 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/

Thank you for attending!

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