“CRE Mechanisms and their Importance for Infection Prevention”

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Director, Clinical Microbiology Laboratory
Loyola University Medical Center
pschrecken@lumc.edu
<table>
<thead>
<tr>
<th>Type of Financial Interest</th>
<th>Name of Commercial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salaried Employee</td>
<td>Loyola University Medical Center</td>
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<tr>
<td>Stocks/Stock Options</td>
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<tr>
<td>Independent contractor/Speaker’s Bureau</td>
<td>Accelerate Dx., Beckman Coulter, bioMerieux, BioFire, Cepheid, Hardy Diagnostics, Merck, Thermo Fisher Scientific</td>
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<tr>
<td>Consultant/Advisory Committees</td>
<td>BioFire, Cempra, Cepheid, GenMark, Quidel, Thermo Fisher Scientific, Theravance</td>
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<td>Research Grants</td>
<td>Accelerate Dx, Becton-Dickinson, Beckman Coulter, BioFire, bioMerieux, Bruker, Cepheid,</td>
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Learning Objectives

At the conclusion of this session, participants will be able to:

1. Describe the five major types of CRE
2. Review conventional and new approaches to detecting CRE
3. Explain the CSTE CRE definition proposal and its implications for labs
4. Evaluate their own laboratories readiness for detecting and reporting CRE
Penicillin nucleus

Cephalosporin nucleus
MODE OF ACTION OF BETA LACTAMS IN GRAM NEGATIVES

SUSCEPTIBLE

β-Lactam Antibiotic

Diffusion through Outer Membrane

Diffusion through Peptidoglycan

Penicillin Binding Proteins

Cell Death

RESISTANT

Porin Blocks Entry

Efflux Pump

Beta-Lactamase Hydolyzes Beta-Lactam

Changes in PBP results in Failure to Bind to β-Lactam
## The β-lactam family of antibiotics

<table>
<thead>
<tr>
<th>Penicillins</th>
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ESBLs hydrolyze all Penicillins Cephalosporins Monobactams
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**ampCs hydrolyze all**

- Penicillins
  - 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> Cephalosporins
  - Cephamycins
  - Cephalosporins
  - Monobactams
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Metallo BL hydrolyze all Penicillins Cephalosporins Cephamycins Carbapenems
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KPCs hydrolyze all Penicillins, Cephalosporins, Cephamycins, Carbapenems, and Monobactams.
Carbapenem-Resistance in Enterobacteriaceae

• Two mechanisms of resistance
  – **Carbapenemase** (β-lactamase that can hydrolyze carbapenems)
  – **Cephalosporinase** combined with porin loss
    ▪ Some cephalosporinases (e.g., AmpC-type β-lactamases or certain ESBLs i.e. CTX-M) have a low-level carbapenemase activity
    ▪ Porin loss limits entry of the carbapenem into the periplasmic space
Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

• Carbapenemase
  – Isolate likely to be resistant to all carbapenems and other β-lactam agents
  – May need to change susceptible reports to resistant for β-lactam drugs
  – Need to implement infection control measures such as contact precautions and possibly active surveillance testing
  – These are an Infection Control Emergency
Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

• Cephalosporins combined with porin-loss
  – Class A ESBL’s (CTX-M) + reduced permeability
  – Class C High AmpC + reduced permeability
• These hydrolyze ertapenem more than meropenem or imipenem
  – Not necessarily resistant to all carbapenems (i.e., would not need to change susceptible results to resistant reports for β-lactam drugs)
• These isolates are clearly MDR and infection control measures are recommended. Healthcare institutions may reserve more aggressive measures for carbapenemase-producing isolates
## 5 Most Common Carbapenemases

<table>
<thead>
<tr>
<th>Class</th>
<th>Carbapenemases</th>
<th>Enterobacteriaceae</th>
<th>Non-fermenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (^1)</td>
<td>KPC(^2)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>B (metallo)</td>
<td>NDM(^3), IMP, VIM,</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>D</td>
<td>OXA-48-like</td>
<td>+++</td>
<td>+/-</td>
</tr>
</tbody>
</table>

\(^1\)also includes SME; \(^2\)most common in USA; \(^3\)increasing in USA

….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)
Strategy for Laboratory Detection of Carbapenemases

• **Antibiogram** – CDC approach: if any Enterobacteriaceae tests non-susceptible to any carbapenem call it CRE.

• **Phenotypic testing**
  – Modified Hodge Test
  – Boronic Acid Synergy Test
  – EDTA inhibition test (MBL Etest)

• **Rapid Colorimetric**
  – Carba NP
  – NEO-Rapid CARB Kit by Rosco Diagnostica (Hardy, Key Scientific)
  – RAPIDEC® CARBA NP (bioMerieux)
  – EPI-CRE® (Pilots Point, Sarasota, FL)

• **Molecular** – PCR

• **Other**
Strategy for Laboratory Detection of Carbapenemases

• CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  - “Laboratories should perform the modified Hodge test (MHT), the Carba NP test, and/or a molecular assay when isolates of Enterobacteriaceae are suspicious for carbapenemase production”
Strategy for Laboratory Detection of Carbapenemases

• CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  – Disk zone of < 22 mm for ertapenem or meropenem
  – MIC of >1 μg/ml for imipenem, ertapenem or meropenem

• Procedure Notes
  – Imipenem disk test is not a good screen
  – Imipenem MIC does not work as a screen for Proteus/Providencia/Morganella due to slightly elevated MICs in this group by mechanisms other than carbapenemases
Modified Hodge Test

- Inoculate MH agar with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streak for confluent growth using a swab.
- Place 10-µg ertapenem or meropenem (best) disk in center.
- Streak each test isolate from disk to edge of plate.
- Isolate A is a KPC producer and positive by the modified Hodge test.

Modified Hodge Test

Neg Control  
-  

KPC  
+  

NDM  
False  -  

OXA 232  
+  

(UCLA  

(slided courtesy Janet Hindler)
Potentiation of carbapenems by APB in *K. pneumoniae* producing KPC-2. (A) Ertapenem (10 μg); (B) ertapenem plus APB (300 μg); (C) meropenem (10 μg); (D) meropenem plus APB (300 μg).

Rosco Diagnostica IMI/EDTA Disks
MBL Etest bioMerieux

EDTA Etest = Pos

IMI alone = 19 mm

IMI + EDTA = 27 mm

(Only Detects MBL’s eg. NDM, IMP, VIM)
What is the Carba NP test?

- A colorimetric test for carbapenemase production by Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter*
  - Uses imipenem as the target substrate, phenol red as the pH indicator; positive hydrolysis turns yellow
  - Color usually turns fast, test ends at 2 hours
  - Good at detecting KPC, NDM, VIM, SPM, and SME, not so good at OXA
  - Will pick up carbapenem resistance if the MIC is 2 or 4 and you haven’t changed your breakpoints
Carba NP Test for Carbapenemase Production

♦ Isolated colonies (lyse)
♦ Hydrolysis of imipenem
♦ Detected by change in pH of indicator (red to yellow/orange)
♦ Rapid <2h
♦ Microtube method


(slide courtesy Janet Hindler)
### Results for Patient and QC Tubes

<table>
<thead>
<tr>
<th>Solution A</th>
<th>Tube “a”: Solution A (serves as internal control)</th>
<th>Tube “b”: Solution B</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red or red-orange</td>
<td>Red or red-orange</td>
<td>Negative, no carbapenemase detected</td>
<td></td>
</tr>
<tr>
<td>Red or red-orange</td>
<td>Light-orange, dark yellow, or yellow</td>
<td>Positive, carbapenemase producer</td>
<td></td>
</tr>
<tr>
<td>Red or red-orange</td>
<td>Orange</td>
<td>Invalid</td>
<td></td>
</tr>
<tr>
<td>Orange, light-orange, dark yellow, or yellow</td>
<td>Any color</td>
<td>Invalid</td>
<td></td>
</tr>
</tbody>
</table>

**Solution A**

- Red
- Red
- Red
- Red-orange
- Red-orange

**Tube “b”**

- Orange
- Light Orange
- Dark Yellow
- Yellow

**Interpretation**

- Invalid

*Slide courtesy Janet Hindler*

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**M100-S25. p.120-126.**
Carba NP Test Materials/Reagents

- Testing simple
- Reagent Preparation takes time

Reagents Must be Prepared Fresh
10 mM Zinc sulfate heptahydrate
Phenol red solution
0.1 N NaOH
Carba NP Solution A
(phenol red + zinc solutions)
Carba NP Solution B
(Carba NP Solution A + imipenem)

(slide courtesy Janet Hindler)
Carba NP Test

Blank  Neg  KPC  OXA48  OXA181  NDM  IMP  VIM  SME

UCLA

(slide courtesy Janet Hindler)
Commercial Test
Rapid CARB Screen Kit

- Commercial kit; similar to Carba NP
- Enterobacteriaceae and *P. aeruginosa*
- Tablets
  - Imipenem + indicator
  - Negative control
- ≤2 hours
- CLSI study isolates – UCLA results:
  - More difficult to read than Carba NP
  - Good agreement with Carba NP but more initial invalids that required repeating
  - Most problems with *Acinetobacter baumannii* – NDM (not indicated for this species)

www.rosco.dk

NOT FDA cleared
# Enterobacteriaceae Carbapenemase Detection

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Carba NP</th>
<th>Rapid CARB Screen Kit</th>
<th>MHT</th>
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<tbody>
<tr>
<td>1</td>
<td>235</td>
<td>97% sens 100% spec</td>
<td>98% sens 83% spec</td>
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<tr>
<td>2</td>
<td>92</td>
<td>91% sens 100% spec</td>
<td>73% sens 100% spec</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>-</td>
<td>98% sens 100% spec</td>
<td>75% sens 91% spec</td>
</tr>
</tbody>
</table>


Rapid CARB Screen Kit discontinued !!!!  
Reformatted Product is Neo-Rapid CARB Screen Kit

(slide courtesy Janet Hindler)
Commercial Test
RAPIDEC® CARBA NP

1) Phenol red: pH indicator
2) A carbapenem: imipenem (carbapenemase substrate) + Zinc, required for the detection of metallodependent carbapenemase-producing strains

Detects (without distinction) Class A, B and D Carbapenemases

bioMerieux

NOT FDA cleared

https://www.youtube.com/watch?v=3YXCBs34zyA
It’s Easy to See...

Specifications

Time to Results: **Positive** – as soon as the sample changes from gold to magenta.

**Negative** – after 24 hours if no color change from gold occurs.

Storage: From 2 to 28 °C under dry conditions, EPI-CRE® is stable for 1 year from date of manufacture.

Sensitivity & Specificity: EPI-CRE® detects ONLY living bacteria. It is 100% specific.

Regulatory: CE/IVD approved.

NOT FDA cleared
## EPI-CRE®

<table>
<thead>
<tr>
<th></th>
<th>MBL E-test</th>
<th>Modified Hodge Test</th>
<th>EPI-CRE</th>
<th>PCR</th>
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<tbody>
<tr>
<td></td>
<td>Pos Neg Total</td>
<td>Pos Weak Neg Total</td>
<td>Pos Neg Total</td>
<td>Pos Neg Total</td>
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<tr>
<td><strong>KPC</strong></td>
<td>0 13 13</td>
<td>13 0 0 13</td>
<td>13 0 13</td>
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<td>1 16 9 26</td>
<td>26 0 26</td>
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<td><strong>OXA48</strong></td>
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<td>2 1 0 3</td>
<td>3 0 3</td>
<td>3 0 3</td>
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<tr>
<td><strong>ESBL</strong></td>
<td>0 20 20</td>
<td>0 0 20 20</td>
<td>0 20 20</td>
<td>0 20 20</td>
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<tr>
<td><strong>AmpC</strong></td>
<td>0 21 21</td>
<td>0 0 21 21</td>
<td>0 21 21</td>
<td>0 21 21</td>
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<tr>
<td><strong>Total Tested</strong></td>
<td>26 57 83</td>
<td>16 17 50 83</td>
<td>42 41 83</td>
<td>42 41 83</td>
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<tr>
<td><strong>Total CRE</strong></td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>42</td>
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<tr>
<td><strong>Sensitivity (%)</strong></td>
<td>61.9</td>
<td>38.1</td>
<td>100</td>
<td>100</td>
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<tr>
<td><strong>Specificity (%)</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
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EPI-CRE inoculated with 50 µl 0.5 McFarland suspension

EPI-CRE®

Table 3. Cumulative Percentage of Positives

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<th></th>
<th>KPC</th>
<th>MBL</th>
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<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<td>1</td>
<td>54%</td>
<td>54%</td>
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<tr>
<td>2</td>
<td>96%</td>
<td>96%</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>96%</td>
<td>85%</td>
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EPI-CRE inoculated with 50 µl 0.5 McFarland suspension

Molecular Tests for Carbapenemases

- **Biofire** *
  - KPC
- **Nanosphere** *
  - KPC, NDM, OXA, IMP, VIM
- **BD Max**
  - KPC, NDM, OXA-48
- **Cepheid**
  - KPC, NDM, OXA-48, IMP-1, VIM
- **Check-Points**
  - KPC, NDM, OXA-48, IMP, VIM
- **Others?**

* FDA cleared

(slide courtesy Janet Hindler)
Tests for Carbapenemases in *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

<table>
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<th></th>
<th>MHT</th>
<th>Carba NP</th>
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<tbody>
<tr>
<td><strong>Use</strong></td>
<td>Enterobacteriaceae</td>
<td>Enterobacteriaceae</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P. aeruginosa</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acinetobacter</td>
<td>Acinetobacter</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>Simple</td>
<td>Rapid</td>
<td>Determines type of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carbapenemase</td>
</tr>
<tr>
<td><strong>Limitation</strong></td>
<td>Some false pos (eg, ESBL/ampC +</td>
<td>Special “fresh” reagents</td>
<td>Special reagents</td>
</tr>
<tr>
<td></td>
<td>porin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some false neg (eg NDM)</td>
<td>Some invalid results</td>
<td>Specific to targeted</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae only</td>
<td>False neg for OXA-type</td>
<td>gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carbapenemase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High Cost</td>
</tr>
</tbody>
</table>

(Slide courtesy Janet Hindler)  M100-S25. p. 112.
Other New Approaches

• Immunochromatographic confirmatory test for the detection of OXA-48
Other New Approaches

Ote Isabelle, et al. Development of a novel immunochromatographic confirmatory test for the detection of OXA-48 carbapenemase in Enterobacteriaceae, ECCMID 4-26-15

https://www.youtube.com/watch?v=BbiX5-aWQ9w
Other New Approaches

• Electrochemical Detection of Imipenem Hydrolysis
  • Validation of a new electrochemical assay (BYG Carba test) for the rapid laboratory detection of carbapenemase-producing Enterobacteriaceae
  • P. Bogaerts, S. Yunus, Y. Glupezynndki
    National Reference Laboratory for monitoring antimicrobial resistance in Gram-negative bacteria, Belgium ECCMID 4-26-15

• Based on modification of conductivity of sensor Polyaniline which is coated on the electrode which results due to change in pH and redox potential during imipenem hydrolysis

• 324 clinical isolates 178 CPE (KPC, OXA, VIM, NDM) No False Pos, 9 False Neg. Test result in 30 min.
For the first time, the speed and simplicity of molecular diagnostics is combined with the antibiotic susceptibility information that is critical for MDRO surveillance and guiding antibiotic therapy.

<table>
<thead>
<tr>
<th>Test Applications</th>
<th>Direct-from-Patient Sample</th>
<th>Same-Shift</th>
<th>MDRO Detection and Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance Programs</td>
<td>e.g., nasal swab, rectal swab</td>
<td>≤4 hours</td>
<td>MDROs of interest (e.g., MRSA, CRE, FSE)</td>
</tr>
<tr>
<td>Guiding Therapy</td>
<td>e.g., urine, +blood culture, wound</td>
<td>≤4 hours</td>
<td>Ruling in therapies that will work</td>
</tr>
</tbody>
</table>
### MALDI-TOF MS
Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALDI-TOF Assay</td>
<td>77%</td>
<td>100%</td>
</tr>
<tr>
<td>Carb NP Test</td>
<td>76%</td>
<td>100%</td>
</tr>
<tr>
<td>MALDI-TOF BIC Assay</td>
<td>98%</td>
<td>100%</td>
</tr>
</tbody>
</table>

BIC Assay includes addition of 50 mM NH$_4$HCO$_3$ to reaction buffer

Both methods experienced problems with subset of 19 isolates producing OXA-48 carbapenemase

Papagiannitsis CC et al.  
Why is Carbapenem Resistance a Public Health Problem?

• Significantly limits treatment options for life-threatening infections

• No new drugs for gram-negative bacilli

• Emerging resistance mechanisms, carbapenemases are mobile

• Detection of Carbapenem Producing Organisms (CPO’s) and implementation of infection control practices are necessary to limit spread
Alphabet Soup: CRE, CPE, CPO

- What is the difference between CPO, CPE and CRE?
  - The differences depend on type of bacteria being included and the mechanisms of resistance to carbapenem antibiotics.
  - **Carbapenem Resistant Enterobacteriaceae (CRE)** refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli*, *Klebsiella*, etc) that are resistant to carbapenem antibiotics regardless of the method of resistance, as there are a number of different ways.
Alphabet Soup: CRE, CPE, CPO

What is the difference between CPO, CPE and CRE?

Carbapenemase Producing Enterobacteriaceae (CPE) refers to bacteria in the family of Enterobacteriaceae (e.g. E.coli, Klebsiella, etc) that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.
Alphabet Soup: CRE, CPE, CPO

• What is the difference between CPO, CPE and CRE?

  – Carbapenemase Producing Organisms (CPO) refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli*, *Klebsiella*, etc) and those that do not belong to this family such as *Pseudomonas* and *Acinetobacter*, that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.
Alphabet Soup: CRE, CPE, CPO

• Why are other countries using the term CPO?
  – Genes for carbapenem resistance can be transferred to bacteria in the Enterobacteriaceae family and to bacteria not within this family
  – The term CPO includes the larger group of potentially affected bacteria. This is important for surveillance purposes so that we do not miss any groups of bacteria that may be carrying and spreading these antibiotic resistant genes.
  – CPO’s are what laboratories should be looking for and what Infection Preventionists should be reporting.
CSTE Definition of CRE

• The 2012 definition for CRE was: *E. coli, Klebsiella spp.*, and *Enterobacter spp.* nonsusceptible to imipenem, meropenem, or doripenem and resistant to all 3rd-generation cephalosporins tested (e.g., ceftriaxone, cefotaxime, ceftazidime) Ertapenem was excluded.

• Proposed 2015 definition for CRE is: *E. coli, Klebsiella spp.*, and *Enterobacter spp.* resistant to imipenem, meropenem, doripenem, or ertapenem or production of a carbapenemase (e.g. KPC, NDM, VIM, OXA-48) demonstrated by a recognized test (e.g. PCR, MBL test, MHT, Carba NP
Problems with CSTE Definition

- MYSPACE Bugs (Morganella, Yersinia, Serratia, Providencia, Aeromonas, Citrobacter, Enterobacter, possess chromosomal AmpC beta-lactamase) may test ertapenem non-susceptible if also have porin mutation. These are not CPO’s and are not an IC threat.
- At LUMC, 12% of *E. cloacae* test non-susceptible to ertapenem.
- In 2014, 40 patients would have been called CRE (that were not CPO’s) and would have been placed in isolation and reported to XDRO registry.
Problems with CSTE Definition

- Imipenem vs. Proteeeae (i.e., Morganella morganii, Proteus spp., Providencia spp.)
- MIC\(_{90}\) of imipenem ≤ 1 ug/mL for most Enterobacteriaceae, but is 4-8 ug/mL for Proteeeae and may test non-susceptible to imipenem using new CLSI/FDA BPs
- Some *P. mirabilis* are more resistant, with imipenem MICs ranging from 16 to 64 ug/mL
- Higher MICs seen with imipenem vs. *P. mirabilis* are not due to carbapenemases but rather diminished expression of penicillin-binding protein (PBP) 1a and reduced binding of imipenem by PBP2
Problems with CSTE Definition

• Proteeeae that are non-susceptible to imipenem are not CPOs and are not an IC threat.
• At LUMC in 2014, 239 Proteeeae were NS to imipenem (141 *P. mirabilis*, 11 *P. vulgaris*, 17 *Providencia* spp., 70 *Morganella* spp.)
• These patients should not be placed in isolation and should not be reported to the XDRO registry
• *P. aeruginosa* and *Acinetobacter baumannii* have both been reported to have CPO’s yet these are not reported using the CSTE definition.
**Klebsiella pneumoniae or Escherichia coli** reported as non-susceptible (R or I) to any carbapenem (Imipenem, Ertapenem, Meropenem, Doripenem)?

- Yes
  - Was a CRE Data Collection Form already submitted within the last 30 days from your facility on this patient for the same organism (from any body site)?
    - Yes
      - Submit CRE Data Collection Form
    - No
      - Check MIC values of carbapenems. Are any of the following true?
        - Imipenem 2 ug/ml OR 4 ug/ml
        - Meropenem 2ug/ml OR 4 ug/ml
        - Ertapenem 2 ug/ml
          - Yes
            - Was Modified Hodge Test (MHT) performed?
              - Yes
                - Result POSITIVE
              - No
                - Result NEGATIVE
            - No
          - No
            - (or none of these dilutions are available on panel)
            - Do NOT submit CRE Data Collection Form

- No
Why labs should continue to perform MHT and EDTA Inhibition Test on isolates that test Non-Susceptible to carbapenems

- Knowing the resistance mechanism is important
- Some require changes in antibiotic reporting, some require infection control notification, some require reporting to State Lab, and some require no action
- Can you tell the difference between them by MIC alone?
Patient History Case 1

• 58 y/o male, morbidly obese (>500 lbs)
• Presented to ER with episode of hypoxia and hypotension during dialysis
• PMH
  – Pt has trach for hypercapnea (COPD and OSA), vent dependent
  – Chronic foley catheter
  – Diabetes mellitus type 2
  – ESRD
• Exam:
  – Afebrile
  – Multiple decubitus ulcers (sacrum, spine, right leg)
  – Urine is grossly dirty
• Concerned that septic => Pan-cultures
  – Urine: *Klebsiella*…
Double Disk Potentiation Method – Case 1

Imipenem - S
Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation
Case 1 - MHT Positive

Positive control

Negative control

Patient
And the Answer is ........
### 5 Most Common Carbapenemases

<table>
<thead>
<tr>
<th>Class</th>
<th>Carbapenemases</th>
<th>Enterobacteriaceae</th>
<th>Non-fermenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ¹</td>
<td>KPC²</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>B (metallo)</td>
<td>NDM³, IMP, VIM,</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>D</td>
<td>OXA-48-like</td>
<td>+++</td>
<td>+/-</td>
</tr>
</tbody>
</table>

¹also includes SME; ²most common in USA; ³increasing in USA

….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)
Patient Report Case 1

• If using former CLSI/FDA breakpoints change all carbapenems to resistant
• If using new CLSI/FDA breakpoints report interpretations as tested
• Add following statement to report:
  “Carbapenem resistant Enterobacteriaceae (CRE) detected by Modified Hodge Test – probable KPC type. Implement infection control measures according to facility policy.”
• Submit CRE Data Collection Form
Double Disk Potentiation Method – Case 2
Blood Culture with *Enterobacter cloacae*

Imipenem - S
Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation
Case 2 - MHT = Neg

Positive control

Patient
And the Answer is ...........
And the Answer is ………..

Chromosomal AmpC (Derepressed mutant) + Porin mutation
Patient Report Case 2

- Susceptibility pattern in Case 2 is identical to susceptibility pattern in Case 1, except in Case 2 we have a chromosomal AmpC that is not MDRO, is not an infection control risk, and does not require modification of susceptibility report.
- Add following statement to report:
  “This organism is known to possess an inducible β-lactamase. Isolates may become resistant to all cephalosporins after initiation of therapy. Avoid β-lactam-inhibitor drugs”
- **DO NOT** Submit CRE Data Collection Form
CDC Lab Training Resources

• 5 e-learning courses in the basic curriculum–direct link: http://www.cdc.gov/labtraining/basic_courses.html

• Curriculum on antimicrobial susceptibility testing called MASTER – 3 e-learning courses offered: http://www.cdc.gov/labtraining/master_courses.html

• E-learning course on Packaging and Shipping Division 6.2 Materials. Relevant for facilities who need to send specimens to other labs for testing. Individuals who pass this course are eligible to be certified to pack and ship by their employer. http://www.cdc.gov/labtraining/course_listing/1043824.html